Malaria Policy Advisory Committee (MPAC) Meeting

17-19 October 2017
Chateau de Penthes, 18 Chemin de l'Impératrice, Pregny-Chambésy, Geneva, Switzerland

PROVISIONAL PROGRAMME*

Wednesday, 18 October 2017			
	Session 5	**Open**	**for information**
09:00 – 10:00	Update on the Vector Control Advisory Group	Dr Tom Scott	
10:00 – 11:00	Outcomes of the ERG on comparative effectiveness of vector control tools/Presentation/Information note	Dr Azra Ghani	**for decision**
11:00 – 11:30	*Coffee break*		
	Session 6	**Open**	

World Health Organization

11:30 – 12:00	Proposed ERG on border malaria/Presentation	Dr Li Xiao Hong	**for guidance**
12:00 – 12:30	WHO Research & Development Observatory/ Presentation	Dr David Schellenberg Dr Taghreed Adam	
12:30 – 14:00	*Lunch*		
	Session 7	**Open**	
14:00 – 14:45	Gaps in malaria programme coverage	Dr Richard Cibulskis Dr Andrea Bosman	
14:45 – 15:30	Integrated Community Case Management of Malaria: Results from the Rapid Access Expansion Programme	Dr Salim Sadruddin	**For information**
15:30 – 16:00	Malaria threats map presentation 1/ Presentation 2	Dr Tessa Knox Dr Jane Cunningham Ms Amy Barrette	
16:00 – 16:30	*Coffee break*		
	Session 8	**Open**	
16:30 – 17:30	Outcomes of the ERG on malaria in pregnancy outside of Africa /Presentation	Dr Larry Slutsker	**for decision**
17:30 – 18:00	Update on the establishment of the Malaria Elimination Oversight Committee and Malaria Elimination Certification Panel /Presentation	Dr Kim Lindblade	**For information**
18:00	*End of day*		

** Provisional Programme and may be subject to change*

World Health Organization

The WHO Vector Control Advisory Group (VCAG)

A JOINT ACTIVITY OF NTD AND GMP

Presentation to MPAC

Thomas W. Scott, Chair VCAG

Vector Control Advisory Group (VCAG)

Established in 2012 as an independent advisory body to WHO on the public health value of new vector control tools and approaches for the prevention of vector-borne diseases

- VCAG guides innovators on documentation requirements and data, and advises WHO on the public health value of new tools, technologies and approaches
- Jointly established by the Global Malaria Program and the Department of Control of Neglected Tropical Diseases

General Objectives

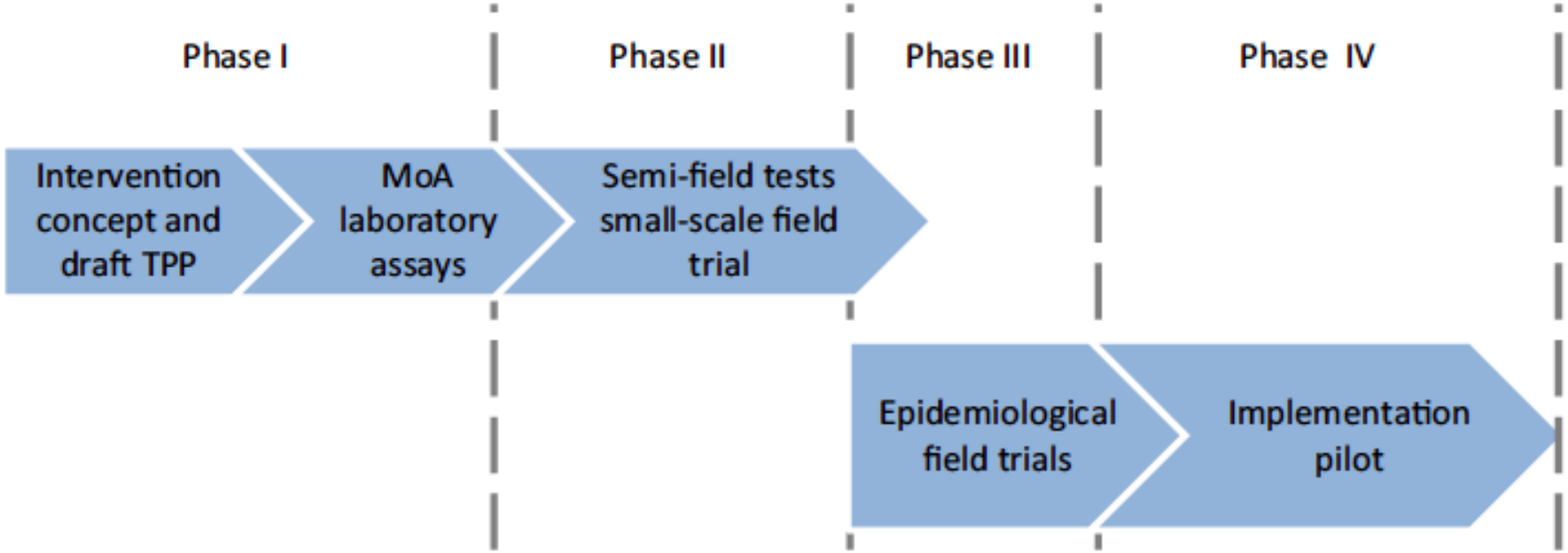
- Conduct an initial review of a new intervention concept and determine data and study designs required to (1) validate the product class, claim or variation and (2) support the formulation of a WHO policy recommendation
- Advise WHO and applicants on the process of generating required data for policy recommendations
- Assess evidence for new vector control tools and approaches
- Develop or refine the target product profiles of new vector control classes
- Provide guidance to WHO and its policy advisory groups (MPAC and STAG) on the public health value of new tools and approaches, including updates on evidence gaps preventing such assessment

Stages in Development of a New Vector Control Product

Review
Trends in Parasitology August 2015, Vol. 31, No. 8
CellPress

Evidence-based vector control? Improving the quality of vector control trials

Anne L. Wilson[1], Marleen Boelaert[2], Immo Kleinschmidt[3], Margaret Pinder[1,4], Thomas W. Scott[5,6], Lucy S. Tusting[7], and Steve W. Lindsay[1]



- **Public health value:** A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans
- **Phase III and IV studies** enable development of policy recommendations by WHO & country-level by member states

New Vector Control Product Classes (n=17)

New Product - Variation	Generic Exemplar	Product Example
Treated walls against IR vector (extend IRS)	IRS/wall linings for IR pop	No claim reviewed
Peri-focal residual spraying (extend IRS)	Outdoor RS	PFS formulation, Bayer
Insecticide-treated curtain (extend ITN)	Fully screened house	FSH pyrethroid netting
New Product Class – (chemical)	**Generic Exemplar**	**Product Example**
ITN against IR Vector	Pyrethroid + PBO	Olyset Plus, PermaNet 3.0
	Pyrethroid + Chlorfenapyr	Interceptor G2
	Organophosphate	Yorkool LN G2.0 and G2.1
Attract and kill baits	Attractive Toxic Sugar Bait	Bait station
Spatial repellents	Passive emanator	Metofluthrin or Transfluthrin
ITM for specific risk groups	ITM	Blanket, Clothes
Vector traps	Adulticidal Oviposition traps	ALOT, AGO, TNK, IN2TRAP
Lethal house lures	Eave tubes	Eave tubes
Systemic insecticide	Rodent bait	Imidicloprid based bait
New Product Class – (biological)	**Generic Exemplar**	**Product Example**
Microbial control in adult vectors	Bacterial infection	wMel *Wolbachia* in *Ae. aegypti*
Pop. reduction through genetic manipulation	GMM, self limiting	OX513A *Ae. aegypti* (RIDL)
	GMM, gene-drive	CRISP/Cas9 in *An. gambiae*
Pop. alteration of malaria vector mosquitoes	GMM, gene-drive	CRISP/Cas9 anti-parasite
SIT & incompatible insect technique (IIT)	Radiation + bacterial infection	Sterilized *Aedes* spp. + *Wolbachia*

New Vector Control Product Classes (n=17)

Stage 3 epi trials (n=10)

New Product - Variation	Generic Exemplar	Product Example
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SIT & incompatible insect technique (IIT)	Radiation + bacterial infection	Sterilized *Aedes* spp. + *Wolbachia*

VCAG Members

Vector ecology, genetics and population biology
Thomas W. Scott (**Chair VCAG**)
Heather Ferguson
Audrey E. Lenhart (*new member 2017*)

Insecticide resistance and resistance mechanisms
Hilary Ranson (*new member 2017*)
Fabrice Chandre (*new member 2017*)

Development and/or evaluation of public health products
Marc Coosemans

Study design and statistics
Steven W. Lindsay
Thomas Smith
Robert Reiner *(new member 2017)*

Epidemiology of vector borne diseases
Immo Kleinschmidt
Salim Abdulla *(new member 2017)*

- *Ad hoc* expert advisors used as needed
- Expertise needs
  - Product development
  - Regulatory
  - Molecular gene drive

6th VCAG: Reviewed updates and new submissions

Product Class / Category	Description of entomological and epidemiological mode of action	Prototype / product reviewed
Genetic manipulation of vectors for disease control	Reduction or alteration of vector populations through genetic manipulation	Oxitec OX513A
Lethal House Lures	The concept exploits vector behaviour using occupants of a house to lure vectors to material treated with a bioagent that kills the vector. The product should have an overall effect on vectorial capacity and reduce infection or disease in humans.	Eave tubes
Microbial control of human pathogens in adult vectors	Introduction of micro-organisms into vectors to prevent biological transmission of the pathogen to humans.	wMel strain Wolbachia in *Aedes aegypti*
Spatial Repellents	Spatial repellents interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, offering protection (personal and/or community) from medically important vectors and nuisance pests.	Transfluthrin passive emanator
New LLINs	First-in class LLINs based on non-pyrethroid insecticides, and intended to be used for malaria control for pyrethroid-resistance	Interceptor® G2, Yorkool G2.0 and G2.1

7th VCAG: October 24-26 2017

New Product - Variation	Generic Exemplar	Prototype product
Non-pyrethroid IRS (extend IRS)	New IRS product	BASF product Sylando

New Product Class – (chemical)	Generic Exemplar	Prototype product
Non-pyrethroid ITN against IR Vector	Pyrethroid + Chlorfenapyr	Interceptor G2
Attract and kill baits	Attractive Toxic Sugar Bait	Bait station
Spatial repellents	Passive emanator	metofluthrin or transfluthrin
ITM for specific risk groups	ITM	Treated clothing for malaria control in Mekong
Vector traps	Adulticidal Oviposition traps	ALOT, AGO, TNK
	Autodissemination traps	IN2TRAP
Lethal house lures	Eave tubes	Eave tubes
Systemic insecticide	Rodent bait	Imidicloprid based bait
LLIN + IGR	Pyrethroid + Pyriproxifen	Royal Guard

New Product Class – (biological)	Generic Exemplar	Prototype product
Microbial control in adult vectors	Bacterial infection	wMel *Wolbachia* in Ae. aegypti
Pop. reduction through genetic manipulation	GMM, self limiting	OX513A *Ae. aegypti* (RIDL)

DESIGN
OF EPIDEMIOLOGICAL TRIALS FOR VECTOR CONTROL PRODUCTS

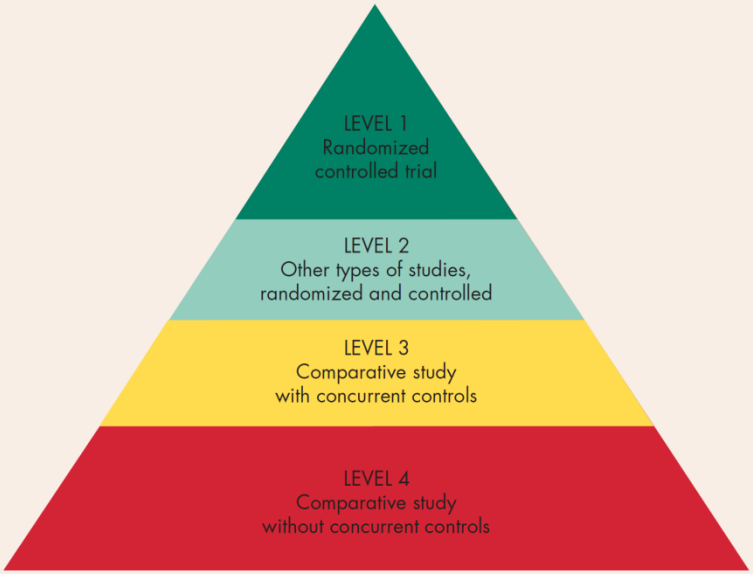
REPORT OF A WHO EXPERT ADVISORY GROUP

CHÂTEAU DE PENTHES, GENEVA,
24–25 APRIL 2017

World Health Organization

ERG on Design of Epidemiological Trials

Box 1. Hierarchy of study designs used to evaluate the public health value of new vector control tools



Study designs recommended by WHO to assess the public health value of a new intervention or product	
Level 1. Randomized controlled trial: individual or cluster randomized	Recommended
Level 2. Randomized controlled trial: step-wedge, cross-over, factorial design	Recommended
Level 3. Non-randomized trial with control: before-and-after studies, cohort study, case–control study, cross-sectional study, time-series or interrupted time-series	Recommended on a case-by-case basis
Level 4. Trials without a control or using a historical control group: such as time series or interrupted time series without control group	Not recommended

Recommendations: ERG on Design of Epidemiological Trials

In brief, the following recommendations were made.

Hierarchy of trial designs: Level 1 and level 2 study designs are the only designs that WHO considers acceptable to substantiate the public health value of new tools that do not fall within an already existing class and hence are not covered by a policy recommendation. In exceptional situations where there is no possibility of randomization, WHO will accept data generated from a trial with a "level 3" study design.

End-points for studies to demonstrate the public health value: Primary end-points are (in order of priority): (i) incidence of disease or infection (e.g. detection of new infections); (ii) prevalence of infection; and (iii) validated proxies of infection (e.g. sero-conversion for viral infections). The source of data for primary end-points can be: (i) prospective, active case detection (e.g. active follow-up of cohorts), (ii) passive reporting or case detection where robust quality-assured data are provided by the routine reporting system; and (iii) cross-sectional prevalence surveys. Trials must also generate robust representative entomological data.

Measurement of cost effectiveness: Collection of data on costs is encouraged during the evaluation of new vector control products, particularly during phase IV studies. While VCAG will not draw on these data to assess the public health value of a product, costing data will be useful to inform the formulation of policy recommendations and programmatic guidance. It was noted that initially costly new interventions may later benefit from economies of scale, thereby becoming considerably more affordable once they are deployed.

Recommendations: ERG on Design of Epidemiological Trials

Efficacy trials for non-pyrethroid LLINs: For LLINs containing a non-pyrethroid active ingredient either alone or in combination with a pyrethroid, entomological data are not considered reliable predictors of epidemiological impact. Therefore, until a policy recommendation is made that covers these new types of products, epidemiological data must be generated for the “first in class” product for all new non-pyrethroid LLINs. The potential use of entomological surrogates to evaluate LLINs will benefit from further investigation to establish whether reliable correlations between entomological and epidemiological outcomes can be established. If so, WHO will consider these findings for updating product evaluation procedures for LLINs.

Claims of public health value against insecticide-resistant vectors should be evaluated through the VCAG review process because such claims are not covered by existing WHO policy recommendation.

Recommendations: ERG on Design of Epidemiological Trials

IRS formulations with slow-acting insecticides and other tools that may require altered or new test approaches: Unlike LLINs, for which specifications to date are based on a single class of active ingredient (pyrethroid) and covered by current WHO policy, several active ingredients of different classes have been shown to be effective for use in IRS. WHO policy recommendations can therefore be expanded to cover a new IRS product for which entomological data are available to indicate an entomological effect that complies with the current WHO policy recommendation for IRS products. The relevant data will be generated from proof of concept in the laboratory, experimental hut studies and large-scale field trials.

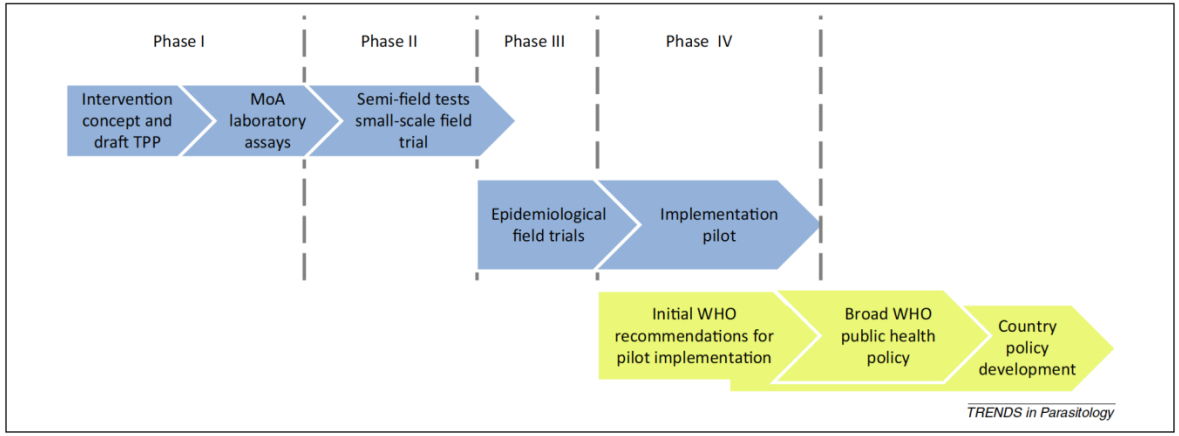
IRS products for which epidemiological trials are not required before assessment by the vector control group of the WHO Prequalification Team should undergo effectiveness trials (phase IV) to verify that entomological effectiveness translates into epidemiological impact and to generate cost-effectiveness data. Effectiveness trials can be conducted during operational roll-out.

A new IRS product for which data do not indicate a similar entomological effect to IRS products currently covered by a WHO policy recommendation will be considered a new product class. In this case, guidance on acceptable epidemiological study designs should be followed (Box 1). Close interaction with VCAG is recommended during the development of the study protocol.

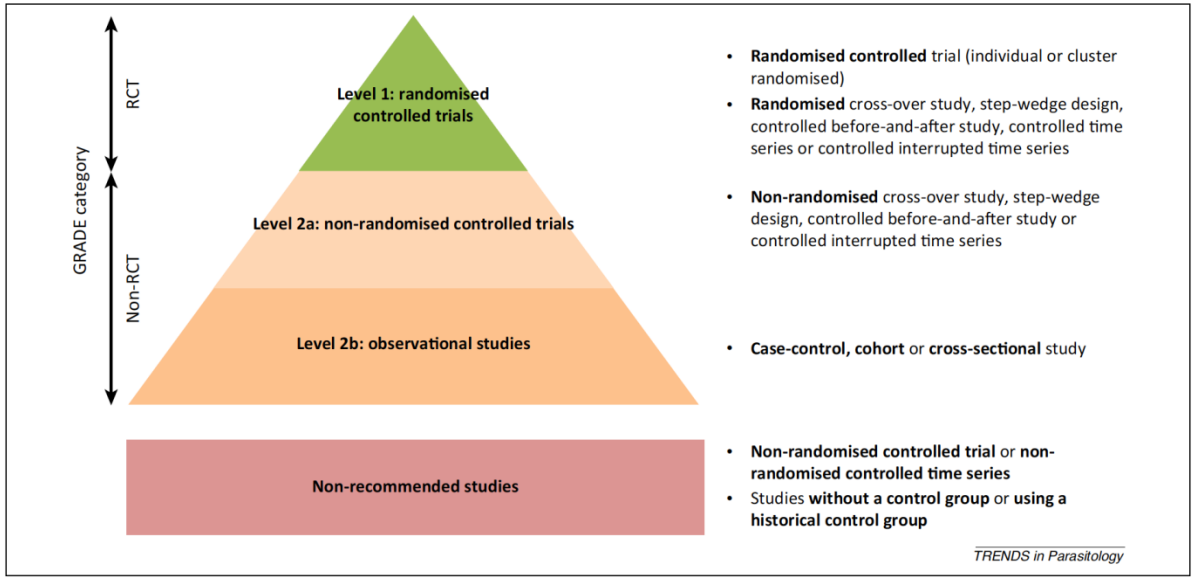
Ongoing Activities

- 7th VCAG Meeting held 24-26 October 2017, review of 12 product classes
- ERG on Data requirements and methods to inform potential extension of WHO policy to new vector control products and to verify performance of products entering an established class, Sept 12-14, draft report circulated to MPAC
- Guidance for testing of GMMs with driving transgenes. Participation in meeting held by FNIH in Geneva in July 2017. An expert group will be convened to update WHO-TDR Guidance Framework, and develop specific guidance for new GMM tools
- Guidelines for efficacy testing of traps for mosquito vectors
- Study design manual on epidemiological trials for vector control trials
- Testing guidelines (formerly WHOPES), including non-inferiority and testing for efficacy against insecticide resistant mosquitoes
- 8th VCAG Meeting planned for April 2018: new product review, focus on biological technologies
- Planning meeting for risk assessment for GMMs

Stages in Development of a New Vector Control Product



Hierarchy of Study Designs



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- Phase III and IV studies enable development of policy recommendations by WHO & country-level by member states

- Grading of Recommendations Assessment, Development & Evaluation (GRADE) methodology for evaluating evidence for policy & guideline recommendations
- Randomized controlled trials (RCTs) are rated as high-quality evidence & non-RCTs as low quality
- Due to low risk of selection bias, RCT "gold standard" for evaluating efficacy of protective intervention
- **Efficacy trial:** estimate the effect of an intervention under highly controlled conditions
- **Effect size:** the magnitude of difference between treatment & control groups
- **To advance evidenced based policy** need to improve quality of design, conduct, analysis & reporting for vector interventions (Lancet 2014)

Key Terms

Entomological effect: Refers to a product's effect on a disease vector in terms of killing, deterring, and reducing fertility or susceptibility to infection. Products with different biochemical modes of action may have similar entomological effects on target insects.

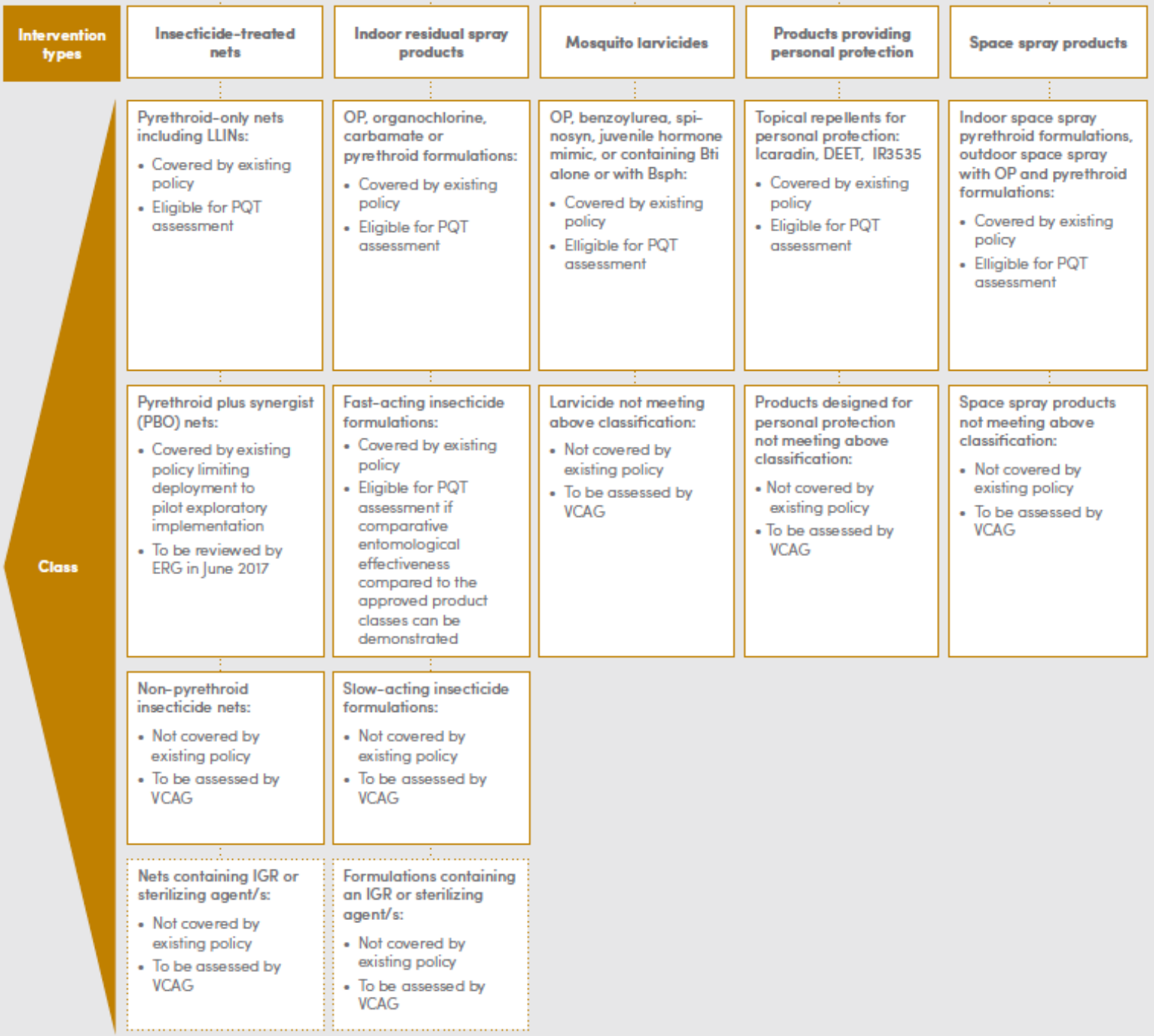
Product class: A group of products that share a common entomological effect by which it reduces pathogen transmission and thus reduces infection and/or disease in humans. For products in a class not currently recommended by WHO, efficacy trials with a 'first in class' product must generate epidemiological evidence of protective efficacy against infection and/or disease.

First in class: For the first product with a novel entomological effect (e.g., reducing human–vector contact, or decreasing vector survivorship, biting rates or susceptibility to infection or transmission), VCAG assesses public health value based on its entomological efficacy against vectors and epidemiological efficacy against human infections and/or disease. Once the public health value of a 'first in class' product is ascertained, a new product class is established.

Public health value: A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.

Product claim: Information contained in the product's label and advertisement materials. For vector control products this includes the product's chemical content, target arthropod vector, entomological effect, epidemiological effect, duration of effect, and role in mitigating insecticide resistance.

Target product profile (TPP): A detailed technical description that defines the preferred characteristics of a product and guides the development process to demonstrate its performance. A product class may contain one or more TPPs depending on the intended effect of the product(s) and claim(s).


Intervention types
Insecticide-treated nets
Indoor residual spray products
Mosquito larvicides
Products providing personal protection
Space spray products
Class
Pyrethroid-only nets including LLINs:
• Covered by existing policy
• Eligible for PQT assessment
OP, organochlorine, carbamate or pyrethroid formulations:
• Covered by existing policy
• Eligible for PQT assessment
OP, benzoylurea, spinosyn, juvenile hormone mimic, or containing Bti alone or with Bsph:
• Covered by existing policy
• Elligible for PQT assessment
Topical repellents for personal protection: Icaradin, DEET, IR3535
• Covered by existing policy
• Eligible for PQT assessment
Indoor space spray pyrethroid formulations, outdoor space spray with OP and pyrethroid formulations:
• Covered by existing policy
• Elligible for PQT assessment
Pyrethroid plus synergist (PBO) nets:
• Covered by existing policy limiting deployment to pilot exploratory implementation
• To be reviewed by ERG in June 2017
Fast-acting insecticide formulations:
• Covered by existing policy
• Eligible for PQT assessment if comparative entomological effectiveness compared to the approved product classes can be demonstrated
Larvicide not meeting above classification:
• Not covered by existing policy
• To be assessed by VCAG
Products designed for personal protection not meeting above classification:
• Not covered by existing policy
• To be assessed by VCAG
Space spray products not meeting above classification:
• Not covered by existing policy
• To be assessed by VCAG
Non-pyrethroid insecticide nets:
• Not covered by existing policy
• To be assessed by VCAG
Slow-acting insecticide formulations:
• Not covered by existing policy
• To be assessed by VCAG
Nets containing IGR or sterilizing agent/s:
• Not covered by existing policy
• To be assessed by VCAG
Formulations containing an IGR or sterilizing agent/s:
• Not covered by existing policy
• To be assessed by VCAG

4.3 IMPORTANT CONSIDERATIONS FOR TRIAL DESIGN

(a) Study questions should be formulated to include a clear statement about study population.

(b) Randomization, control and intervention should be randomly allocated to individuals or clusters.

(c) Sample size should be based on powered calculations with clearly stated assumptions for both epidemiological and entomological outcomes.

(d) Studies should be blinded where possible. Where blinding of participants is not possible, outcome assessors and those conducting analysis can and should be blinded.

(e) Comprehensive baseline information should be collected on transmission and disease setting.

(f) Follow-up should occur over at least two transmission seasons.

(g) Data on entomological end-points should be collected in randomly sampled
locations.

Update 3. ERG on Design of Epidemiological Trials

In brief, the following recommendations were made.

- **Consensus recommendations on the hierarchy of trial designs**

Level 1 and level 2 study designs are the only designs that are acceptable to substantiate the public health value of new tools that do not fall within an already existing class and hence are not covered by a policy recommendation. Level 3 designs may be accepted in exceptional circumstances.

- **End-points for studies to demonstrate the public health value of new tools, strategies and approaches for vector control**

Primary end-points for epidemiological efficacy (phase III) studies are, in order of priority, incidence of disease or infection, prevalence of infection, or a validated correlate (e.g., sero-conversion for viral infections).

- **Consensus statement on measurement of cost effectiveness**

Collection of cost and cost–effectiveness data is encouraged during evaluation of vector control products, particularly through phase IV studies. Although VCAG will not draw on these data to assess the public health value of a product, costing data will be useful to inform formulation of policy recommendations and programmatic guidance. Costly interventions may benefit from economies of scale and become considerably more affordable once they are produced and deployed in large quantities.

Recommendations: ERG on Design of Epidemiological Trials

Efficacy trials for non-pyrethroid LLINs: For LLINs containing a non-pyrethroid active ingredient either alone or in combination with a pyrethroid, entomological data are not considered reliable predictors of epidemiological impact. Therefore, until a policy recommendation is made that covers these new types of products, epidemiological data must be generated for the "first in class" product for all new non-pyrethroid LLINs. The potential use of entomological surrogates to evaluate LLINs will benefit from further investigation to establish whether reliable correlations between entomological and epidemiological outcomes can be established. If so, WHO will consider these findings for updating product evaluation procedures for LLINs.

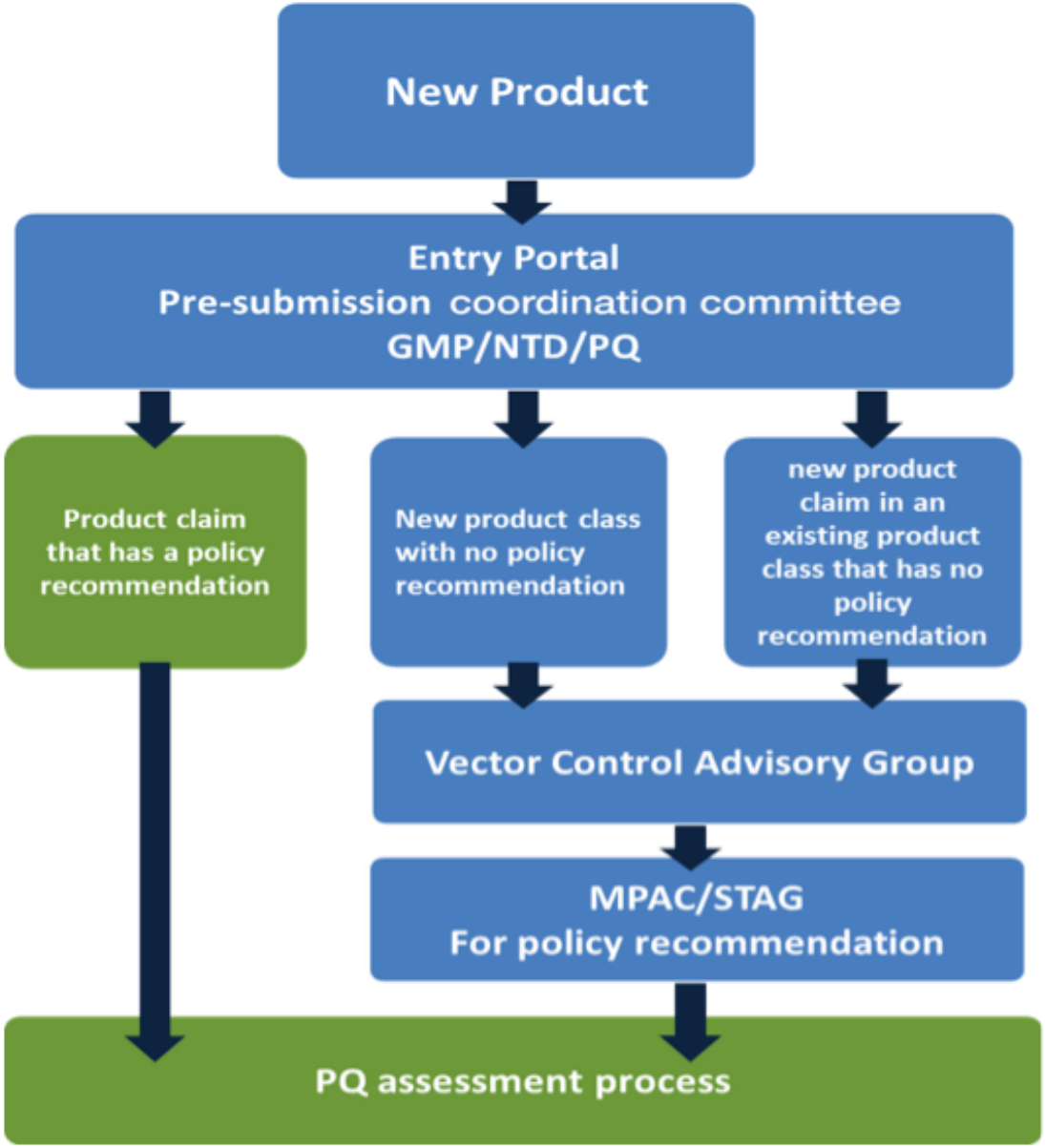
Claims of public health value against insecticide-resistant vectors should be evaluated through the VCAG review process because such claims are not covered by existing WHO policy recommendation.

i. Laboratory and small-scale field trials to test claims of insecticide resistance according to the WHO 2017 guidelines for efficacy testing of LLINs.2

ii. At least two randomized epidemiological trials conducted in different settings and ideally covering two transmission seasons. Studies should be performed in settings of high to medium insecticide resistance. The comparator should be the standard best practice used for vector control in the study area. The two studies should be conducted concurrently to minimize delays in generating evidence to assess their public health value; if the outcome is unclear or contradictory, further investigations may be required.

iii. Requirements to collect data on attrition, fabric integrity and assessment of insecticide residual activity, as previously stipulated by the WHO Pesticide Evaluation Scheme, remain valid and should be met concurrently with phase III epidemiological studies.

Summary of the Pathway for New Vector Control Products Submitted to WHO



- VCAG assesses the data, provides guidance, makes recommendations on efficacy & public health application

  Step 1: Proof of concept
  Step 2: Entomological efficacy
  Step 3: Epidemiological efficacy

- WHO, advised by MPAC/STAG, sets policy on public health application (advised by EAGs) & develops operational guidance on deployment
- WHO policy recommendation is based on **evidence of epidemiological efficacy** that substantiates public health value (proven reduction in human infection &/or disease)
- After **policy recommendation** further assessment within that class or claim will be done by WHO's Prequalification (PQ) program

Malaria Policy Advisory Committee Meeting
17–19 October 2017, Geneva, Switzerland
Background document for Session 5

Meeting report of the WHO Evidence Review Group on Assessing Comparative Effectiveness of New Vector Control Tools

12–14 September 2017 Geneva, Switzerland

1. Executive summary

The World Health Organization (WHO) recommends tools, technologies and approaches for use in public health based on demonstrated evidence of their impact on diseases, as well as their safety and quality. The WHO process for evaluating vector control products has been revised in order to better meet the needs of countries endemic for, or at risk of, vector-borne diseases. Under the revised process, the evaluation pathway to be followed is determined by whether or not a product is part of a product class with an existing WHO policy recommendation *(1)*.

Products covered by an existing WHO policy recommendation will follow the Prequalification Pathway, while all new tools, technologies and approaches will follow the New Intervention Pathway, supported by the Vector Control Advisory Group (VCAG). VCAG will validate whether the intervention under assessment has public health value.[1] Once public health value has been demonstrated, WHO will issue a policy recommendation.

On the basis of a request from the Malaria Policy Advisory Committee (MPAC) in March 2017, WHO is reviewing the data requirements associated with the evaluation of new vector control interventions in order to ensure that new interventions can be deployed as soon as possible, while ensuring that the policy recommendations guiding deployment remain evidence-based.

With the move to a revised evaluation system *(2)* and the arrival of new products, WHO must also guide the assessment of products that clearly fall under an established intervention class, but that differ in their product specification and/or differ from the first-in-class product for which epidemiological data are available. Examples of such new products include mosquito nets treated with a pyrethroid and the synergist piperonyl butoxide (PBO), new indoor residual spray (IRS) chemistries, and new mosquito larvicides and space spray products. For such products, WHO requires reassurance of similar performance (in terms of disease or vector control) in order to provide normative guidance to vector control programmes faced with the challenge of selecting reliable products.

[1] A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.

WHO/HTM/GMP/MPAC/2017.20

To discuss these topics in detail and to provide recommendations to MPAC and WHO, an Evidence Review Group (ERG) was convened on 12–14 September 2017. The ERG was tasked with reviewing summarized laboratory and field trial data for selected new vector control products and using these as case studies with which to develop both product-specific policy recommendations and general recommendations on the evaluation of new vector control tools, technologies and approaches.

The product-specific and general recommendations will be published as a WHO recommendation following endorsement by MPAC.

2. Background

The WHO process for the evaluation of vector control products has been revised to better meet the needs of countries endemic for, or at risk of, vector-borne diseases. The revised process came into effect on 1 January 2017 and is designed to accelerate product evaluation to support the continued scale up of core malaria vector control interventions, to strengthen vector control for neglected tropical diseases, and to address key challenges, such as emerging vector resistance to insecticides.

The key objectives of the revised process are to:

1. Enable access to safe, effective and high-quality vector control products;
2. Enhance evidence-based guidance to promote best use and management of vector control tools, technologies and approaches;
3. Promote product quality throughout the product's life cycle.

Under the revised process, the evaluation pathway to be followed is determined by whether or not a product is part of a product class with an existing WHO policy recommendation. A policy recommendation is a position statement or recommendation issued by WHO, the most recent of which takes precedence over any previously issued recommendation.

Following a request from MPAC, WHO is investigating whether the data requirements for evaluating new vector control interventions can be minimized in order to enable rapid deployment of new technology; at the same time, policy recommendations to guide deployment must remain evidence-based and justifiable. Data requirements to support WHO policy development could potentially be reduced for products that have a similar entomological effect to products in an existing product class, but that belong to a new chemical class not currently covered by the policy. For IRS, for example, products are evaluated based on the percentage kill of the vector (in experimental huts, on well-characterized strains, and in large-scale field trials, on well-characterized wild vector populations) at specific time points following the vector's exposure to the insecticide and on the duration of residual efficacy on common wall materials (cement, mud and wood). If a new product performs similar to or better than the IRS products currently covered by WHO policy in terms of its residual effect on wild or colony strains and performs equally or better on wild flying vectors, it may be assumed that the new product's epidemiological impact should be at least as good as that of the comparator products. It could then be argued that the existing WHO policy recommendation for IRS could be extended to the new product, provided it meets some essential efficacy and performance criteria (as currently

defined by WHO guidelines for testing different classes of vector control products covered by WHO policy), and has passed risk assessment for safety. This principle would allow the new product's deployment on the proviso that it is accompanied by the collection of epidemiological data to confirm the assumption of its epidemiological impact. To discuss these issues in more detail and to provide recommendations on the data requirements and methodology needed to support an extension of the existing policy, WHO convened an ERG to study the available data for a specific IRS product – SumiShield® 50WG. In part 1 of the meeting, the ERG deliberated on this IRS product.

With the increased development of new products to add to the "toolbox" needed to solve many vector control challenges, WHO must also guide the assessment of products that clearly fall under an established intervention class, but that differ substantially in their design from the first-in-class product(s) for which epidemiological data are available. An example of this is the case of mosquito nets treated with a pyrethroid and the synergist PBO, referred to as pyrethroid-PBO nets. While some epidemiological data on impact are available for one product in this class, namely the Olyset Plus net produced by Sumitomo Chemicals Co. Ltd, four other products are available in this class, but they all differ from Olyset Plus in terms of their design. Key differences between products are the location of the PBO (e.g., in all panels of a bed net or just the top panel), the PBO loading dose, the wash retention of the PBO and its bioavailability over a period of time.

Generating new epidemiological data to demonstrate impact on disease is likely to be impractical for such new products entering an existing class, but reassurance of similar or superior performance is nevertheless required in order to provide normative guidance to vector control programmes faced with the challenges of selecting reliable products.

The ERG discussed this topic in more detail in part 2 of the meeting, with the aim of providing advice to WHO on the data requirements and methodology needed to determine whether products entering an established class have similar performance to the first-in-class product.

In part 2, the ERG also discussed the evaluation of larvicides and space spray products, which raise similar questions.

3. Meeting objectives

Part 1

1. To advise WHO on the data requirements and methodology needed to determine whether the existing WHO policy for a class of products can be extended to a new vector control product that is not part of the class, but for which entomological effects are sufficiently similar, in order to facilitate deployment.

2. To apply criteria formulated under objective 1 to the assessment of SumiShield® 50WG, and to advise WHO on whether current policy recommendations for IRS products should be extended to this new insecticide and, if so, whether there should be conditions associated with the extension of the policy.

Part 2

3. To advise WHO on the data requirements and methodology needed to determine whether new vector control products that enter an established class should be assessed for similar or better performance compared to the first-in-class product. If so, what methodology should be used for this purpose?

4. To advise WHO on the data requirements and methodology needed to assess products with two active ingredients and the process to establish a new product class.

4. Review of SumiShield® 50WG

Summary of WHOPES experimental hut and large-scale community trials to evaluate efficacy

SumiShield® 50WG is an IRS product containing clothianidin 50.0% (w/w). This is a neonicotinoid-based IRS formulation that contains a new chemical active ingredient (AI) compared to existing IRS products with a WHO policy recommendation. In its assessment of SumiShield® 50WG, the ERG reviewed data from trials conducted in four countries following the WHO Pesticide Evaluation Scheme (WHOPES) guidelines for testing IRS products. The most comprehensive assessment was based on data from laboratory studies (WHOPES Phase 1) (Box 1), field trials conducted in the United Republic of Tanzania (Box 2), and supported by preliminary assessment of the results from trials in three other countries (Box 3).

Box 1. Summary of residual efficacy test

Test parameters – laboratory evaluation (WHOPES Phase I)

Following studies were conducted:

- Intrinsic toxicity of clothianidin AI by topical application on susceptible, pyrethroid resistant (kdr) and organophosphate/carbamate resistant (Ace1R) strains of *An gambiae*;
- Cross-resistance test: Comparing 1) the KD and mortality induced by clothianidin and deltamethrin AIs, at the discriminating concentrations, against pyrethroid-resistant mosquitoes; 2) mortality induced by clothianidin and propoxur at the discriminating concentrations, against organophosphate/carbamate resistant strain;
- Efficacy and residual activity evaluation of SumiShield® 50WG in cone tests on different substrates (cement, mud and wood) against susceptible *An. gambiae* at the dosage of 200 mg AI/m² and 300 mg AI/m², with 30 minutes exposure; 60 minutes post-exposure KD; and scoring mortality at 0, 1, 2, 3, 4, 6, 8, 10 and 13 months after treatment of substrates.

Summary of findings:

- SumiShield® 50WG demonstrated a residual activity (≥ 80% mortality) of more than 12 months on wood and cement substrates with 200 mg AI/m² and 300 mg AI/m² dosage. The highest dosage (300 mg AI/m²) also gave a residual activity for 10 months on mud substrate when considering the mosquito mortality at 72 hours post exposure. The dose of 300 mg/m² should be applied in the context of traditional houses where walls are mainly made up of mud.

- Using topical application, no cross-resistance to pyrethroid, organophosphate and carbamate insecticides was observed for resistant *Anopheles* strains having target site mutations on voltage dependent sodium channels (kdr mutation L1014F) or acetylcholinesterase (Ace-1R, G119S).

Box 2. Summary of trials to evaluate SumiShield® 50WG for IRS in the United Republic of Tanzania

Experimental hut – small-scale field trials (WHOPES Phase II)

Design: Single-blinded, partially randomized, Latin square evaluation with five treatment arms (four IRS products, one negative control) in 10 huts; allocation of treatment by lottery method; investigators/participants blinded; 8 months of follow-up observations

Outcomes: Immediate and delayed vector mortality, blood feeding inhibition, insecticide residual activity, deterrence and induced exophily, as well as infectivity (sporozoite) rate and Entomological inoculation rate (EIR)

Summary of findings

- Local wild *An. arabiensis* was resistant to pyrethroids and susceptible to all other classes of insecticides (organophosphate – pirimiphos methyl, fenitrothion and malathion; carbamate – bendiocarb; and organochlorine – DDT); local wild *An. funestus* was resistant to pyrethroids and organochlorine DDT, partially resistant to carbamate (bendiocarb), and susceptible to organophosphate (pirimiphos methyl, fenitrothion and malathion) and organochlorine (dieldrin).
- Mortality induced by SumiShield® 50WG in cone bioassay tests on sprayed walls against pyrethroid-susceptible *An. gambiae s.s.* was less than 80% after 30-minute exposure at 24-hour holding time; the same was observed for comparator products (K-Othrine® 250WG , Actellic® 300CS and Ficam® 80WP). Mortality induced by SumiShield® 50WG increased substantially with a prolonged holding time of 72 hours.
- SumiShield® 50WG showed greater mortality in the mosquito vector than the three comparator insecticides (pyrethroid, carbamate and organophosphate), against wild *An. arabiensis* at 24-hour holding time.
- SumiShield® 50WG continued to kill a greater proportion of wild *An. arabiensis* than the three comparator insecticides up to 8 months after spray application using a 24-hour holding time.

- SumiShield® 50WG demonstrated increasing toxicity to *An. arabiensis* at holding times beyond 24 hours and at each holding time killed a greater proportion of *An. arabiensis* than the other three insecticides.

Community study – Large-scale field trials (WHOPES Phase III)

Design: Single-blinded, two IRS treatment arms with five clusters per arm, around 200 households/cluster with clusters 2 km apart; treatment arms: SumiShield® 50WG and Actellic® 300CS

Outcomes: Residual and biological efficacy of insecticide, insecticide susceptibility of target vector species, vector density, vector longevity, vector mortality, infectivity rate (sporozoite rate)

Summary of findings

- Primary vector *An. funestus* and secondary vector *An. arabiensis* were resistant to all types of pyrethroids and susceptible to organophosphate- pirimiphos-methyl.
- Performance of SumiShield® 50WG applied at 300 mg AI/m2 was equal or superior to the reference product Actellic® 300CS applied at 1 g AI/m2 for each of the outcomes measured.
- The residual efficacy ($\geqslant$80% vector mortality in cone bioassay) of SumiShield® 50WG and Actellic® 300CS applied to baked brick houses against pyrethroid-susceptible *An. gambiae s.s*. was:
    - 3 months measured at a 24-hour holding time for both products;
    - 7 months for SumiShield® 50WG and 4 months for Actellic® 300CS at a 72-hour holding time.
- The mortality of wild mosquitoes was greater in the SumiShield® 50WG arm than in the Actellic® 300CS arm for both the *An. arabiensis* and *An. funestus* vector species in the area.
- There was no statistical difference between the infectivity rates of the two treatment arms for both vector species.
- There was no statistical difference in the density of vectors (*An. arabiensis* & *An. funestus*), infectivity (sporozoite) rates and EIRs between the SumiShield® 50WG and Actellic® 300CS arms.

Overall conclusions

Over 8 months in experimental huts, SumiShield® 50WG showed superior efficacy to the other three IRS products based on 24-hour vector mortality. SumiShield® 50WG demonstrated a duration of efficacy comparable to that of Actellic® 300CS, i.e., 3 months at 24-hour holding and 7 months at 72-hour holding time in the community randomized trial. SumiShield® 50WG was effective at the current standard 24-hour mortality cut-off criteria. This result would have satisfied the efficacy criteria under the former WHOPES evaluation process. Data from the cluster randomized trial were insufficient to measure non-inferiority, but this was not required under the former WHOPES process.

Box 3. Summary of trials to evaluate SumiShield® 50WG in Benin, Côte d'Ivoire and India

The ERG assessed findings based on trials conducted in Benin (two studies Phase II: in Cové and Malanville), Côte d'Ivoire (one each Phase II and III) and India (one each Phase II and III). This assessment by the ERG is preliminary because it is based on a rapid review of the available data. The ERG made the following observations:

- SumiShield® 50WG induced a mortality of >80% (24-hour holding time) on a fully susceptible vector strain in bioassays for up to 3 months of IRS in Benin (Cové) and India, 4 months in Benin (Malanville) and 6 months in Côte d'Ivoire. Mortality increased substantially for fully susceptible and resistant strains of vectors with a prolonged holding time of 72 hours.
- Slow killing effect of SumiShield® 50WG (clothianidin at 300 mg AI/m^2) was also seen against both susceptible and resistant Anopheles populations. Comparator products also showed increased delayed mortality but to a lesser degree than with SumiShield® 50WG.
- Efficacy of SumiShield® 50WG was beyond 6 months.
- The effect of clothianidin on fertility (i.e., number of eggs and viability of embryos) is unknown.

A detailed review and critical analysis of data from these studies (conducted in Benin, Côte d'Ivoire and India) is necessary in order to add to the evidence base on the efficacy of SumiShield® 50WG.

Specific discussion on SumiShield® 50WG based on data reviewed

Current efficacy criteria require an IRS product to demonstrate at least 80% mortality of insecticide-susceptible anopheline mosquitoes held in a cone bioassay for 24 hours after exposure to insecticide applied to the most common wall substrates. This mortality effect needs to continue for at least 3 months after the application of the insecticide to the substrate, usually cement, mud and wood. Besides cone bioassay studies, cross-resistance studies in laboratory settings against mosquito strains with different resistance mechanisms should also be conducted, and the killing effect and blood feeding inhibition effect on wild vector populations in experimental huts should be assessed in comparison to a positive control *(3)*.

The mortality of fully susceptible mosquitoes exposed in a cone bioassay to walls treated with a target dose of 300 mg AI/m^2 of SumiShield® 50WG was equal to or greater than 80% at 24 hours for most studies, and at 72 hours for all studies, for 4–8 months. The evidence also showed improved performance for extended holding times post-exposure in cone bioassays, indicating improved efficacy with longer exposures. Based on data from the studies in the United Republic of Tanzania, which compared SumiShield® 50WG to the pyrethroid deltamethrin (K-Othrine® 250WG at 25 mg AI/m^2), the organophosphate pirimiphos methyl (Actellic® 300CS at 1 g AI/m^2) and the carbamate bendiocarb (Ficam® 80WP at 400 mg AI/m^2), SumiShield® 50WG was found to perform as well as or better than these comparator products. On the basis of these findings, and with the results of additional small-scale and community entomological trials, SumiShield® 50WG would meet the current WHOPES efficacy criteria for IRS products.

Under the former WHOPES process, SumiShield® 50WG would have been recommended for deployment on the basis of the evidence reviewed by this ERG. Considerations surrounding deployment guidance should be discussed by another group, particularly to address the utility of this product for insecticide resistance management.

SumiShield® 50WG has only been assessed for efficacy as an IRS product, not against a claim of being effective in controlling insecticide-resistant mosquitoes. SumiShield® 50WG is the first neonicotinoid-based IRS product. Potentially, this product may provide an alternative for use in insecticide rotation as a strategy to manage insecticide resistance in vector control programmes. Neonicotinoid-based products are widely used in agriculture; this has caused selection pressure leading to the development of resistance, as demonstrated by widespread metabolic resistance in crop pests due to enhanced cytochrome P450 activity *(4)*. Based on the data reviewed, cross-resistance against SumiShield® 50WG cannot be excluded. First, the mortality induced by SumiShield® 50WG on wild mosquitoes was around 30% for up to a 168-hour holding time after 30-minute exposure. Second, mortality rates in cone bioassays for a 24-hour holding time were higher against the susceptible strain than against the pyrethroid-resistant strain tested.

Data reviewed also indicate that SumiShield® 50WG's efficacy is at a >80% mortality threshold for a 72-hour holding time. This should be considered in the assessment of the product. In the future evaluation of IRS products, data from 30-minute exposures in cone bioassays with both 24-hour and 72-hour holding times should be used to assess delayed effects on target vectors.

General discussion on the evaluation of IRS products

Given the limited epidemiological data for IRS linking entomological surrogates to epidemiological impact, the current standard is to rely on data from experimental hut studies with a study design that is properly powered and randomized with adequate replication. At present, evidence that entomological effects determined in laboratory or small-scale field studies predict epidemiological outcomes determined in cluster randomized trials (CRTs) is scant, mainly due to the limited number of CRTs conducted. The relationship between experimental hut trials and CRTs can be explored in multiple ways. For example, experimental hut trials can be conducted in the vicinity of CRTs in order to assess entomological outcomes in relation to the spatial heterogeneity in vector species (composition, behaviour and insecticide resistance).

This ERG sees the value of large-scale effectiveness (Phase IV) studies to verify the relevance of current entomological measurements for predicting epidemiological impact. Also, the group encourages multiple comparisons across different IRS products of different chemical classes in experimental hut studies in order to identify the appropriate comparators for community randomized trials (WHOPES Phase III) or epidemiological CRTs with disease endpoints. Data based on multiple comparators are also useful for informing the rotation of active ingredients for resistance management.

Future IRS products will include new AIs with novel mechanisms of action. New AIs such as chlorfenapyr, which targets cellular and mitochondrial respiration under circadian rhythm control, may not reach 80% mortality after 30-minute exposure in cone bioassays under daytime conditions. Innovators are encouraged to think 'outside the box' and not feel tied to cone mortality thresholds, as these seem to be better criteria for the neuro-acting AIs of the IRS products commonly used in public health.

Key conclusions on SumiShield® 50WG

The ERG made the following observations based on the results of experimental hut and long-term community trials from four sites (United Republic of Tanzania, India, Côte d'Ivoire and Benin).

1. SumiShield® 50WG satisfies the current criteria for efficacy according to the WHOPES guidelines for testing the efficacy of IRS products. This observation is based on the review of data on the mortality of fully susceptible mosquitoes exposed to substrates and walls treated with a target dose of 300 mg AI/m^2. Percentage mortality in cone bioassays after 30-minute exposure at a 24-hour holding time was equal to or greater than 80% for most studies and exceeded this threshold after a 72-hour holding period in all studies for a duration of 4–8 months following the application of the insecticide.

2. SumiShield® 50WG also showed improved performance for extended holding times post-exposure, indicating improved efficacy with longer exposure. A similar trend was seen with all comparator IRS products, which included pyrethroid-, carbamate- and organophosphate-based IRS formulations recommended by WHO.

3. Novel SumiShield® 50WG product claims will need to be defined and assessed with the support of WHO.

5. Review of pyrethroid-PBO nets

Current status

Five pyrethroid-PBO net products were evaluated under WHOPES to determine whether they met the criteria established for classification as a pyrethroid-treated long-lasting insecticidal net (LLIN) *(5)*.The WHOPES Phase I and II evaluation assessed the biological activity and wash resistance of the pyrethroid treatment and the PBO component. Given that no manufacturer of submitted products claimed that PBO provided added efficacy against pyrethroid-resistant mosquitoes, the WHOPES recommendations for pyrethroid-PBO nets are based on an evaluation of the efficacy of the nets' pyrethroid components against susceptible mosquitoes.

Of the five pyrethroid-PBO nets evaluated by WHOPES, all underwent experimental hut evaluations, and two are currently undergoing long-term field evaluations (WHOPES Phase III) with entomological endpoints. A cluster randomized controlled trial (CRCT) in the United Republic of Tanzania has generated new epidemiological evidence for pyrethroid-PBO nets. Results of the first 2 years of the Tanzanian trial were reviewed by the WHO ERG on pyrethroid-PBO nets held in June 2017 in order to assess whether the new data demonstrated the public health value of pyrethroid-PBO nets in terms of the control of malaria where vectors are pyrethroid-resistant. Based on this review, the recommendations on the conditions for deployment of pyrethroid-PBO nets have been updated *(6)*.

The ongoing trial in the United Republic of Tanzania will provide 3rd-year data on durability and the effect of pyrethroid-PBO nets on disease outcomes, thus generating evidence on the long-term efficacy of pyrethroid-PBO nets. A second randomized controlled trial is planned in Uganda; this trial will include two pyrethroid-PBO nets (one with PBO in all panels and another with PBO on the roof alone). Results will provide further data on the

performance of two main types of pyrethroid-PBO nets and inform choices for appropriate future comparators for this new product class.

Available data on the efficacy of pyrethroid-PBO nets against pyrethroid resistance do not cover all known resistance mechanisms. It is necessary, therefore, to assess the efficacy of such products against strains that represent all types of resistance mechanisms, particularly oxidase-mediated resistance.

Assessment of PBO retention and bioavailability

In order to meet the current WHO criteria for an LLIN, the pyrethroid content in a pyrethroid-PBO net must withstand at least 20 standard washes in laboratory and 3 years of field performance (efficacy). Both chemical and physical durability are critical in terms of an LLIN's effectiveness. The synergistic effect of PBO on pyrethroid can only be maintained if the PBO is biologically available on the surface of the netting fibres. In order to maintain the efficacy of a pyrethroid-PBO net, ideally both the pyrethroid and PBO components need to remain biologically available for at least 20 laboratory washes and throughout the expected life of the net in field (at least 3 years), in which case it can qualify as a pyrethroid-PBO LLIN (long-lasting for both the AI and the synergist).

WHOPES wash-resistance testing is currently used to assess the nets' retention of the chemical content (AI and PBO) during the wash procedure. The amount of AI/PBO lost in each consecutive wash is taken as the chemical content that was available on the net's surface prior to washing. Currently, there is no other chemical method to determine the surface content of the AI or PBO. Therefore, the bioavailability of this surface content is determined in a proxy way through cone bioassays using susceptible mosquitoes after different wash points (e.g., 0, 1, 3, 5, 10, 15, 20 or more washes).

A broad review of WHOPES trial outcomes indicates that for pyrethroid-PBO nets, PBO retention after 20 washes in laboratory studies (Phase I) and experimental hut studies (Phase II) is for the most part lower than pyrethroid retention on those same nets. This discrepancy is probably due to the fact that since PBO is lipophilic, repeated washes with soap remove the PBO content. However, the curve of the retention rate according to the number of washes is more informative than the average retention rate. When there is no decline in PBO content between consecutive washes (e.g., between 5, 10, 15 and 20 washes), it implies that PBO is no longer being released from the inner core of the net fibres onto the surface. In the field, however, in addition to washing, aging and environmental factors may also contribute to accelerated or greater reductions in AI and PBO as the nets degrade over time. Further data are needed to understand whether current washing procedures reliably correlate with the degradation of AIs and synergists in the field.

The PBO retention after 1 and 2 years of household use of the nets in a large-scale community trial (Phase III) has been found to be still lower than the retention with wash procedures in Phase I and II studies. This suggests that, in addition to a higher release rate of PBO, some chemical degradation of PBO may occur over time due to environmental factors and local wash practices. Epidemiological data from one CRCT conducted in the United Republic of Tanzania suggest that pyrethroid-PBO nets may have additional public health value *(6)*. However, no clear pattern was observed between the PBO content of a range of different pyrethroid-PBO nets assessed in WHOPES Phase I and II trials and their measured entomological efficacy. This suggests that total PBO retention alone is not

sufficient to estimate the efficacy of pyrethroid-PBO nets; bioavailability data against susceptible and resistant species should be investigated during field use of the nets.

To date, there are insufficient data to define the relationship between PBO content and its biological efficacy against resistant mosquitoes over time. Based on the data reviewed, the ERG was not able to define what number of washes is essential for PBO availability and its duration of synergist effect with pyrethroid AI on the net to define it as a PBO LLIN. This question needs to be reviewed when more field data become available. New criteria will likely be required to assess the persistence and bioavailability of PBO over time. Such criteria include the amount of PBO retained in the net fabric, released and bioavailable on the surface of the net fibres. Obtaining these data will involve the further development of chemical and bioassay methods for all assessments.

Entomological surrogate for disease impact

Experimental hut trials are designed to assess the entomological efficacy of nets and to assess the durability (wear and tear) of nets under field conditions. These aspects are then subsequently tested in Phase III field trials either using entomological outcomes alone or including epidemiological outcomes. At present, it is unclear as to whether entomological efficacy estimates obtained from experimental hut trials are sufficient to evaluate either the entomological or the epidemiological impact of LLINs or PBO-LLINs, and in particular whether they are sufficient to establish non-inferiority[2] to existing LLINs.

To improve our understanding of the entomological correlates of disease outcomes, it would be beneficial to conduct hut trials and large-scale CRTs (with disease endpoints) at the same site. Furthermore, conducting experimental hut trials to re-test LLINs that were previously tested in WHOPES Phase III trials with disease outcomes (or in CRCTs such as the Tanzanian trial) may be helpful to establish entomological surrogates of efficacy. While current proxies for the impact of new LLINs are based on experimental hut data, there remains a concern that experimental huts may not capture the efficacy of LLINs or pyrethroid-PBO nets in real-life situations. This may result in an underestimation or overestimation of mortality counts due to the impact of hut size on vector behaviour, which may affect, for example, the likelihood that a vector rests on the top (PBO-containing) panel of a net. A full-sized hut may therefore be better for estimating variations in pyrethroid-PBO location.

Until new data are available for review, current experimental hut procedures, as described in the WHO guidelines for testing LLIN products, should be followed for new LLIN products with PBO synergists. Furthermore, it is important to emphasize that the evaluation of vector control products such as LLINs must be based on robust and well-implemented study designs. The ERG therefore recommends that WHO convene a group of experts to provide guidance on the design, execution and reporting of experimental hut studies.

[2] A vector product under evaluation shows non-inferiority when it demonstrates an equal or better entomological effect and/or protective efficacy against infection and/or disease in humans in reference to a comparator product. Non-inferiority relies on a measurement of effect whereby the difference should be only a small amount, called the non-inferiority margin, or delta. Delta is pre-specified based on the desired clinical (or entomological) effect. Specifying a smaller delta for a non-inferiority trial can test whether a new product's performance is similar to that of a comparator product (i.e., difference of effects is <delta), but demonstrating statistical significance may require larger sample sizes.

Choice of comparator net to evaluate new and existing pyrethroid-PBO nets

Given the diversity of nets in relation to where the PBO is located (e.g., on the net as a whole or on the roof panel only), it is not clear what kind of comparator product should be chosen for subsequent in-class products. Data from the CRCT in the United Republic of Tanzania have demonstrated the epidemiological impact of pyrethroid-PBO nets with PBO on all panels *(5)*. This product therefore represents the "first-in-class" for the new product class.

Ongoing community randomized trials involving variations in PBO nets (i.e., PBO in all panels vs. PBO on the roof alone) will provide more evidence to enable broad recommendations on PBO nets and the choice of comparator for subsequent evaluations. Until more data are available, the evaluation of nets with PBO should, at minimum, include a single comparator that represents the standard of care where the trial is implemented.

In order to encourage innovation, future investigations should consider multiple comparators with different types of pyrethroid-PBO nets and LLINs with new AIs, as well as standard pyrethroid-PBO nets, in order to assess differential effectiveness among various types of LLINs.

Key conclusions specific to pyrethroid-PBO nets

1) The current definition of a long-lasting net applies to the pyrethroid components in LLINs, which must withstand 20 washes in laboratory and 3 years efficacy in the field in order to qualify under the pyrethroid-LLIN product class. There is currently insufficient evidence to define the required durability of the PBO component; this will need to be reviewed as more data become available.

2) Evaluation of nets with PBO should, at minimum, include a single comparator that represents the standard of care where the trial is implemented. Multiple comparisons between pyrethroid-PBO nets (variants) are encouraged to inform implementation.

3) The relationship between entomological efficacy in experimental hut studies and entomological and epidemiological efficacy in CRTs should be further explored to assess whether experimental hut studies can be used in the future to assess the non-inferiority of new net products.

6. Larvicide products

Specific discussion on the Larvasonic SD-Mini device

The Larvasonic SD-Mini is a device that emits underwater sound pulses that cause rapid larval death by rupturing larval dorsal tracheal trunks. The intervention is a larvicidal device that is placed in containers or bodies of water, and as such can be used to target mosquitoes breeding in urban containers. The manufacturer of the product claims that it will be effective against all species at all aquatic stages (larvae and pupae), that it does not affect non-target organisms, and that it will not induce insecticide resistance.

VCAG reviewed the first prototype, Acoustic Larvicide™, in 2014. Acoustic larvicides, like chemical larvicides, kill larvae and thus require that each larval habitat be located and treated. Based on the evidence presented, VCAG concluded that this product falls under an

established class of larvicides that includes insecticide-based, juvenile hormone mimics and biological actives (e.g., Bti). Given the novelty in the mode of action of this mechanical larvicide and its potential utility in public health vector control, particularly for dengue-endemic regions, VCAG concluded that this tool could be evaluated using the WHOPES guidelines for laboratory and field testing of mosquito larvicides.[7]The ERG concurs with VCAG's conclusions and recommends that evaluations of the Larvasonic SD-Mini device follow existing WHOPES guidelines, including a safety validation and risk assessment of acoustic sound on non-target organisms. The comparator should be a classic larvicide product with a WHOPES recommendation. Subsequent evaluation of a second-in-line sonic device should ideally be evaluated against a first-in-class sonic device in addition to a classic larvicide.

General discussion on larvicides

Currently, WHO recommends larviciding for malaria control as a supplement to LLINs or IRS, only in areas where the anopheline larval habitats are few, fixed and findable *(8)*. Larviciding is widely used to treat *Ae. aegypti* larval habitats and should be considered a complement to environmental management – except in emergencies – and restricted to containers in which larvae cannot be otherwise eliminated or managed. Currently, one CRT being conducted at sites in Nicaragua and Mexico, with community participation in larval source reduction measures, has shown the impact of larvicide in reducing the number of dengue cases *(9)*.

Generally, however, there have been few studies on the effects of larvicides/larvicidal devices on disease endpoints *(10)*. Such evidence should be generated and systematically reviewed to support the use of these interventions for public health purposes.

Key conclusions on larvicides

1) Current WHO guidelines on testing larvicides will apply to this mechanical larvicide device, Larvasonic SD-Mini.

2) The ERG recommends that WHO review the policies on larval source management intervention types in order to guide the generation of the required additional evidence with which to determine their public health value.

7. Space spray products

Specific discussion on Fludora® Co-Max EW

This is the first space spray product with a mixture of two AIs: flupyradifurone (a neonicotinoid) and transfluthrin (pyrethroid). The efficacy of both AIs can be measured using the same efficacy endpoints currently specified by WHO. This product complies with a category of space spray class covered by the current WHO policy and, as such, should be evaluated following the WHOPES guidelines for the efficacy testing of insecticides for indoor and outdoor ground-applied space spray applications *(11)*.

The rationale for a mixture space spray with more than one AI from different insecticide classes is based on the claim that both AIs intend to kill; hence, having more than one AI should reduce the emergence or spread of resistance. High-dose, short-lived AIs are most

appropriate for managing resistance, because it is unlikely that such situations will lead to enhanced selection pressure for resistance.

This being the first space spray product with a mixture of two AIs from different insecticide classes, it may be necessary to include an additional efficacy claim. If the product claims efficacy against resistant mosquitoes, this will need to be demonstrated. This may require additional guidance from WHO on how to demonstrate such claims and a revision of existing WHO test procedures.

Space spray evaluations can be done through indoor and/or outdoor applications that involve scoring the mortality of susceptible mosquitoes in control cages. The current test procedure does not require the assessment of the efficacy of the product against wild mosquitoes in test cages. While current test guidelines outline procedures to be used for operational field trials for assessing the product's efficacy against wild mosquito populations, due to the practicality of implementing such trials, they are not currently part of the efficacy evaluation. In order to improve the feasibility of such evaluation and ensure robust assessment, expert advice on study design and sample size calculation is needed. Alternative trial designs should be considered, such as a stepped-wedge design, to allow for adequate replication.

In general, there is a lack of evidence on the impact of space spraying on disease outcomes for diseases such as malaria and dengue. The aim of space spraying is to cause massive killing with frequent spray cycles, leading to a rapid reduction of the adult vector population. Any control method that reduces the number of infective adult mosquitoes, even for a short time, should reduce parasite or virus transmission during that time; however, it remains unclear as to whether the impact of space treatments is epidemiologically significant. Factors such as the insecticide susceptibility of the target vector, droplet size in space sprays, application rate, and frequency of spraying and indoor penetration of the insecticide droplets are all crucial to the efficacy of this method. Currently, space spraying is recommended for control only in emergency situations to suppress an ongoing dengue/arboviral disease epidemic or to prevent an incipient one. A recent review concluded that indoor space spraying is an effective adulticidal intervention against *Aedes* mosquitoes *(12)*. As the current policy recommendations for space spraying are based on historical data and grey literature, there is a need to generate strong evidence on the impact of space spraying on wild mosquito populations and to assess the impact on disease in order to determine whether the intervention has public health value.

Key conclusions

1) The ERG recognizes that there is a lack of evidence on the impact of space spraying on disease endpoints. This body of evidence should be generated in order to support the use of space sprays for public health.

2) The group recommends that WHO conduct a review of the policies for space spraying in order to guide the generation of the additional evidence required to determine the intervention's public health value.

Annex 1. Agenda

General objectives

1. To advise WHO on the data requirements and methodology needed to determine whether the existing WHO policy for a class of products can be extended to recommend the deployment of a new vector control intervention that is not part of the class, but for which entomological effects are sufficiently similar to consider an extension of the policy.

2. To apply criteria formulated under objective 1 to the assessment of SumiShield® 50WG, and to advise WHO on whether current policy recommendations for IRS products should be extended to this new insecticide and, if so, whether there should be conditions associated with the extension of the policy.

3. To advise WHO on the data requirements and methodology needed to determine whether new vector control products that enter an established class should be assessed for similar or better performance than the first-in-class product. If so, what methodology should be used for this purpose?

4. To advise WHO on the data requirements and methodology needed to assess products with two active ingredients and the process required to establish a new product class.

Specific questions to be addressed under each of these objectives are outlined in the ERG's Terms of Reference.

Provisional programme

Tuesday 12 September 2017		
Open Session		
09.00 – 09.15	Registration	
09.15 – 09.45	Opening remarks and welcome	Dr Pedro Alonso
09.45 – 09.50	Declaration of interest	Dr Pedro Alonso
09.50 – 10.00	Background, objectives and expected outcomes	Dr Emmanuel Temu
10.00 – 10.30	*Coffee break*	
Part I: Data and methodology to inform potential extension of existing policy recommendations to new interventions		
Open Session		
10.30 – 10.45	Overview of the revised WHO evaluation process for vector control products	Dr Raman Velayudhan
10.45 – 11.00	SumiShield® 50WG Phase 1 Data and WHOPES evaluation	Dr Rajpal Yadav
11.00 – 11.30	SumiShield® 50WG for IRS (India and Cote d'Ivoire data)	Dr Marc Coosemans
11.30 – 12.00	SumiShield® 50WG for IRS (Tanzania Data)	Dr Sarah Moore

12.00 – 12.30	Discussion of trial data	Chair
12.30 – 13.30	*Lunch*	
13.30 – 15.00	Determination of SumiShield® 50WG performance based on current IRS evaluation guidelines. Would the product have received a WHOPES recommendation?	Chair
15.00 – 15.30	*Coffee break*	
15.30 – 17.00	Can existing policy for IRS be extended, as a prerequisite for PQ listing to allow deployment of SumiShield® 50WG? If so, based on which criteria?	Chair
17.00 – 17.30	Summary of decisions reached on Day 1	Chair
Wednesday 13 September 2017		
Open Session		
Part II: Presentation of current evidence on a selection of new vector control tools & determination of the data and methods required to comparative effectiveness		
09.00 – 9.45	Brief introduction to WHOPES evaluation of LLINs/nets	Dr Rajpal Yadav
09.45 – 10.00	PBO nets with WHOPES recommendation	Dr Rajpal Yadav
10.00 – 10.30	Discussion & determination of criteria required to include other pyrethroid + PBO nets into the class established by Olyset Duo	Chair
10.30 – 11.00	*Coffee break*	
11.00 – 11.15	Brief introduction to WHOPES evaluation of	Dr Anna Drexler
11.15 – 11.45	Larvicial products (Larvasonic SD-Mini device)	Dr Anna Drexler
11.45 – 12:30	Discussion & determination of how new larvicides and larvicidal devices should be assessed to inform extension of policy	Chair
12.30 – 13.30	*Lunch*	
13.30 – 13.45	Brief introduction to WHOPES evaluation of space sprays	Dr Raman Velayudhan
13.45 – 14.15	Space sprays (Fludora® Co-Max EW)	Dr Velayudhan /Amy Morrison
14.15 – 15.00	Discussion & determination of how space sprays should be assessed to inform extension of policy	Chair
15.00 – 15.30	*Coffee break*	
15.30 – 17.00	Discussion on data requirements and methodological issues identified during day 2	Chair
17.00 – 17.30	Summary of decisions reached on Day 2	Chair

Thursday 14 September 2017		
Closed Session		
Part III: Formulation of draft recommendations		
09.00 – 10.30	Drafting of recommendations on the assessment of new tools that do not fall within an established class but for which entomological effects seems sufficiently similar to consider extension of policy (and hence avoid epidemiological studies prior to deployment)	Chair
10.30 - 11.00	*Coffee break*	
11.00 - 13.00	Drafting of recommendations on the assessment of products falling within an established class. Does such assessment need to inform whether they perform as well as, or better than, the first-in-class product (or another suitable comparator)?	Chair
13.00 - 14.00	*Lunch*	
14.00 - 15.30	Final discussions and next steps	Chair
15.30 – 15.45	Meeting closure	Dr Pedro Alonso

Annex 2 – LIST OF PARTICIPANTS

Chair

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Outcomes from Evidence Review Group on data requirements and methods to inform potential extension of WHO policy to new vector control products and to verify performance of products entering an established class

Malaria Policy Advisory Group Meeting

Geneva, Switzerland

18 October 2017

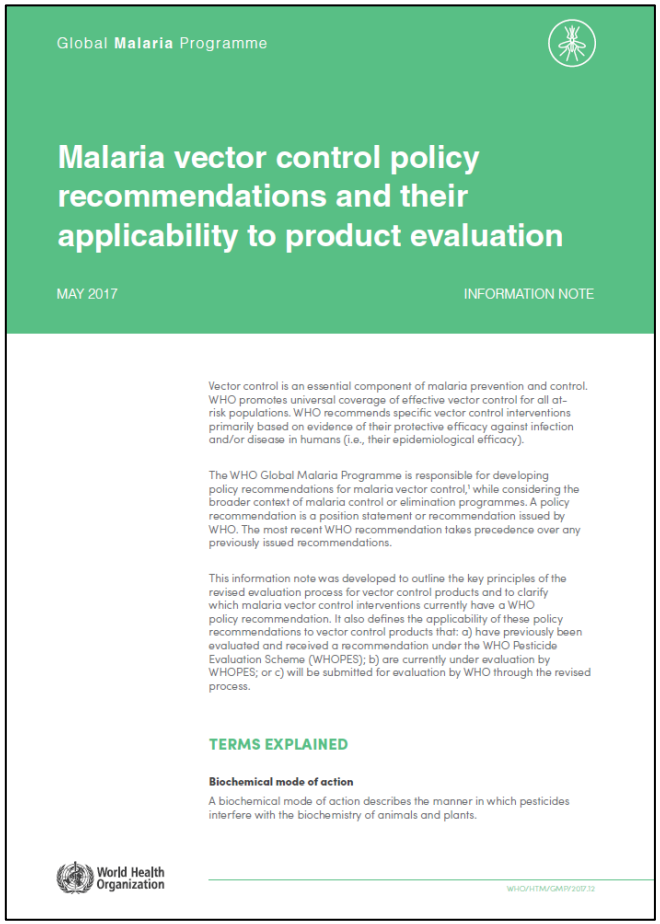
Global **Malaria** Programme

World Health Organization

Background

- WHO process for evaluation of vector control tools, technologies & approaches recently revised
- Evaluation pathway determine by whether part of a "*product class*" with an existing WHO policy recommendation for use
- Two pathways:
  1) Prequalification pathway: products covered by existing WHO policy recommendation
  2) New Intervention pathway: all new tools, technologies & approaches – supported by Vector Control Advisory Group (VCAG)

Vector control product pathway



Global **Malaria** Programme

Malaria vector control policy recommendations and their applicability to product evaluation

MAY 2017 INFORMATION NOTE

Vector control is an essential component of malaria prevention and control. WHO promotes universal coverage of effective vector control for all at-risk populations. WHO recommends specific vector control interventions primarily based on evidence of their protective efficacy against infection and/or disease in humans (i.e., their epidemiological efficacy).

The WHO Global Malaria Programme is responsible for developing policy recommendations for malaria vector control,[1] while considering the broader context of malaria control or elimination programmes. A policy recommendation is a position statement or recommendation issued by WHO. The most recent WHO recommendation takes precedence over any previously issued recommendations.

This information note was developed to outline the key principles of the revised evaluation process for vector control products and to clarify which malaria vector control interventions currently have a WHO policy recommendation. It also defines the applicability of these policy recommendations to vector control products that: a) have previously been evaluated and received a recommendation under the WHO Pesticide Evaluation Scheme (WHOPES); b) are currently under evaluation by WHOPES; or c) will be submitted for evaluation by WHO through the revised process.

TERMS EXPLAINED

Biochemical mode of action

A biochemical mode of action describes the manner in which pesticides interfere with the biochemistry of animals and plants.

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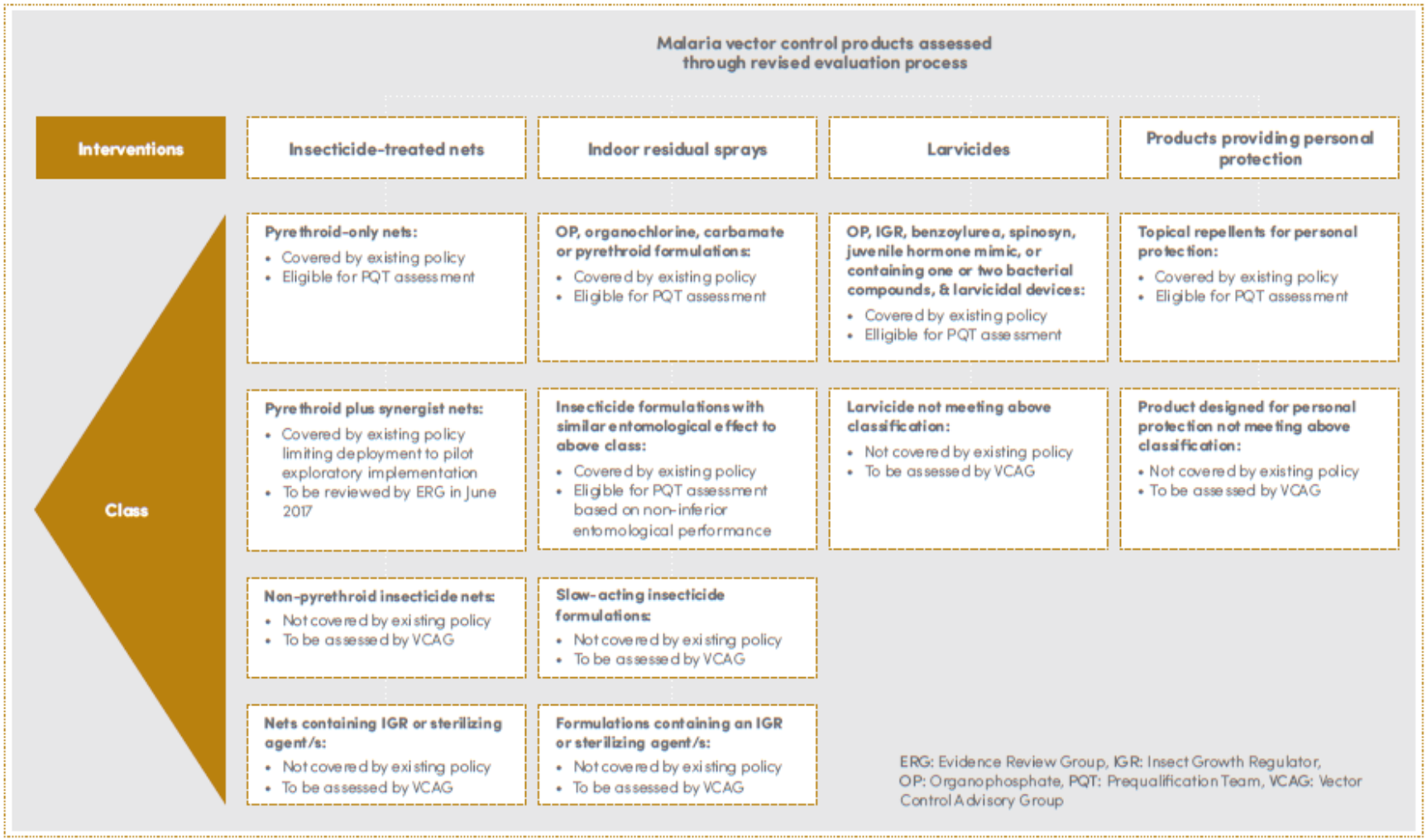
Product Class: A product class in vector control is a group of products that share a common entomological effect by which it reduces pathogen transmission and thus reduces infection and/or disease in humans. A product class may contain one or more target product profiles (TPPs) depending on the intended effect of the product(s) and claim(s).

Vector control product pathway

FIGURE 1.

Overview of intervention types and product classes for malaria vector control products, including a) applicability of WHO policy recommendations and b) related assessment pathways under the revised WHO evaluation process



2017 ERG objectives

ERG convened from 12-14 September 2017

Tasks:

- Consider four selected new vector control products as “case-studies”:
  - **SumiShield® 50 WG:** IRS product containing clothianidin (neonicotinoid-based formulation) – a new chemical active ingredient (AI).
  - **Pyrethroid-PBO nets:** 5 net products evaluated under WHOPES based on classification as pyrethroid LLIN
  - **Larvasonic SD-Mini device:** new device that emits underwater sound pulses resulting in larval death
  - **Fludora® Co-Max EW:** first space-spray with a mixture of two AIs (flupyradifurone - a neonicotinoid - and transfluthrin - a pyrethroid)
- Review summarised laboratory and field trial data for each
- Develop product-specific policy recommendations and general recommendations to support the evaluation process

ERG conclusions & recommendations

SumiShield® 50 WG

- This meets the current WHO efficacy criteria for IRS products (based on review of mortality data for fully susceptible mosquitoes)
- Has a similar entomological effect to other IRS products currently covered by a WHO policy recommendation
- Therefore recommend that existing WHO policy recommendation for IRS should be extended to include SumiShield® 50 WG. Any other neonicotinoid insecticide required to demonstrate minimum efficacy criteria for IRS
- National malaria control programmes and partners should consider deploying SumiShield® 50 WG – and encouraged to collect data on epidemiological impact through deployment
- SumiShield® 50 WG cannot currently be recommended for insecticide resistance management as only assessed as IRS product

ERG conclusions & recommendations

General recommendations (1)

1. New IRS, space spray & larvicide products should be considered as covered by existing product classes if they:
   a) Have the same entomological effect as products is classes covered by WHO policy
   b) Meet the WHO efficacy testing criteria for the relevant product class, even if their biochemical mode of action differs
2. New IRS, space spray & larvicide products that do not meet current WHO testing criteria need to be assessed by VCAG to determine public health value
3. New LLIN products that are not covered by an existing WHO policy need to be assessed by VCAG to determine their public health value

General recommendations (2)

4. New vector control products that have the same biochemical mode of action & entomological effect as a product in a class covered by WHO policy should:
   a) Meet current testing criteria for the product class based on laboratory, small-scale field trials and large-scale field trials with entomological endpoints
   b) Demonstrate non-inferiority to at least one existing product by means of small-scale field trials (e.g. experimental hut studies). This comparator should be current best practice used by the national programme.
   c) For pyrethroid-PBO nets, a set of criteria need to be defined for PBO persistence over time to ensure not only retained by also replenished and bio-available in the surface fibres

ERG conclusions & recommendations

General recommendations (3): to support work with the aim to refine or modify current evaluation procedures

- Assessment of non-inferiority of products within a class: recommend in-depth assessment of existing trial data & statistical methods to provide specific guidance
- Review design, execution & reporting of entomological field trials to develop additional guidance to support high quality studies & standardized reporting
- Investigate relationship between entomological outcomes from laboratory & small-scale field studies with entomological and epidemiological outcomes from CRTs to determine whether reliable entomological surrogates can be established
- Encourage multiple comparisons of products of different chemical classes in small scale field studies (e.g. experimental huts) to identify appropriate comparator for large-scale field trials

ERG conclusions & recommendations

General recommendations (4): further generation of evidence

- For IRS products, recommend that evidence for ≥80% mortality following 72 hour holding period should be considered in product assessment
- Request a review of policies for space sprays and larvicides/larvicidal devices to guide the generation of additional evidence to determine their public health value and hence provide evidence-base to support continued use given current paucity of evidence
- Space sprays: current test methods should be reviewed to ensure products demonstrate efficacy against wild mosquitoes
- WHO should update all test guidance to include testing in laboratory studies against resistant mosquito strains including all major mechanisms
- Encourage development and evaluation of products explicitly designed to control insecticide-resistant mosquitoes

Data requirements and methods to support the evaluation of new vector control products

DECEMBER 2017

RECOMMENDATIONS

BACKGROUND

WHO's process for the evaluation of vector control tools, technologies and approaches has been revised to better meet the needs of countries endemic for, or at risk of, vector-borne diseases. Under the revised process, the evaluation pathway to be followed is determined by whether or not a product is part of a product class with an existing WHO policy recommendation for its use.[1]

Products covered by an existing WHO policy recommendation will follow the *Prequalification Pathway*, while all new tools, technologies and approaches will follow the *New Intervention Pathway,* supported by the Vector Control Advisory Group (VCAG). VCAG will validate whether the intervention under assessment has public health value.[2] Once public health value has been demonstrated, WHO will issue a policy recommendation.

Following a request from the Malaria Policy Advisory Committee (MPAC) in March 2017, WHO is reviewing the data requirement associated with the evaluation of new vector control interventions to ensure that these can be deployed as soon as possible, while also ensuring that policy recommendations to guide deployment remain evidence-based.

With the move to a revised evaluation system and the arrival of new vector control products, WHO must also guide assessment of products that clearly fall within an established intervention class, but that differ in product specification and/or design (e.g. location of insecticide or synergists on panels of mosquito nets) from the first-in-class product that established the class and for which epidemiological data are available. For such new products, WHO requires reassurance of similar performance (for disease or vector control) to provide normative guidance to vector control programmes faced with the challenge of selecting a reliable product. Examples of such

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products included mosquito nets treated with a pyrethroid and the synergist piperonyl butoxide (PBO), new indoor residual spray (IRS) chemistries, and new mosquito larvicides and space spray products.

To discuss these areas in detail so as to provide recommendations to MPAC and WHO, an evidence review group (ERG) was jointly convened by the WHO's Global Malaria Programme, the Department of Control of Neglected Tropical Diseases, and the Prequalification Team for Vector Control Products from 12–14 September 2017.[3] The ERG was tasked with reviewing summarized laboratory and field trial data for selected new vector control products and to use these as case-studies to develop both product specific policy recommendations and general recommendations in support of the evaluation process for new vector control tools, technologies and approaches.

CONCLUSIONS AND RECOMMENDATIONS

On the basis of the current evidence, the ERG advises WHO as follows:

Specific conclusions and recommendations on SumiShield® 50WG

Conclusions and recommendations in this section are based on a review of summarized results from a laboratory study (IRD, France) and experimental hut[4] and long-term large-scale[5] community trials from Tanzania, India, Côte d'Ivoire and Benin. These trials measured entomological endpoints only.

1. **SumiShield® 50WG meets the current WHO efficacy criteria for IRS.**[6] This conclusion is based on the review of mortality data for fully insecticide susceptible *Anopheles* mosquitoes exposed in cone-bioassays to walls treated with a target dose of 300 mg AI/m^2. Percentage mortality 24 hours after 30-minute exposure was equal to or greater than 80% for most studies and exceeded this threshold after a 72-hour holding period in all studies for a duration of 4–8 months following application of the insecticide to walls. If the trial results had been assessed by a former WHOPES Working Group, SumiShield® 50WG would have met the efficacy criteria and been recommended for use as an IRS product.

2. **SumiShield® 50WG has a similar entomological effect to other IRS products that are currently covered by a WHO policy recommendation.** A similar entomological effect is here defined in terms of the speed with which SumiShield® 50WG kills mosquitoes over defined holding/recovery time periods (24–72h) after a standard exposure time (30 minutes) and as measured by means of post-exposure percentage mortality with cut-off of ≥80%. Based on data from the studies in Tanzania, which explicitly compared SumiShield® 50WG (target dose: 300 mg AI/m^2) to the pyrethroid deltamethrin (K-Othrine 250 WDG; target dose 25 mg AI/m^2), the organophosphate pirimiphos methyl (Actellic 300 CS; target dose 1g AI/m^2) and the carbamate bendiocarb (Ficam 80WP; target dose: 400 mg AI/m^2), SumiShield® 50WG was found to perform as well as, or better than, these comparator products. The evidence presented also indicated improved performance for extended holding times post exposure in cone bioassays (i.e. higher mortality after 72 hours when compared to 24 hours and adjusting for mortality in controls). A similar effect was seen for the positive control products.

3. **Existing WHO policy recommendations for IRS should be extended to include SumiShield® 50WG.** While the insecticide belongs to a different chemical class – the neonicotinoid insecticides – its similar entomological effect to that of other IRS products currently covered by WHO policy supports the extension of this policy to SumiShield® 50WG. Any other neonicotionoid insecticide submitted for evaluation to WHO will also be required to demonstrate that it meets the minimum efficacy criteria for IRS to be covered under current policy.

4. **National malaria control programmes and their implementing partners should consider deployment of SumiShield® 50WG for IRS.** Deployment must only be considered in situations where coverage with effective vector control (primarily long-lasting insecticidal nets (LLINs) or IRS) will not be reduced; the primary goal must remain the achievement and maintenance of universal coverage for all people at risk of malaria.

5. **Data generation to document the epidemiological impact achieved through deployment of SumiShield® 50WG is strongly encouraged.** The extension of WHO policy to the neonicotinoid insecticide SumiShield® 50WG is based only on entomological data, and an assumption that a similar or better entomological effect observed when compared to other IRS products covered by WHO policy will translate into at least a similar epidemiological impact. This assumption requires confirmation following deployment of SumiShield® 50WG in control programmes.

GENERAL RECOMMENDATIONS

1. **New IRS, space spray and larvicide products should be considered as covered by the WHO policy for those product classes if they (1) have the same entomological effect as products in the classes covered by WHO policy and (2) meet the WHO efficacy testing criteria for the relevant product class, even if their biochemical mode of action differs.** The key criteria to be met are based on current WHO testing guidelines[6,7] and are as follows:

    - IRS products will need to demonstrate insecticidal action against susceptible anopheline mosquitoes above the efficacy cut-off point in WHO cone bioassays. Accordingly, the duration during which mosquito mortality is ≥80% after 30 minutes exposure on the treated substrate and a 24-hour holding period is recorded. Knockdown after 60 minutes post-exposure is also recorded, but there is no WHO cut-off for this parameter. Other entomological parameters are also investigated in experimental hut studies to demonstrate the behavioural and insecticidal action of the candidate insecticide products.

    - For space spray products the minimum dosage needs to be determined that gives at least 90% mortality after 60 minutes of exposure and 24 hours holding against laboratory reared non-blood fed susceptible strains held in confined screen cages in the field.

    - For larvicides the minimum dosage needs to be determined that achieves 80% or 90% mortality, or adult emergence inhibition (the desired level of control).

    The ERG recommends that revision of current testing guidelines, as outlined under general recommendation 5, includes a review of current testing criteria with a view of enhancing their clarity.

2. **New IRS, space spray and larvicide products that do not meet the current WHO testing criteria, and hence differ in their entomological effect from products covered by WHO policy, need to be assessed by VCAG to determine their public health value.** Part of this evaluation process consists of the establishment of testing criteria for the new product and for the new intervention class that this "first-in-class" product creates. The requirement will be to demonstrate public health value.[2] A claim of efficacy against resistant mosquitoes or any other specific claim will need to be demonstrated as part of the evaluation. It is recognized that demonstration of claims, such as efficacy against insecticide-resistant mosquitoes, may require additional guidance from WHO and revision of the existing WHO test procedures (see general recommendation 5) and thresholds. For novel product classes (and to stimulate innovation) manufacturers should not feel tied to test procedures or threshold criteria established for existing classes during their development of new product classes.

3. **New LLIN products that are not covered by an existing WHO policy need to be assessed by VCAG to determine their public health value.** This requirement is based on the complexity of how LLINs provide personal and community-level protection, whereby entomological outcomes are currently not considered to be reliable indicators of epidemiological impact, especially in areas of pyrethroid resistance.[8] As part of the evaluation process, testing criteria will need to be established for the new product and for the new LLIN intervention class that this "first-in-class" product creates.

4. **New vector control products that have the same biochemical mode of action and entomological effect as a product in a class covered by WHO policy should be required to:**

    - Meet current testing criteria for the product class based on laboratory and small-scale field trials[4] and large-scale field trials[5] with entomological endpoints. Current guidance for each intervention type (LLINs, IRS, larvicide, etc.) should be consulted and will need to be updated to include details on determination of non-inferiority (see below).

    - Demonstrate non-inferiority[9] to at least one existing product in the product class by means of small-scale field trials (i.e. experimental hut studies in the case of LLINs and IRS products).

    - For pyrethroid-PBO nets, a set of criteria will need to be defined for PBO persistence over time, including not only that PBO is retained in the net but is also replenished and bio-available as a synergist on the surface of the netting fibres.

    If a manufacturer wishes to expand the claim of a product covered by WHO policy, for example to include efficacy against insecticide resistant vectors, data to substantiate this claim will need to be reviewed by WHO.

5. **To support the general recommendations made under points 1–4, WHO is requested to conduct further work in a number of key areas with the aim of refining or modifying current evaluation guidance and procedures:**

    - Assessment of non-inferiority of products within a class. While entomological field studies, in particular experimental huts, may provide a suitable approach for the determination of non-inferiority, the design of such trials needs to be reviewed and additional guidance developed to support implementation of a standardized and rigorous study design and analysis. An in-depth assessment of existing experimental trial

data from different settings and a comparison of statistical methods to analyse new and existing experimental trial data are required. Based on these analyses, specific guidance on assessment of non-inferiority should be developed and incorporated into a revision of current WHO testing guidelines.

- The design, execution and reporting of entomological field trials need to be reviewed and additional guidance developed to support implementation of high quality studies and standardized reporting to facilitate assessment of data by WHO advisory groups. Revised guidance should include details on randomization, replication and power calculations.

- Investigation of the relationship between entomological outcomes, generated through laboratory and small-scale field trials,[4] and epidemiological and vector-transmission outcomes (e.g. reductions in entomological inoculation rate and vector density), generated through cluster randomized trials (CRTs), should be explored to determine whether entomological markers of intervention effects can be identified that are reliable surrogates for effects on disease endpoints. At present, there is a paucity of evidence to assess whether entomological effects determined in laboratory or small-scale field trials[4] predict epidemiological outcomes determined in CRTs. This is, at least partially, due to the limited amount of data from CRTs available to explore such relationships, as few CRTs were conducted to assess vector control interventions in recent years. It is recommended that experimental hut trials (in the case of IRS, LLIN and other indoor acting products) be carried out, if possible, in the vicinity of the CRT to establish or improve knowledge of the relationship if there is spatial heterogeneity in local species or its resistance profile. It is also recommended that investigation of potential surrogate markers and critical efficacy thresholds should focus on sampling the products during CRT evaluation and test in laboratory bioassay, experimental huts or semi-field system. Investigation of potential surrogate markers should focus initially on products that have demonstrated public health value in CRTs or are undergoing CRT evaluation. These should be tested in a variety of entomological laboratory and small-scale field trials[4] to identify which, if any, testing methods generate data that provide reliable entomological surrogates for effects on disease endpoints.

- For space sprays, the current test methods should be reviewed to ensure that products also demonstrate efficacy against wild mosquitoes in large-scale field trials.[5] Additional guidance and criteria will need to be developed, including the requirement for cage controls of field derived target species mosquitoes and for droplet counts to ensure that products are applied according to target dosage or manufacturers requirements.

- To better allow assessment of product efficacy in the field in the presence of resistance, WHO should update testing guidance to include testing in laboratory studies against resistant mosquito strains, including all major resistance mechanisms. In addition, in field studies, product efficacy against local mosquito populations representative of prevailing patterns of resistance should be assessed.

- For IRS products, the ERG recommends that, in case where convincing evidence is presented for ≥80% mortality following a 72-hour holding period this criteria should be considered in the assessment of the product; revision of testing guidelines should include this criteria. For all new IRS products, data from 30-minute exposure in cone bioassays with both 24-hour and 72-hour holding periods should be presented to

allow assessment of delayed mortality. The ERG also recommends that a minimum threshold for the duration of insecticidal efficacy of three months, after application of the insecticide to the walls, be included as a criteria for minimum efficacy.

- Discussion around deployment guidance was not within the scope of this ERG, and should be discussed by another WHO advisory group, particularly to address utility of products for insecticide-resistance management.

6. **Generation of high quality evidence beyond that generated through existing evaluation methods is encouraged to facilitate product evaluation and the formulation of policy and programmatic guidance.**

   Specific areas in which WHO is requested to conduct further work are listed below:

   - The WHO Department of Control of Neglected Tropical Diseases and the Global Malaria Programme are requested to conduct a review of the policies for the evaluation of space sprays and larvicides/larvicidal devices to guide the generation of the required additional evidence to determine their public health value and hence provide an evidence-base to support continued use of these products, technologies or approaches. Larviciding with chemicals is used widely to treat *Aedes aegypti* larval habitats, and should be considered as complementary to environmental management and should be restricted to containers or fixed habitats that cannot otherwise be eliminated or managed. Overall, there is a paucity of evidence of effects on disease endpoints for vector control measures such as space spraying and larvicides/larvicidal devices. Such evidence should be generated and systematically reviewed to support the use of these interventions for public health purposes. Space spraying is currently recommended for control only in emergency situations to suppress an ongoing dengue/arboviral disease epidemic or to prevent an incipient one. The objective of space spraying is the massive, rapid destruction of the adult vector population. Any control method that reduces the number of infective adult mosquitoes, even for a short time, should reduce virus transmission during that time, but it remains unclear whether the transient impact of space treatments is epidemiologically significant. Factors such as insecticide susceptibility, droplet size, application rate, frequency and indoor penetration of the insecticide are all crucial to the efficacy of application of this method for controlling *Ae. aegypti*. A recent review concludes that indoor space spraying is an effective adulticidal intervention against *Aedes* mosquitoes.[10] However, WHO needs to periodically review and build a stronger evidence base for the impact of indoor space spraying on the disease.

   - Multiple comparisons of products of different chemical classes in experimental hut studies[4] are encouraged to identify the appropriate comparator product for large-scale field trials.[5] Such data are also helpful to inform rotation of active ingredients for resistance management.

7. **In view of the existing threat caused by insecticide resistance, the development and evaluation of products that are explicitly designed to control insecticide-resistant mosquitoes is encouraged.** These products should come with a claim of being effective in settings where the vectors are resistant to one or more insecticide classes and should be evaluated against this claim.

Endnotes

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

2. A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.

3. The present document reflects the content of a document presented to MPAC under the title *Data requirements and methods to inform the potential extension of WHO policy to new vector control products and to verify the performance of products entering an established class* by the ERG on Assessing Comparative Effectiveness of New Vector Control Tools (http://who.int/entity/malaria/mpac/mpac-oct2017-erg-comparative-effectiveness-report-session5.pdf).

4. Formerly referred to as WHOPES Phase II evaluation

5. Formerly referred to as WHOPES Phase III evaluation

6. Guidelines for testing mosquito adulticides for indoor residual spraying and treatment of mosquito nets. Geneva: World Health Organization; 2006 (http://apps.who.int/iris/bitstream/10665/69296/1/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf)

7. Guidelines for laboratory and field testing of mosquito larvicides. Geneva : World Health Organization ; 2005. (http://apps.who.int/iris/bitstream/10665/69101/1/WHO_CDS_WHOPES_GCDPP_2005.13.pdf)

8. Malaria vector control policy recommendations and their applicability to product evaluation. Geneva : World Health Organization; 2017 (http://www.who.int/malaria/publications/atoz/vector-control-recommendations/en/)

9. A vector product under evaluation shows non-inferiority when it demonstrates an equal or better entomological effect and/or protective efficacy against infection and/or disease in humans than the comparator product. Non-inferiority relies on a measurement of effect whereby the difference should be only a small amount, called delta. Delta is pre-specified based on the desired clinical (or entomological) effect. Specifying a smaller delta for a non-inferiority trial can test whether a new product's performance is similar to that of a comparator product (i.e., effect is <delta), but demonstrating statistical significance may require larger sample sizes.

10. Maoz et al. (2017) Community effectiveness of indoor spraying as a dengue vector control method: A systematic review. PLoS Negl Trop Dis. 2017 Aug 31;11(8):e0005837

Malaria Policy Advisory Committee Meeting
17–19 October 2017, Geneva, Switzerland
Background document for Session 6

Proposal for an Evidence Review Group on Border Malaria

October 2017, Geneva, Switzerland

Background and rationale

Border malaria is a frequently cited challenge to malaria elimination. Countries nearing elimination often find their last few cases occurring along international borders with countries that have not achieved substantial reductions in malaria transmission. However, despite many member states pointing to border malaria as a hindrance to achieving elimination or maintaining malaria-free status, there is no clear definition of the problem or understanding of the various issues underpinning border malaria. In general, the term "border malaria" is used to refer to malaria transmission in border areas as well as malaria imported across international borders by travellers, migrants and refugees; however, the epidemiological characteristics of these situations may differ significantly. A number of factors may be associated with malaria transmission across international borders. These include porous borders, asymmetrical access to health care, and differences in the implementation of malaria activities. However, the true scope of the problem and the implications for malaria transmission in general are not clearly understood, likely due to insufficient data and the lack of a systematic review.

In order to define and characterize the problem of border malaria and assess its implications for malaria control, elimination and prevention of re-establishment, a working group meeting, initiated by ISGlobal and in collaboration with GMP/WHO, was held on 9–10 August 2017 in Geneva. Building on a literature review and a plenary discussion, a definition of border malaria was proposed as "**malaria transmission or potential for transmission that takes place across adjacent administrative areas that share an international border (or lie at a specified distance from an international border)**". Border malaria occurs because the contiguous areas share a common ecology, related human populations, and related malaria parasites and vectors; accordingly, there is frequent mixing of people, parasites and vectors. The relevance of border malaria increases when there is a transmission differential across the border due to a gradient in receptivity or intervention coverage. Border malaria differs from transnational malaria, which is defined as cases of malaria that cross a border or enter a country, but do not affect transmission within the border area per se.

Border malaria is occurring widely throughout the globe. It is a common concern for countries both in eliminating malaria and in preventing re-establishment of transmission. Building on the current knowledge and evidence, WHO aims to characterize border malaria in general and with respect to specific categories, so as to provide recommendations and develop tools and strategies with which the affected countries can tackle border malaria. Where knowledge gaps still exist, the aim is to identify research and operational research priorities and to propose studies to generate the required data.

WHO/HTM/GMP/MPAC/2017/14

Objectives of the Evidence Review Group

1. To review literature and grey literature on border malaria, including a brief analysis of border malaria occurring in about 30 countries throughout the globe, and to summarize the characteristics of border malaria and its different categories;

2. To review and comment on case studies and to make specific recommendations for tackling the different categories of border malaria;

3. To evaluate the effectiveness of the current tools or interventions targeting border malaria;

4. To draw evidence from other global/eradication initiatives where cross-border risks have played an important role in disease transmission (polio; measles; guinea worm; lymphatic filariasis/onchocerciasis);

5. To define a research agenda for border malaria and a future action plan for the next 2–3 years.

Suggested timetable

Activity	Timeline
Identify ERG members and contact leading writers for each case study	September 2017
Determine an outline for case studies and disseminate to all case leaders	September 2017
Prepare a document with a brief description of border malaria throughout the globe, building on the analysis of E2020 countries but expanded to 30 countries	December 2017
Finalize the summary of the literature review and complete the grey literature review (including reports from border malaria meetings and the border malaria initiative)	December 2017
Complete and finalize case studies	January 2018
Disseminate case studies to ERG members	January 2018
ERG meeting	March 2018

Proposal for an Evidence Review Group on Border Malaria

Dr LI Xiao Hong, Elimination Unit

Malaria Policy Advisory Committee, Geneva, Switzerland, 17-19 October 2017

Global **Malaria** Programme

World Health Organization

Outline

- Background
- Definition of border malaria
- Proposed ERG on border malaria
  - Objectives
  - Workplan

Background

- Border malaria is a frequently cited challenge to malaria elimination
  - 1st Global Forum of malaria eliminating countries, mentioned by 15/20 countries
- Countries nearing elimination often find their **last few cases occurring along international borders** with countries that have not achieved substantial reductions in malaria transmission.

Current WHO definitions related to border malaria

Cross border malaria

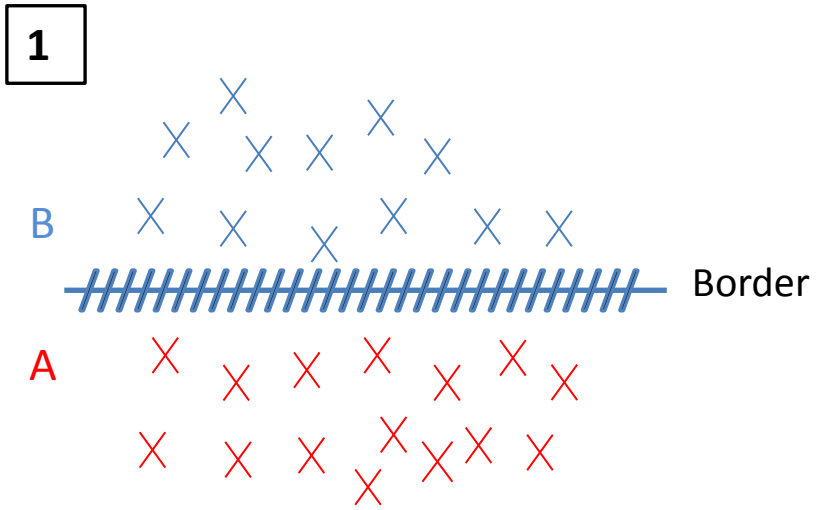
Malaria transmission associated with the movement of individuals or mosquitoes across borders (*WHO malaria terminology*, 2017)

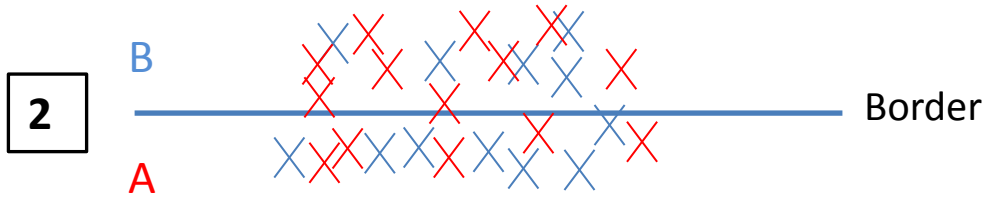
(needs to be updated)

Imported cases

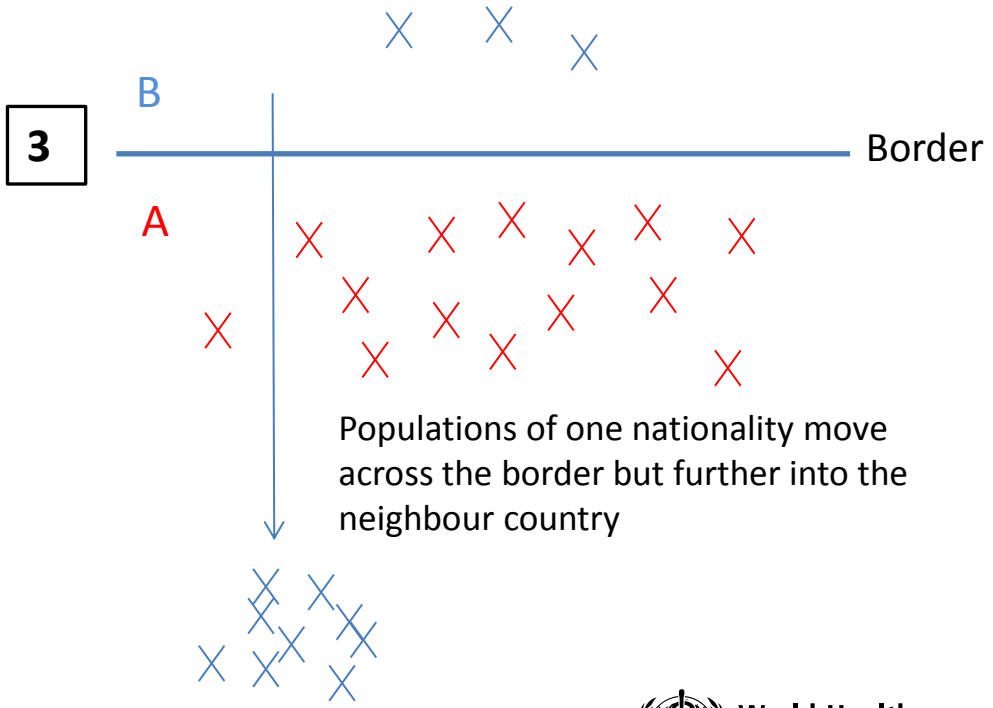
Malaria case or infection in which the infection was acquired outside the area in which it is diagnosed

Population movements across an international border





Populations of two nationalities mixed together in a defined area along border



Populations of one nationality move across the border but further into the neighbour country

X People of nationality A

X People of nationality B

Definition of border malaria

----- Working group meeting on border malaria, 9-10 Aug, Geneva

- Border malaria refers to **malaria transmission or potential for transmission that takes place across adjacent administrative areas that share an international border (or lie at a specified distance from an international border)**

Characteristics of border malaria

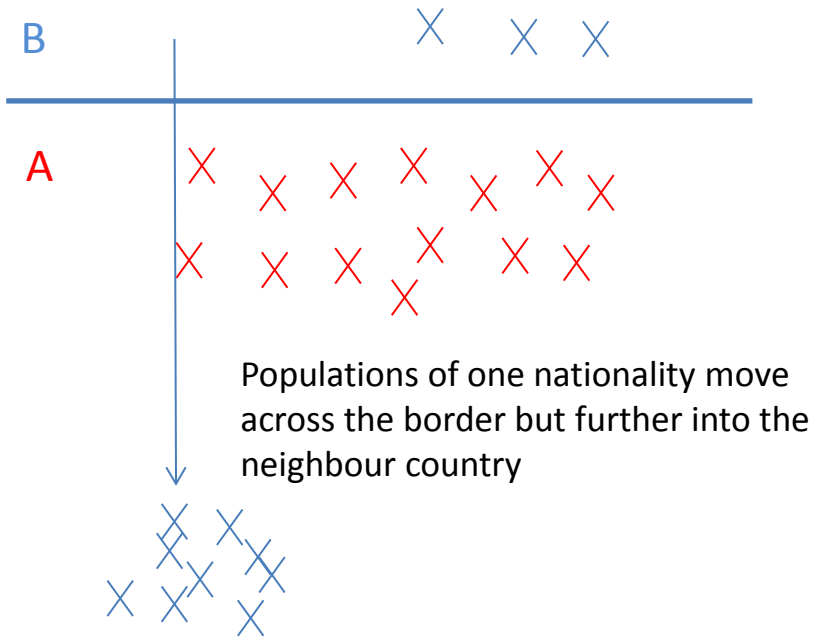
- The two sides of the border share a common ecology
- Related human populations, related malaria parasites and vectors, due to frequent mixing
- It occurs when there is transmission differential across the border due to a gradient in receptivity or intervention coverage

Border malaria is differentiated from transnational malaria

Transnational malaria:

- Cases of malaria that cross a border, or enter a country, but do not affect transmission within the border area per se.
- (Islands)

3



Key questions to be answered

- **Malaria transmission**
  - Does higher malaria transmission in one side of the international border increase transmission in the other side?
- **Effectiveness of current interventions for border malaria**
  - Is border malaria post effective?
  - What are the elements of an effective border collaboration (coordination, implementation, etc.)?
  - What data to be shared and how?
- **Others?**

Figure Distribution of 68 border malaria posts in the border of Yunnan, China

Objectives of Proposed ERG on border malaria

- To review literature and grey literature on border malaria, including a brief analysis of border malaria occurring in about 30 countries throughout the globe, and to summarize the characteristics of border malaria and its different categories;
- To review and comment on case studies and to make specific recommendations for tackling the different categories of border malaria;
- To evaluate the effectiveness of the current tools or interventions targeting border malaria;
- To draw evidence from other global/eradication initiatives where cross-border risks have played an important role in disease transmission (polio; measles; guinea worm; lymphatic filariasis/onchocerciasis);
- To define a research agenda for border malaria and a future action plan for the next 2–3 years.

Case studies

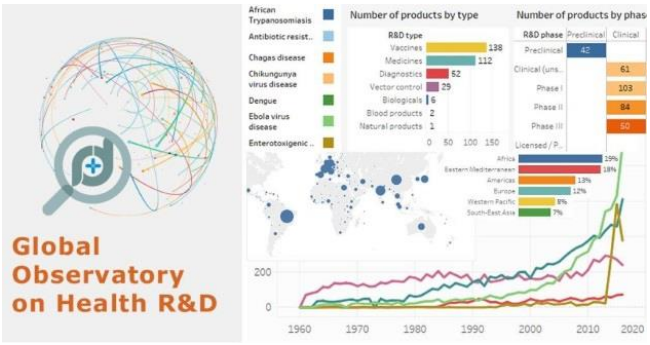
- Namibia and Angola
- Myanmar and China
- Nepal and India
  - Surinam and French Guiana
  - Saudi Arabia and Yemen

Thank you!

Malaria Policy Advisory Committee Meeting
17–19 October 2017, Geneva, Switzerland
Background document for Session 6

The Global Observatory on Health R&D

October 2017, Geneva, Switzerland



The WHO Global Observatory on Health Research and Development (R&D) (hereafter called 'the Observatory') is a centralized and comprehensive source of information and analyses on global health R&D activities for human diseases. It builds on existing data and reports from a wide range of data sources, and gathers new information (where needed and feasible) with the aim of enabling decisions on R&D priorities.

Why is the Observatory needed and what purpose does it serve?

Investments in health R&D are still insufficiently aligned with global public health demands and needs. Governments, policy-makers, funders and researchers, therefore, need an accurate picture of the current situation, so as to spot R&D gaps and ensure that funds and resources are used in the best possible way.

The Observatory[1] is a global-level initiative that aims to identify health R&D priorities based on public health needs by:

- consolidating, monitoring and analysing relevant information on the health R&D needs of developing countries;
- building on existing data collection mechanisms; and
- supporting coordinated actions on health R&D.

How did the Observatory come about?

In May 2013, the Sixty-sixth World Health Assembly specifically mandated the establishment of the Observatory in resolution WHA66.22.[2] The Sixty-ninth[3] World Health

[1] Global Observatory on Health R&D. Geneva: World Health Organization (http://www.who.int/research-observatory/en/, accessed 11 September 2017).
[2] Follow up of the report of the Consultative Expert Working Group on Research and Development: financing and coordination. Geneva: World Health Organization; 2013 (WHA66.22; http://apps.who.int/iris/bitstream/10665/150173/1/A66_R22-en.pdf, accessed 11 September 2017).

WHO/HTM/GMP/MPAC/2017/15

Assembly (May 2016) re-emphasized the Observatory's central role and the importance of expediting its development. It also requested the establishment of an Expert Committee to set priorities for health R&D investments guided primarily by the data and analyses produced by the Observatory.

WHO Member States specifically requested that the WHO Director-General ensure the Observatory tracks R&D needs related to the following two areas of health concern (where current markets and business models are failing):

- antimicrobial resistance and the need to develop new medical products to protect populations from the risks of failing treatments against infectious pathogens (see resolution WHA67.25[4] of the Sixty-seventh World Health Assembly in May 2014);
- a comprehensive R&D Blueprint[5] preparedness plan that allows the rapid activation of R&D activities during future epidemics, such as the epidemic that occurred due to Ebola virus disease. (See EB138/28[6] of the 138th session of the WHO Executive Board.)

What is the Observatory's scope?

As outlined by Member States in World Health Assembly resolution WHA69.23, the primary scope of the Observatory is:

- type II and type III diseases (i.e., diseases incident in both rich and poor countries, but with a substantial proportion of cases in poor countries, and diseases that are overwhelmingly or exclusively incident in developing countries, respectively);
- the specific R&D needs of developing countries in relation to type I diseases (i.e., diseases incident in both rich and poor countries, with large numbers of vulnerable populations in each);
- potential areas where market failures exist;
- antimicrobial resistance and emerging infectious diseases likely to cause major epidemics.

The Observatory adheres to a broad definition of health R&D,[7] including all types of research for health. Its main priority is to inform the development of new health products.

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[3] Follow up of the report of the Consultative Expert Working Group on Research and Development: financing and coordination. Geneva: World Health Organization; 2016 (WHA69.23; http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_R23-en.pdf, accessed 11 September 2017).

[4] Antimicrobial resistance. Geneva: World Health Organization; 2014 (WHA67.25; http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf, accessed 11 September 2017).

[5] A research and development Blueprint for action to prevent epidemics. Geneva: World Health Organization (http://www.who.int/blueprint/en/, accessed 11 September 2017).

[6] Options for strengthening information-sharing on diagnostic, preventive and therapeutic products and for enhancing WHO's capacity to facilitate access to these products, including the establishment of a global database, starting with haemorrhagic fevers: report by the Secretariat. Geneva: World Health Organization; 2015 (EB138/28; http://apps.who.int/gb/ebwha/pdf_files/EB138/B138_28-en.pdf, accessed 11 September 2017).

[7] The WHO strategy for research on health. Geneva: World Health Organization; 2012 (http://www.who.int/phi/WHO_Strategy_on_research_for_health.pdf, accessed 11 September 2017).

As more data and resources become available, the Observatory will expand the diseases and types of health R&D it covers.

How is the Observatory's information developed?

The Observatory aims to be a comprehensive source of information and analyses. It is being built up incrementally, as much of the information on health R&D is not yet standardized or easily accessible.

Analyses produced by the Observatory are led by the Observatory Secretariat, in collaboration with international experts in the respective fields. In order to develop the Observatory, the WHO Secretariat:

- works closely with its technical departments and their established expert groups and committees in order to develop and/or review analyses and syntheses produced by the Observatory;
- seeks regular feedback on the Observatory's structure and outputs from potential users, including national policy-makers, academia, WHO's technical experts, other international governmental organizations and global partnerships, WHO regional offices, civil society and industry stakeholders**.**

How can the Observatory be used?

The Observatory can be used by governments, policy-makers, funders, researchers and civil society to:

- review and query information on current trends in health R&D investment, products in the pipeline and clinical trials;
- look at comparisons of R&D activities between countries, diseases and in relation to relevant information such as burden of disease or macroeconomic indicators;
- review global indicators on health R&D in the context of the Sustainable Development Goals (SDGs);
- consult comprehensive disease-specific analyses on identified needs and priorities (where set);
- find relevant key publications, databases and resources;
- consult the classifications and standards being used by the Observatory as a step towards galvanizing wider discussion and consensus, and harmonizing approaches for the collection and sharing of R&D data.

How does the WHO Expert Committee work?

In May 2016, the Sixty-ninth3 World Health Assembly requested the WHO Director-General to establish a WHO Expert Committee on Health R&D.

This Expert Committee will meet at regular intervals. Its function (as set out by the Sixty-ninth World Health Assembly) is to provide technical advice to the WHO Director-General

on the prioritization of health R&D, basing its advice (among other information) on the analyses provided by the Observatory, together with background documents, reviews and analyses prepared specifically for each meeting by the Observatory Secretariat or by the experts on the Expert Committee.

Members of the Expert Committee will include individuals with the relevant expertise on the topics of each Expert Committee meeting, including expertise in research prioritization, product development, regulatory and product licensure, health systems research, implementation research, burden of disease, equity, and market (including market failure) assessment.

Expert Committee members are appointed by the WHO Director-General. They are selected from WHO Expert Advisory Panels based on their professional competencies and a balanced geographical and gender representation in order to incorporate different approaches and practical experiences from all regions of the world.

What is requested from MPAC?

The Observatory Secretariat is currently in the process of preparing for the first Expert Committee meeting in 2018. This meeting will focus on how to develop and set out recommendations for health R&D prioritization and will guide the approach for subsequent meetings.

Committee members will deliberate on the content and process for developing disease-specific R&D analyses and on prioritization methods that can be taken forward into future meetings.

Malaria R&D was selected as the first case study. MPAC is therefore requested to comment on the analysis of R&D priorities for malaria that will be presented during the MPAC meeting, and to volunteer experts willing to review the detailed draft report that will be refined and then presented to the Expert Committee for consideration during its first meeting.

The WHO Global Observatory on Health Research and Development (R&D)

Taghreed Adam

Scientist
Research, Ethics, Knowledge Uptake (REK)
Health Systems and Innovation Cluster

David Schellenberg

Scientific Advisor
Global Malaria Programme (GMP)
HIV, TB & Malaria Cluster

Malaria Policy Advisory Committee Meeting
Geneva
18th October 2017

What is the Global Observatory on Health R&D?

- The Global Observatory on Health R&D ('the Observatory') is a **centralized and comprehensive source of information** and **analyses** on global health R&D activities for human diseases.

- Observatory aim: to **map and synthesize** health R&D activities to enable evidence-based decisions on **R&D priorities by** the newly established **WHO Expert Committee on health R&D** and other global stakeholders.

- **Target users:** Governments, policy-makers, funders, researchers.

- **URL:** www.who.int/research-observatory/en/

Scope

- Primary scope (as outlined in World Health Assembly resolution **WHA69.23**):
  - **type II and type III diseases** (i.e. diseases incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries, and diseases that are overwhelmingly or exclusively incident in developing countries respectively);
  - the specific R&D needs of developing countries in relation to **type I diseases** (i.e. diseases incident in both rich and poor countries, with large numbers of vulnerable populations in each);
  - potential areas where **market failure** exist;
  - **antimicrobial resistance** and emerging infectious diseases likely to cause **major epidemics**.
- As more data and resources become available, the Observatory will expand the diseases and types of health research it covers.

Status: New expert committee on health R&D

- Work ongoing to:
  - Select and **appoint experts** to a panel (formal process)
  - Produce **comprehensive analysis of malaria R&D** needs and priorities (will serve as prototype for future work)
  - **Develop the methods** for the priority setting process
  - **Plan for the first meeting** of the expert committee and any consultative processes that may be required beforehand

An approach to identify priority challenges and R&D priorities for malaria

WORK IN PROGRESS - FOR INPUT

R&D priorities for malaria

- Malaria – a path-finder for disease-specific R&D prioritisation
- WHO identified the Malaria Eradication Scientific Alliance (MESA) to conduct the analyses
  - Builds on a broad consultative exercise to identify R&D Priorities for malaria eradication – MalERA


PLOS MEDICINE

malERA – a research agenda for malaria eradication

www.plosmedicine.org/malera2011

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Consultations on basic science, drugs, vaccines, vector control, diagnostics, health systems & operational research, M&E and surveillance, modelling

Malaria Eradication Research Agenda

PLoS Med 2011: 8(1): e1000406

MESA Refresh

- MESA currently updating the R&D agenda – further extensive consultation www.malariaeradication.org/malera-refresh
- Asked to expand the prioritisation exercise
  - Consider R&D for control as well as eradication
  - Expand to consider operational research / implementation science

1663 VIEWS

Basic science and enabling technologies →

1619 VIEWS

Insecticide and drug resistance →

1757 VIEWS

Characterizing the reservoir and measuring transmission →

2019 VIEWS

Tools for elimination →

1931 VIEWS

Combination interventions and modelling →

1435 VIEWS

Health systems and policy research →

Overview

Aim

- **Identify challenges and opportunities for future impact**
  - Based on analyses of potentially critical areas of basic, product development and operational research
- Create a **supportive environment for prioritization of challenges and research** by the WHO/GMP
- **Define a 'baseline' for monitoring and evaluation of priorities and progress** through the WHO Global Observatory for Health R&D

Proposal

- Draft a report for initial consultation with GMP & MPAC
- Incorporate MESA Track & other databases of products in development, and include examples of key basic research and delivery science solutions

METHODOLOGY

1. Challenges identified
- Impact on malaria cases/ mortality/ elimination
- Cannot be addressed using current products/strategies

Sources: malERA Refresh, WHO GTS, GMP, WHO guidance and policies

2. Challenges mapped to Problems
- Problems that need to be addressed

Sources: malERA Refresh, WHO GTS, GMP, Literature search

3. Potential product solutions identified
- What kinds of solutions could address the problems?

Sources: malERA Refresh, Literature search

4. Pull together the global pipeline of ongoing projects

Sources: VCAG, IVCC, WHO, FIND, PATH, UNITAID, MVI, Literature search, others tbd

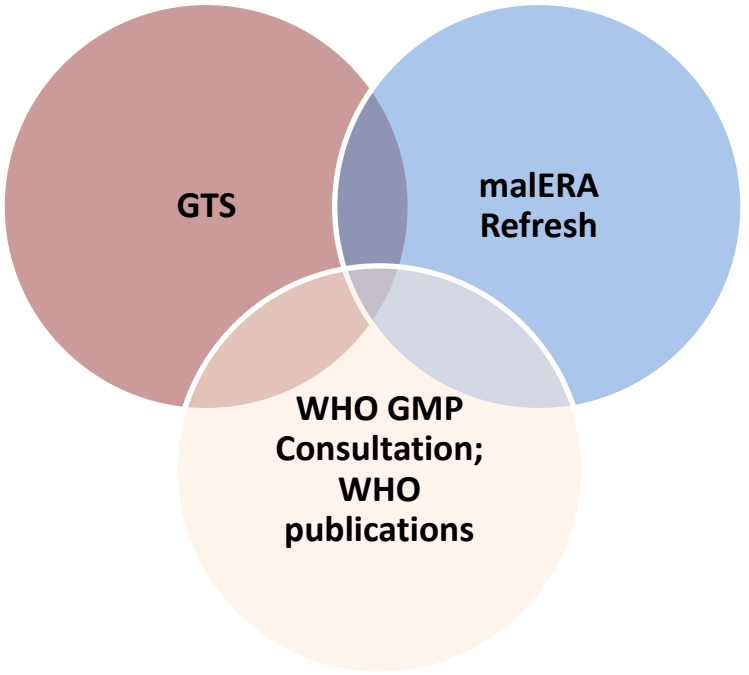
5. Map the pipeline onto potential product solutions

6. Identify, priorities, gaps and opportunities
- Priorities for accelerating R&D
- Gaps where innovation is needed
- Opportunities for potentially disruptive technologies

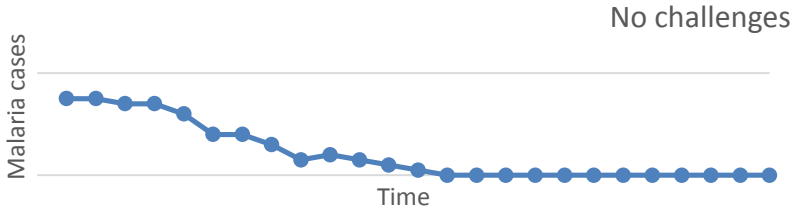
MESA MALARIA ERADICATION SCIENTIFIC ALLIANCE

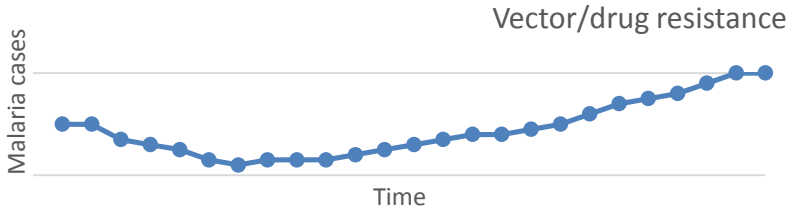
Development of R&D priorities: CHALLENGES

1. CHALLENGES FOR MALARIA WERE IDENTIFIED
Optimizing and managing adaptations to tools and strategies
Regions with high transmission intensity
Residual transmission and accelerating elimination
Achieving universal access (including the "5th child")
Addressing *P. vivax* and non-falciparum species
Achieving, documenting and maintaining elimination



Assumptions: No silver bullet; Multiple products and strategies can potentially address challenges; innovation required to solve each challenge

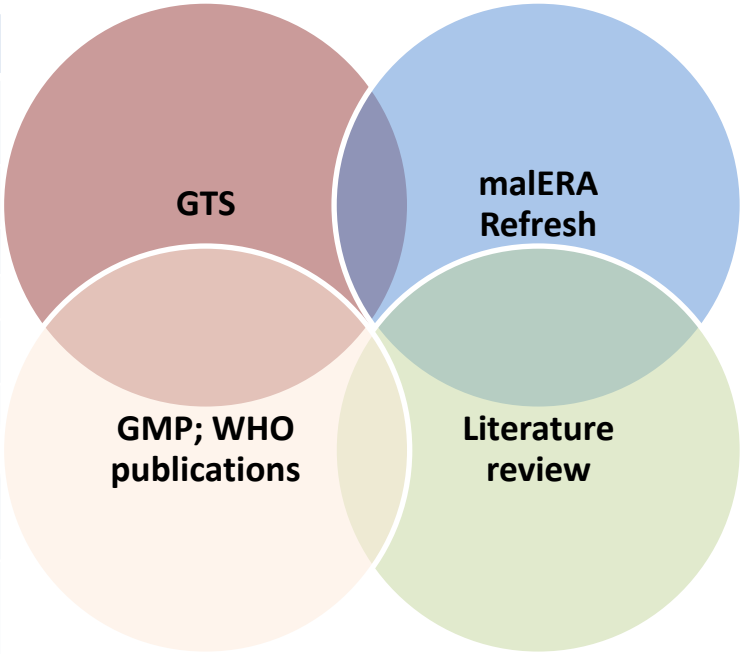




MESA MALARIA ERADICATION SCIENTIFIC ALLIANCE

Development of R&D priorities: PROBLEMS

2. Problems were mapped to challenges	
Optimizing and managing adaptations to tools and strategies	Vector resistance to insecticides (biochemical and behavioral)
	Parasite resistance to drugs
	Selection gene-deleted parasites
Regions with high transmission intensity	Extensive vector populations
	High rates of human to vector transmission
Residual transmission and accelerating elimination	Outdoor/daytime biting & zoophagy (including *P. vivax* vectors)
	Quantifying and targeting the transmission reservoir
Achieving universal access (including the "5th child"	Infrequent contact for prevention and treatment and failure of surveillance
Addressing *P. vivax* and non-falciparum species	Differential diagnosis of *Plasmodium* spp.
	Identifying and targeting hypnozoites and the transmission reservoir
Achieving, documenting and maintaining elimination	Rapid identification of importation, preventing and containing outbreaks



- **QUESTION 1: DO THE CHALLENGES AND PROBLEMS IDENTIFY THE TOP ISSUES THAT COULD DRIVE THE RESEARCH AGENDA?**

MESA MALARIA ERADICATION SCIENTIFIC ALLIANCE

3. Mapping potential product classes to challenges (under development)

Product class	Potential product solution	Challenges 1	2	3	4	5	6	Proven
Vector control	• New insecticide classes used in combination in extended duration LLINs and IRS							
	• Novel vector control tools							
	• Genetic approaches to vector control							
Diagnostics	• Highly sensitive POC diagnostics for identifying low-density, asymptomatic infection							
	• Highly sensitive POC diagnostics for identifying low-density, asymptomatic *P. vivax* infection							
	• RDTs that detect and differentiate all *Plasmodium* species							
	• Sensitive and specific POC diagnostics for *P. vivax*							
	• Diagnostics to identify hy							
	• Affordable, simple and a							
	• Infectivity/gametocyte d							
	• Non-invasive diagnostic t							
	• Stable, valid, specific and							
	• Multiplexed POC tests of							
	• POC diagnostics to ident							
	• POC/health system falsif							
	• High-throughput mosqui							
Drugs	• SERCaP							
	• New drug classes used in							
	• Novel drugs for severe m							
	•							
	•							
	•							
	•							
	•							
	•							
	•							
Vaccines	•							
	•							

CHALLENGES

Optimizing and managing adaptations to tools and strategies
Regions with high transmission intensity
Residual transmission and accelerating elimination
Achieving universal access (including the "5th child")
Addressing *P. vivax* and non-falciparum species
Achieving, documenting and maintaining elimination

- **Question 2:** In progress – clarify which types of solutions have
  - **Proof of Concept confirmed** (TPP, evidence of public health relevance)
  - **Public Health relevance To Be Determined**
  - **Other** (e.g. public health relevance disproved)

- **Is this a USEFUL REFINEMENT TO THE PIPELINE?**

Development of R&D priorities: PIPELINE

4. Identify the pipeline

R&D Observatory

	Sources	
Vector control	• WHOPES • VCAG	• Additional work required
Diagnostics	• WHO list of diagnostics undergoing prequalification evaluation • FIND • UNITAID malaria diagnostics technology and market landscape • Literature search • Policy Cures Research neglected product disease pipeline	
Drugs	• MMV pipeline • UNITAID malaria medicines landscape • Policy Cures Research neglected product disease pipeline	
Vaccines	• WHO Rainbow tables, MVI, EMVI, MESA TRACK	

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Development of R&D priorities: mapping to the pipeline

5. Existing products in the pipeline mapped onto potential product solutions using heat maps

Phase	Product	New drug classes used in combination therapies for malaria treatment	New drugs for severe malaria	New drugs for *P. vivax* radical cure	Drugs for *P. vivax* radical cure and/ or chemoprevention safe in pregnancy, children and G6PD-deficiency	SERCaP	Novel drugs for chemopreventi on	Novel drugs for IPTp	Novel drugs for IPTi, SMC	Endectocides in livestock and humans	New drug combinations suitable for use in MDA/MSAT/ FSAT	Transmission-blocking drugs in *P. falciparum*
Marketed†	Arterolane + piperaquine	*					*		*		*	
Marketed†	Artemisinin + naphthoquine	*										
III	Tafenoquine											
III	Artemether sub-lingual spray		*									
III	Co-trimoxazole						In HIV	In HIV	In HIV			
II	Artefenomel (OZ439) + ferroquine											
II	KAF156 + lumefantrine	*										
II	KAF156											
II	Cipargamin (KAE609)											
II	DSM265											
II	Fosmidomycin + piperaquine	*										
II	Methylene blue + artesunate/amodiaquine	*										
II	SAR97276											
II	Artemisone											
II	AQ-13											
II	Sevuparin (DF02)											
II	MMV048											
II	Ivermectin											
I	P218											
I	SJ733											
I	ACT451840											
I	CDRI 97/78											
I	N-tert butyl isoquine											

Target indication	Possible but not target indication or too early to define	Not indicated or possible

NB: Heat maps for each product class will require verification by experts

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R&D Objectives

6. Based on existing pipeline, potential product solutions classified as to the R&D objective

Objective	Vector control	Diagnostics	Drugs	Vaccines
Accelerate	• Combination LLINs and combination IRS • New insecticide classes are urgently needed • Novel vector control tools, particularly those targeting outdoor biting or for use in high transmission regions	• Sensitive and specific diagnostics for *P. vivax* • Affordable, simple and accurate POC tests for G6PD deficiency • RDTs that detect and differentiate all *Plasmodium* species • Multiplexed POC tests of acute febrile illness • Stable, valid, specific and sensitive RDTs that do not depend on *Pf*hrp2/3 • Highly sensitive POC diagnostics for identifying low-density, sub-clinical infection • Non-invasive diagnostic tests • POC diagnostics to identify drug-resistant parasites • POC/health system falsified drug screening	• New drug classes used in combination therapies for malaria treatment • New drugs for severe malaria • New drugs for *P. vivax* radical cure • SERCaP • Novel drugs for chemoprevention • Novel drugs for IPTp • Novel drugs IPTi/ SMC • Transmission-blocking drugs • Endectocides in livestock and humans • New drug combinations suitable for use in MDA, etc.	• Preventive vaccines for *P. falciparum* • Preventive vaccines for placental malaria • Transmission-blocking vaccines for *P. falciparum*
Innovate	• Additional novel vector control tools, particularly those targeting outdoor biting or for use in high transmission regions • Gene drive methodologies	• Diagnostics to identify hypnozoites • Affordable, simple and accurate POC tests for pregnancy • High-throughput mosquito assays (age, parasites, resistance, host preference) • Infectivity/gametocyte POC diagnostics (research only)	• Drugs for *P. vivax* radical cure/ chemoprevention that are safe in pregnancy, children and G6PD-deficiency	• *P. vivax* targeted preventive and transmission-blocking vaccines • New targets for *P. falciparum* • Novel enhanced adjuvants
Investigate	• *Wolbachia* applications in *Anopheles spp.*	• Ultra-low cost lab-on-a-chip technology	• Alternative drug delivery systems	• Monoclonal antibodies

NB: WORK ONGOING – WILL REQUIRE VALIDATION THROUGH CONSULTATION
NOTE: AT THIS TIME THESE ARE JUST "products", neglects combos, strategies

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Question 3: Are more specific or broader recommendations most useful?

Vector control

- A more proactive approach to identifying, assessing and recommending novel vector control methods is needed

Diagnostics

- Evaluation procedures for non blood-based diagnostics are required
- Standardization of procedures to evaluate molecular methods and their use cases are needed

Drugs

- Opportunities for streamlining assessment and regulatory procedures need to be examined

Vaccines

- RTS,S development needs to be examined and opportunities for the streamlining of assessment and regulatory procedures identified and implemented

- CROSS-CUTTING ISSUES: prioritization and funding for phase 3 trials; regulatory pathway, clinical trial synergies and platforms

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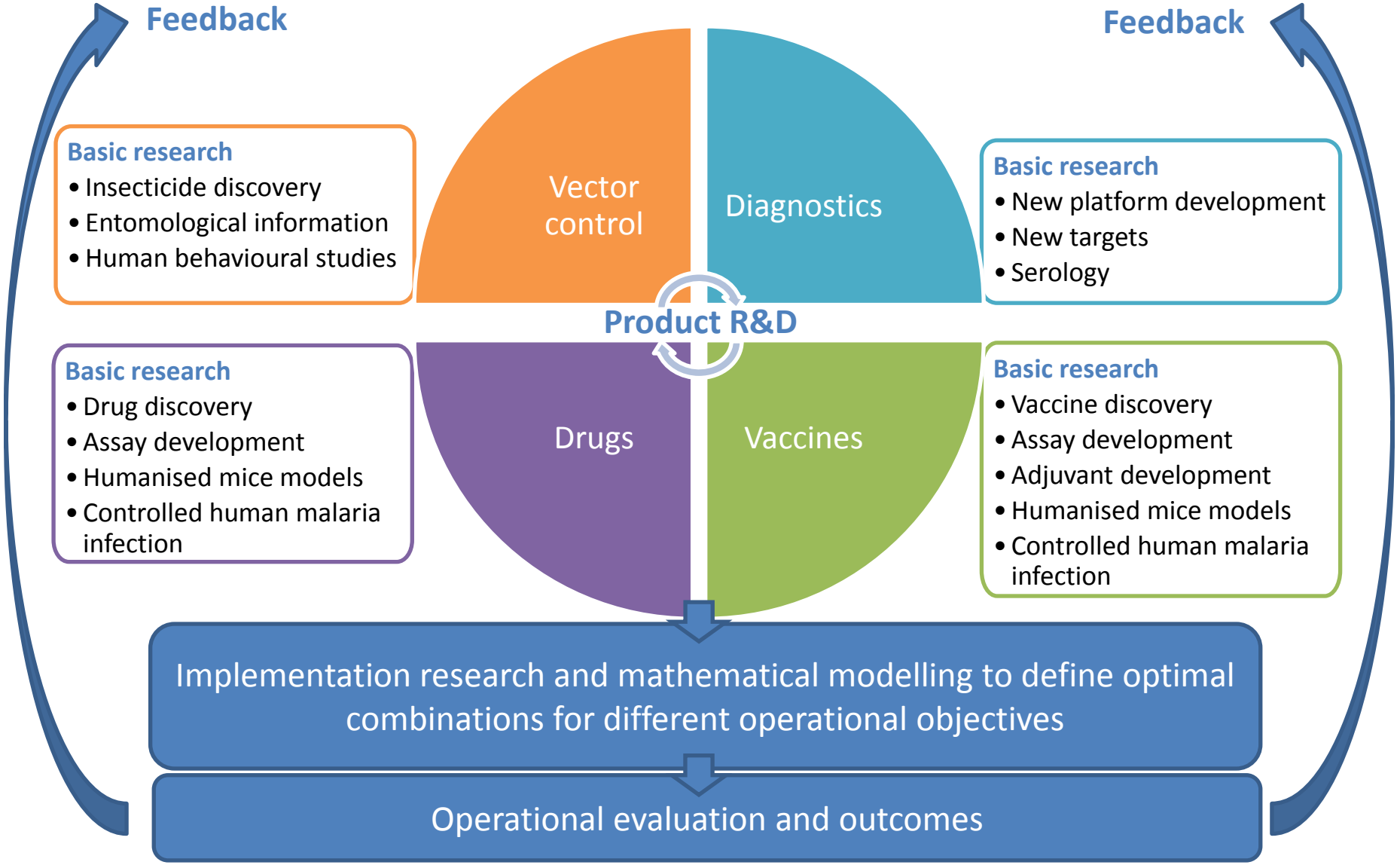
General positioning of product R&D in overall R&D requirements



INCLUSIVITY: Basic and Implementation Science

- The developing document already includes sections on scientific feasibility, as well as technical, regulatory and funding issues for each product class

- **Question 4: WE PROPOSE TO INCLUDE IN THE BREADTH OF RESEARCH NEEDS some critical elements of BASIC RESEARCH and IMPLEMENTATION SCIENCE. Feedback?**

  Basic science rigorously reviewed in MALERA Refresh.

  - Would a more general approach looking at enabling technologies be appropriate?

  Implementation science, including operational research and health systems, reviewed in MALERA Refresh

  - Could be mapped out to Challenges
  - Mindful of potential overlap with regulatory and assessment requirements – needs to be managed?

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Development of R&D priorities: CONSULTATION

MalERA consultation process, including engagement of panels

MESA consultation process, including engagement of panels

GMP review

MPAC review – REQUEST that a minimum of 3 reviewers be identified

Web-based consultation

Expert Committee review

Question 5: Are these plans for consultation adequate?

SUMMARY OF QUESTIONS

- Question 1: Do the challenges and problems identify the top issues that could drive the research agenda?
  - Note that basic and implementation science have not yet been mapped
- Question 2: We propose to indicate which products have proven public health utility, and those products for which public health utility requires 'POC'
- Question 3: Are more specific or general recommendations most useful?
- Question 4: We propose to include in the breadth of research needs some critical elements of basic research and implementation science. Feedback?
- Question 5: Are the plans for consultation adequate?

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What's coming next?
Products in phase III or large-scale field trials – WORK IN PROGRESS

Challenge	Vector control	Diagnostics	Drugs	Vaccines
Resistance to existing control and treatment	• Interceptor® G2 (LLIN)* • PermaNet 3.0® (LLIN)* • Fludora Fusion® (LLIN)* • Sylando® 240SC (IRS) • Lethal house lures • Spatial repellents • Vector traps	• Access Bio Pf RDT • Q-POC™ diagnostic test • Scio falsified drug detection • Q-POC™ drug susceptibility test	• Arterolane + piperaquine† • Co-trimoxazole (in HIV)	• RTS,S and RTS,S fractional dose
Regions with high transmission intensity	• Lethal house lures • Spatial repellents • Vector traps			• RTS,S and RTS,S fractional dose
Residual transmission and accelerating elimination	• Lethal house lures • Spatial repellents • Vector traps	• Alere™ Malaria Ag P.f • Access Bio Pf RDT • Q-POC™ diagnostic test		
Accessing hard to reach populations	• Lethal house lures • Spatial repellents • Vector traps	• Urine Malaria Test™ Pf • Urine Malaria Test™ Pf/Pv		
Addressing *P. vivax*/*P. ovale* and other non-falciparum species	• Lethal house lures • Spatial repellents • Vector traps	• Urine Malaria Test™ Pf/Pv • Q-POC™ diagnostic test • Rapid Assessment of Malaria (RAM) • Magneto-optical Device (MOD) • (PATH G6PD Initiative) POC • (PATH G6PD Initiative) RDT		
Defining and maintaining elimination	• Interceptor® G2 (LLIN)* • PermaNet 3.0® (LLIN)* • Fludora Fusion® (LLIN)* • Sylando® 240SC (IRS) • Lethal house lures • Spatial repellents • Vector traps	• Urine Malaria Test™ Pf • Urine Malaria Test™ Pf/Pv • Alere™ Malaria Ag P.f • Access Bio Pf RDT • Q-POC™ diagnostic test	• Arterolane + piperaquine†	• RTS,S and RTS,S fractional dose

*None of these are a combination of two novel insecticides, so do not strictly meet the requirements for LLINs and IRS using combinations of two new drug classes, so should be regarded as an interim measure. LLINs and IRS that do not include combinations should not be prioritized.

†This is not a combination of two novel drug classes, and will only be of use where piperaquine resistance is absent as an interim measure.

‡ Preventive efficacy of RTS,S and RTS,S fractional dose is insufficient to allow scale back of other malaria control and prevention activities and will not influence transmission. The dosing schedule is not suitable for use in hard to access populations.

MESA MALARIA ERADICATION SCIENTIFIC ALLIANCE

Background: Contents list for full report (DRAFT)

MESA MALARIA ERADICATION SCIENTIFIC ALLIANCE

WHO Technical Consultation on universal access to malaria core interventions

Joint activity of PDT, PSM, SEE and VCU Units of GMP

Richard Cibulskis and Andrea Bosman

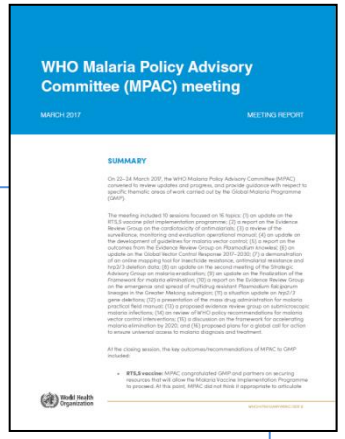
Global **Malaria** Programme

World Health Organization

Outline of the presentation

- Background: steps since last MPAC recommendations
- Updated Objectives
- Ongoing preparations
- Participants list
- Outputs of consultation
- Development of call to action
- Proposed timelines

MPAC conclusions – March 2017


WHO Malaria Policy Advisory Committee (MPAC) meeting

MARCH 2017 MEETING REPORT

SUMMARY

Global call for action to ensure universal access to malaria diagnosis and treatment:

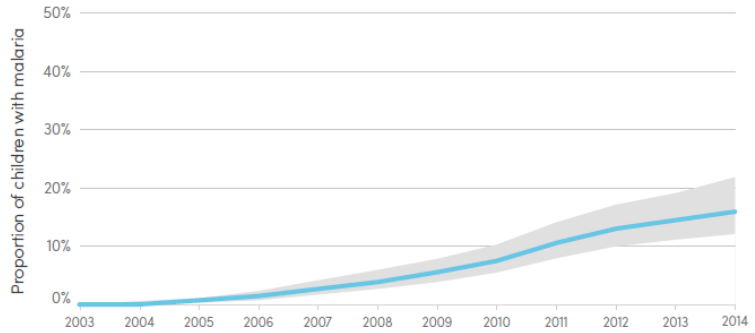
- There was wide support for this initiative and an acknowledgement that it should have been undertaken years ago. MPAC noted the importance of considering the broader health systems issues and how they can be taken into account when recommending a response. Data are limited but and current estimates suggest that large gaps in programme coverage remain.

MPAC conclusions – continued

- There was wide support for this initiative and an acknowledgement that it should have been undertaken years ago. MPAC noted the importance of considering the broader health systems issues and how they can be taken into account when recommending a response. The importance of not only improving access to diagnosis and treatment, but also ensuring that the results are reported through a strengthened routine surveillance system was highlighted.
- The methodological approach should consider distinguishing between broader health systems issues to be addressed and where much work has already been done from malaria-specific issues. Key issues include governance, integration of services compared to vertical programmes, cross-border issues, the ability to measure quality of care in addition to access to care, and working with the private sector. MPAC suggested close coordination with other groups that have worked on equity and access issues and looking at countries with good data to extrapolate lessons learned and distinguishing between high burden settings and elimination settings.
- MPAC noted that although much of this meeting was concerned with elimination, achieving better control in the areas where malaria is still a major burden is of critical importance and that this initiative recognizes this fact.

Access to malaria diagnostics and treatment

Figure 3.13 Estimated proportion of children aged under 5 years with confirmed *P. falciparum* malaria who received ACTs, sub-Saharan Africa, 2003–2014

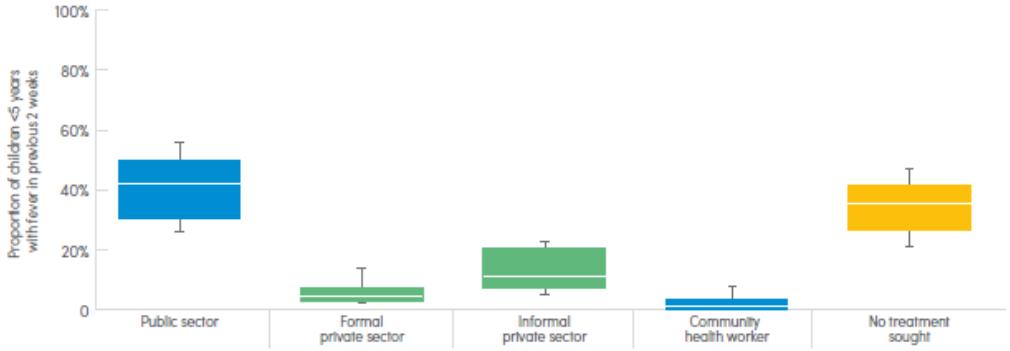


Source: Malaria treatment model from the Center for Applied Malaria Research and Evaluation (Tulane University), the Global Health Group (University of California, San Francisco) and the Malaria Atlas Project (University of Oxford).

World Malaria Report 2015

World Malaria Report 2016

Figure 4.1 Proportion of febrile children seeking care, by health sector, sub-Saharan Africa, 2013–2015. Sources: Nationally representative household survey data from demographic and health surveys, and malaria indicator surveys

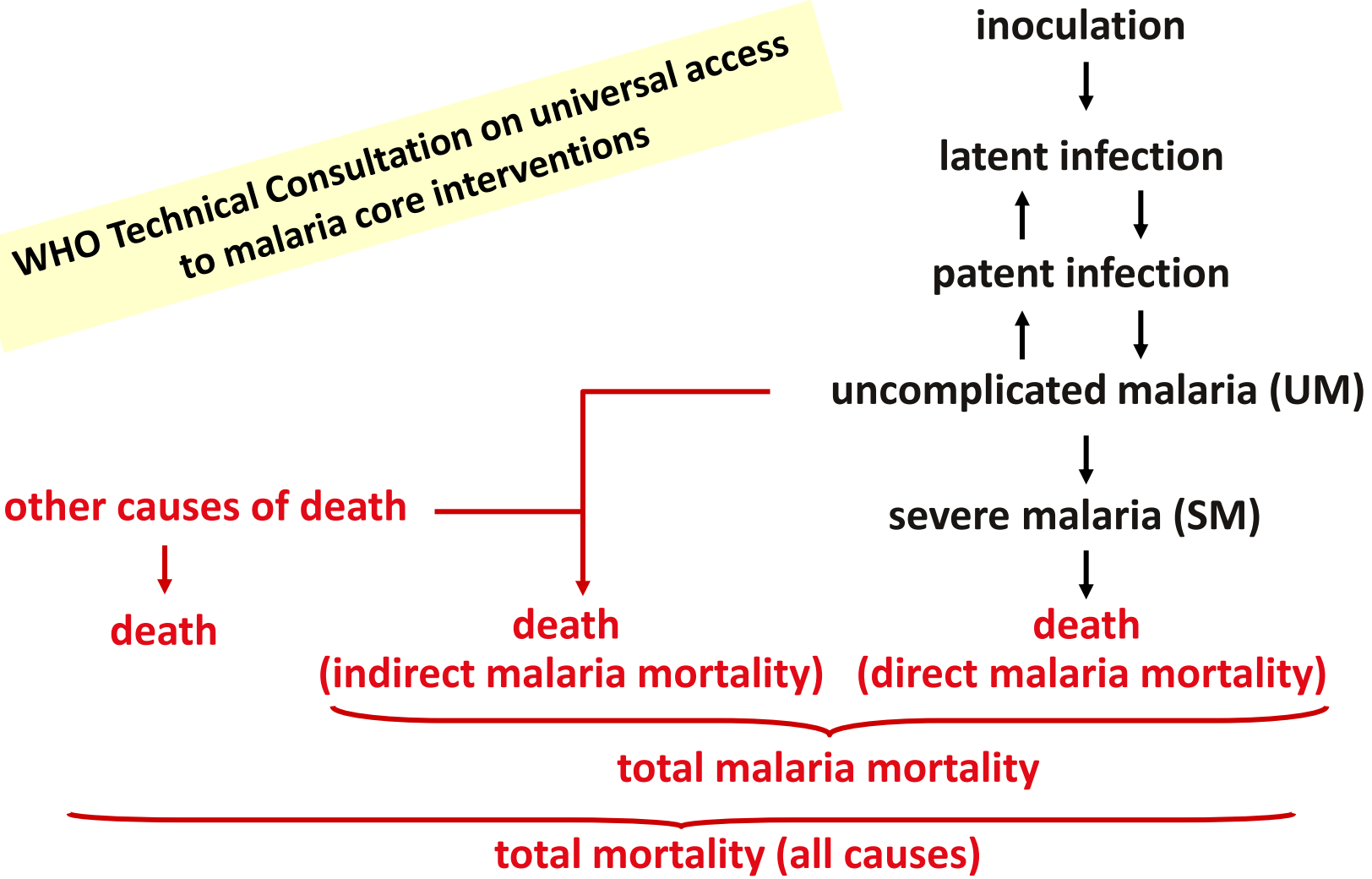


Considerations by WHO/GMP secretariat

- The initiative should align with the first pillar of the G*lobal Technical Strategy for malaria 2016–2030* adopted in May 2015 by the World Health Assembly on ensuring universal access to malaria prevention, diagnosis and treatment and reaching 2020 milestones of 40% reduction in malaria morbidity and mortality.
- Emerging analysis of 2016 data show that we are not on target in meeting the milestones set for 2020 in the Global Technical Strategy.
- 80% of total estimated cases is concentrated in 15 countries, which are, with only exception of India, all in Sub-Saharan Africa. Achieving the 2020 GTS milestones is only possible through universal access to WHO-recommended core interventions in these 15 high burden countries.
- A better understanding of relations between coverage gaps and mortality in high burden countries, why these gaps occur, who is affected by these gaps, and what strategies can be used to overcome them will be the basis for developing a global call to action for universal access to malaria core interventions to reach the milestones and targets outlined in the *Global technical strategy for malaria, 2016-2030*.

Focus on malaria and mortality

WHO Technical Consultation on universal access to malaria core interventions



WHO 98102

Revised objectives

1. To identify particular population sub-groups associated with high mortality and the impact of risk factors, including coverage gaps of core malaria interventions delivered through different platforms (public and private sectors, community programmes).
2. To characterize coverage to current malaria core interventions (long-lasting insecticidal nets, indoor residual spraying, intermittent preventive treatment of pregnant women, seasonal malaria chemoprevention and utilization of malaria diagnostic testing and treatment services), and identify bottle-necks in service provision (whether it is global supply, supply management, policy/regulations, population access to health facilities, availability of staff and equipment, uptake of services by the population etc.).
3. To review existing data sources and methods to estimate access to malaria core interventions and to provide recommendations for strengthening surveillance via routine HMIS, health facility and household surveys in high burden countries.
4. To identify the most effective strategies and enabling interventions to accelerate progress in reducing malaria mortality.
5. To agree on the focus of a global call to action and the core elements of a global response plan to be launched in April 2018, on World Malaria Day.

Preparatory work (ongoing)

Background papers for the WHO Consultation on universal access to malaria core interventions

1. Paper 1 - Child mortality in Africa and access to core malaria interventions
   The paper will present the analysis of relations between under 5 mortality and coverage of malaria core interventions, from a regional-based analysis of most recent household surveys (demographic and health surveys) as well as an individual level analysis from of data from household surveys in target countries. Results will be reviewed by a WHO ERG on 10-12 December 2017 and the outcome of this will be presented at the WHO consultation.

2. Papers 2, 3, 4 and 5 - Coverage gaps of malaria core interventions in high burden countries
   A series of papers will cover recent estimates of coverage of the core malaria interventions, based on multiple sources of data, and review the major non-financing determinants of access to the respective interventions and gaps affecting population groups at greatest risk, analysis, as appropriate delivery and uptake of services in the public sector, private sector, community based programs. The papers will be on: 1) vector control (long-lasting insecticidal nets and indoor residual spraying), 2) intermittent preventive treatment of pregnant women, 3) seasonal malaria chemoprevention and 4) malaria diagnostic testing and treatment.

3. Paper 6 - Economics of increasing access to malaria core interventions
   A review of the economics of access to malaria core interventions, by identifying (i) supply- and demand- side determinants of access and (ii) the strategies to address inefficiencies (availability, quality and affordability). Results from this working paper a standalone paper or combined to working papers 2-5.

Reviews outline and lead contributors

Proposed outline of the pre-reads for the "Malaria Call to action"

BOX – short description of the intervention and access[2] to it

Executive Summary

Background

- Rationale of the review, selection of high burden countries and timeframe (2010-2016)
- Brief description of timing for policy formulation, adoption by countries and implementation
- Expected impact of the intervention on malaria mortality and morbidity

Methodology

- Search methodology, data sources, data collation and analytic methods for gap analysis
- Methodology followed used for the review of programmatic experiences

Results

Part 1 – intervention coverage (Richard for VC, IPTp & case management, MMV for SMC)

- Target population and needs, including changes in the proposed time period [3]
- Trends in coverage by year from 2010 to 2016 (2013-2016 for SMC) [4]
- Identification of groups with poorest access to the intervention
- Quantitative analysis of non-financial determinants of poor access to the intervention

Part 2 – main programmatic determinants of access (Vector Works for VC, Malaria Consoritum and NMCP Cameroon for SMC, JHPIEGO for IPTp, F. Suleman & V. Perumal for case management) in the:

Public sector

- Rapid and efficient delivery of interventions and scale-up of coverage
- Effective interventions to increase demand and uptake by groups with poorest access

Private sector

- Rapid and efficient delivery of interventions and scale-up of coverage
- Effective interventions to increase demand and uptake by groups with poorest access

Community

- Rapid and efficient delivery of interventions and scale-up of coverage
- Effective interventions to increase demand and uptake by groups with poorest access

Discussion

- Opportunities to improve data collection and analysis to guide call to action
- Priority interventions to increase access among groups with poorest access

Conclusions and Recommendations

[2] Availability, affordability, quality and rationale use
[3] Presentation of changes in target population and needs for expanding interventions (e.g. SMC)
[4] For case management, data emerging from health facility surveys and household surveys will be compared.

- Paper 1 - Child mortality in Africa and access to core malaria interventions (Malaria Atlas Project, Oxford University – GMP/SEE)
- Paper 2 – Access to IRS and LLIN (TBI - GMP/VCU)
- Paper 3 – Non financial determinants of access to SMC (MMV and Malaria Consortium and NMCP manager of Cameroon – GMP/PDT)
- Paper 4 – Non financial determinants of access to IPTp (JHPIEGO – GMP/PDT)
- Paper 5 – Non financial determinants of access to malaria medicines and diagnostics (Durban University – GMP/PDT)
- Paper 6 - Financing determinants of access to IPTp, SMC, diagnostic services and antimalarial drugs (Institute of Development Studies – GMP/SEE)

Focus of the analysis

WHO Region	Country	Deaths	Cases	Pop at risk
AFR	Nigeria	110,885	61,181,846	160,681,975
AFR	Democratic Republic of the Congo	42,487	18,726,106	76,107,812
SEA	India	23,672	12,824,590	688,301,527
AFR	Uganda	12,367	8,519,052	39,032,383
AFR	Mozambique	15,179	8,329,604	27,977,863
AFR	Côte d'Ivoire	14,066	7,917,330	22,701,556
AFR	Mali	20,579	7,500,706	16,719,709
AFR	Ghana	13,357	7,303,048	27,409,893
AFR	Burkina Faso	14,631	7,047,531	18,105,570
AFR	Kenya	11,922	6,506,297	39,187,634
AFR	Cameroon	9,161	5,273,189	19,959,273
AFR	United Republic of Tanzania	16,992	5,266,342	46,251,913
AFR	Niger	10,479	5,213,799	14,625,853
AFR	Guinea	9,861	4,637,355	12,608,590
EMR	Sudan	3,471	1,376,502	37,599,497
SEA	Indonesia	1,943	1,274,342	48,803,949
EMR	Pakistan	736	1,029,231	120,182,485
WPR	Papua New Guinea	1,249	902,875	7,390,741
EMR	Somalia	2,119	696,082	8,138,725
AMR	Venezuela (Bolivarian Republic of)	218	227,826	3,328,565
AMR	Brazil	26	184,582	23,486,771
AMR	Peru	4	147,309	6,947,091
AMR	Colombia	18	79,331	6,448,460
WPR	Solomon Islands	51	38,694	577,755

Plans for the WHO Consultation

Proposed dates: 15 -18 January 2018

WHO Technical Consultation on universal access to malaria core interventions: method of work

- Analysis of current situation, determinants and risk groups, based on presentation and plenary discussion of the working papers, with the objective of completing the landscape analysis and documenting cost-effective scale-up strategies targeting the most vulnerable groups (Day 1 -2).
- Working groups on the identification of the most promising strategies to increase access to malaria core intervention in the high burden countries reflecting different regional/health system context (Day 3)
- Presentation of outcome of working groups, discussion and consolidation of the core elements of the WHO global call to action to increase access to malaria core interventions to meet the 2020 milestones set by the Global technical strategy for malaria (Day 4)

List of participants

1. Representatives of relevant MOH programs (malaria, community services, surveillance and central medical stores) from multiple malaria endemic countries from all WHO Regions. One participant per country will be selected in consultation with all RMA, from countries accounting for 80% of the global malaria burden, plus additional high burden countries outside Africa.
2. Representatives of Roll Back Malaria Secretariat and of the relevant RBM working groups, notably on vector control, malaria in pregnancy, case management and advocacy and awareness.
3. Representatives of main malaria technical agencies, WHO Collaborating Centers and NGOs working with MOH programs on improving access and reporting on core malaria interventions.
4. Representatives of main funding agencies, foundations and NGOs working with MOH programs on improving access and reporting on malaria diagnostic and treatment services, including in the private sector.
5. Representatives of research institutions which have contributed to the analytic work on gap analysis and strategies on improving access to core malaria interventions in high burden countries.

End product of the WHO Consultation

- The Rapporteur will prepare a meeting report and based on the consensus emerging from the meeting will draft the text for the global call to action to ensure universal access to core malaria intervention in high burden countries.
- The call to action should be a written document of max 4 pages in length, using formal and technical language, including a consultative process for partners to sign on and add their logos to the end product, based on the consultative process set out before and during the meeting. The document will includes an issue overview, rationale, goals, and recommended actions that are linked to individual target audiences. The communications package for world malaria day 2018 on this should include a press release, social media toolkit, messaging, and other materials for partners to promote dissemination and show support.
- After review by all participants attending the meeting, WHO GMP SMG and WHO RMAs, the latter will be submitted for review and endorsement to the Malaria Policy Advisory Committee in March 2018 before dissemination at World Malaria Day, on 25 April 2015.

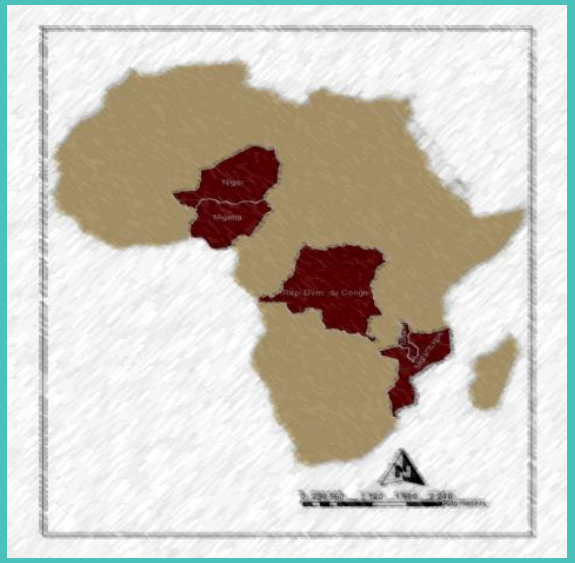
Proposed timelines

Activity	Timeline
Analysis of U5 mortality in Africa	September – November 2017
Preparation of review papers	August – November 2017
ERG review of mortality analysis	10-12 December 2017
Finalisation pre-reads for WHO consultation	December 2017
WHO Technical Consultation	15-18 January 2018
Initial draft of technical report and Call to Action	mid-February 2018
MPAC review of technical report and Call to Action	March 2018
Launch of technical report and Call to Action	25 April 2018
Dissemination to WHO Member States	May – July 2018

Discussion

The RAcE report: endline results

Rapid Access Expansion Programme



Malaria Policy Advisory Committee Meeting

18 October 2017

Global **Malaria** Programme

World Health Organization

Child mortality in sub-Saharan Africa

- In 2015 there were 5.9 million deaths of children under five globally1
- Half of all child deaths (49.6%) occurred in sub-Saharan Africa
- 1.74 million (30%) of those deaths were from malaria, pneumonia and diarrhoea
- Coverage of life saving interventions, especially in sub-Saharan Africa is still unacceptably low due to inaccessible or poor quality of care

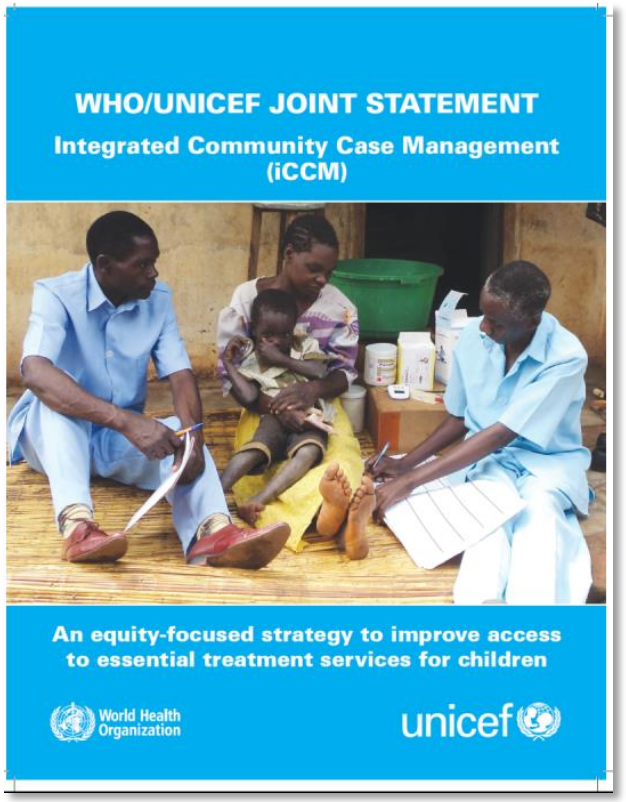
1. Lancet 2016

Integrated Community Case Management (iCCM)

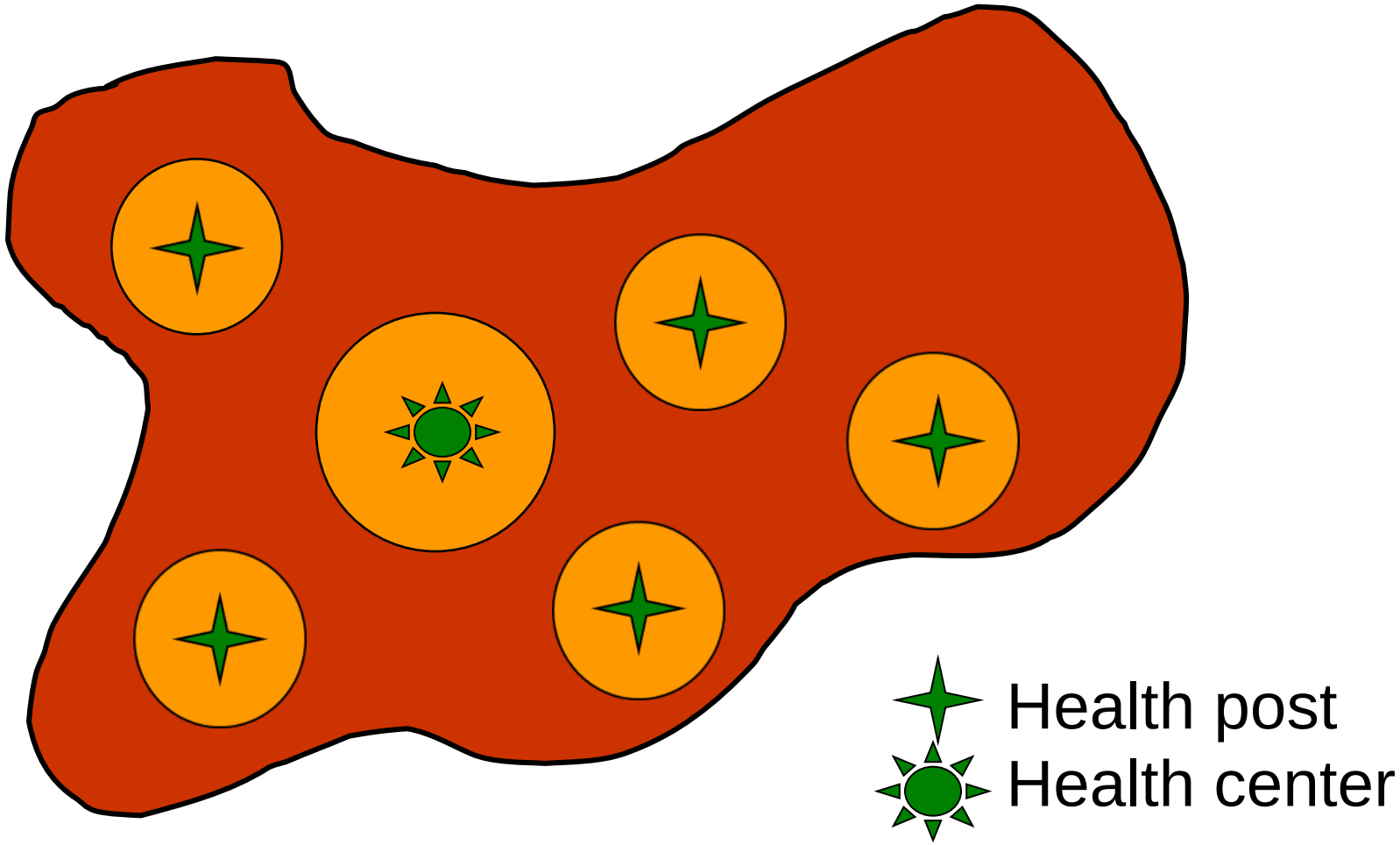
ICCM is a proven strategy to significantly reduce mortality from malaria, pneumonia and diarrhoea

WHO/UNICEF recommends iCCM

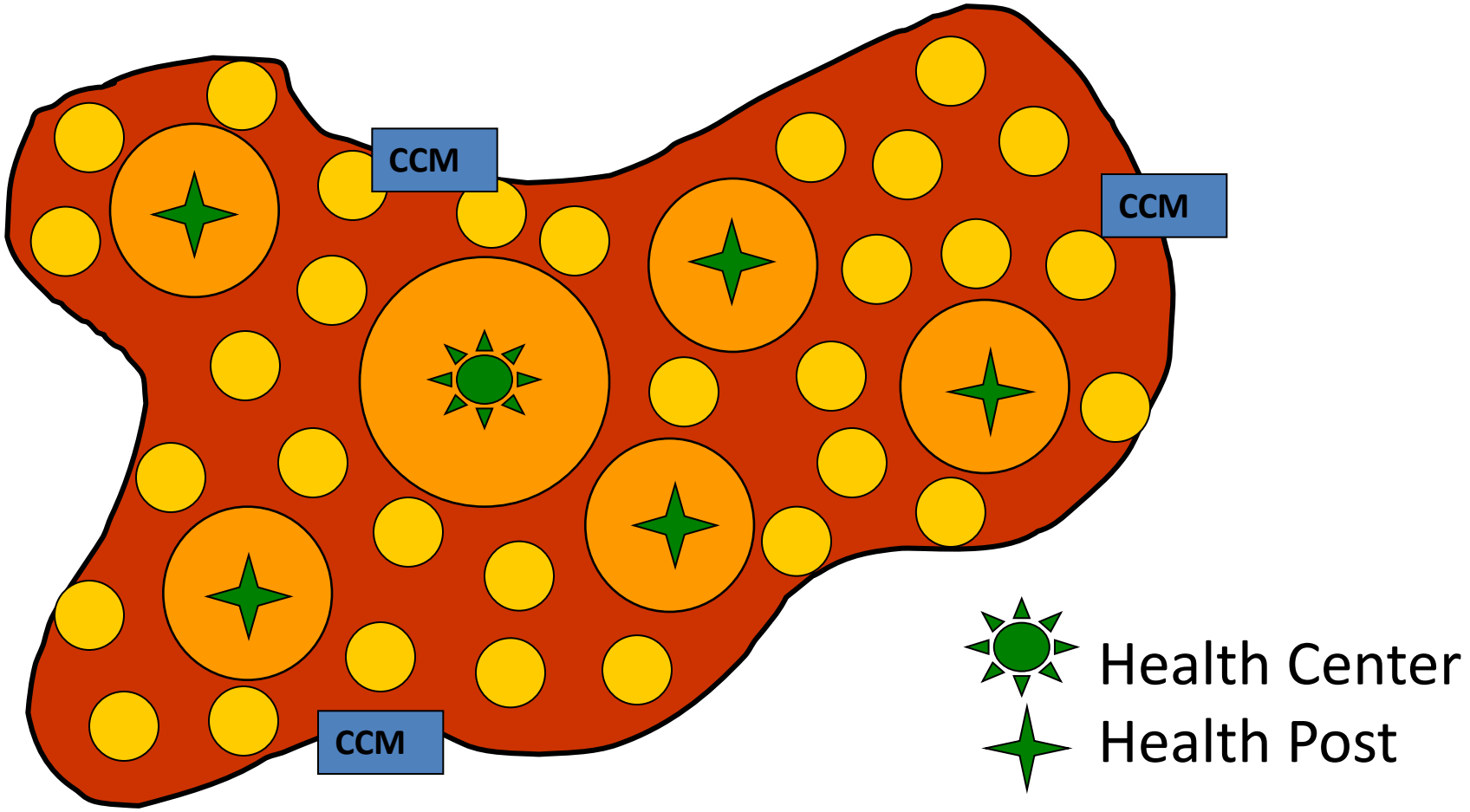
"Appropriately trained and equipped community health workers, provided with the necessary system supports, can deliver iCCM for malaria, pneumonia and diarrhoea as an effective intervention that increases access to and availability of treatment services for children."



ICCM targets remote and vulnerable populations



ICCM brings care closer to children



Rapid Access Expansion Programme (RAcE)

WHO-Global Malaria Programme, funded by Global Affairs Canada from April 2012 to June 2018 to:

1. Contribute to the reduction of child mortality by increasing access to treatment for common childhood illnesses in five African countries; and
2. Stimulate policy updates and catalyze scale-up of iCCM.

Overview

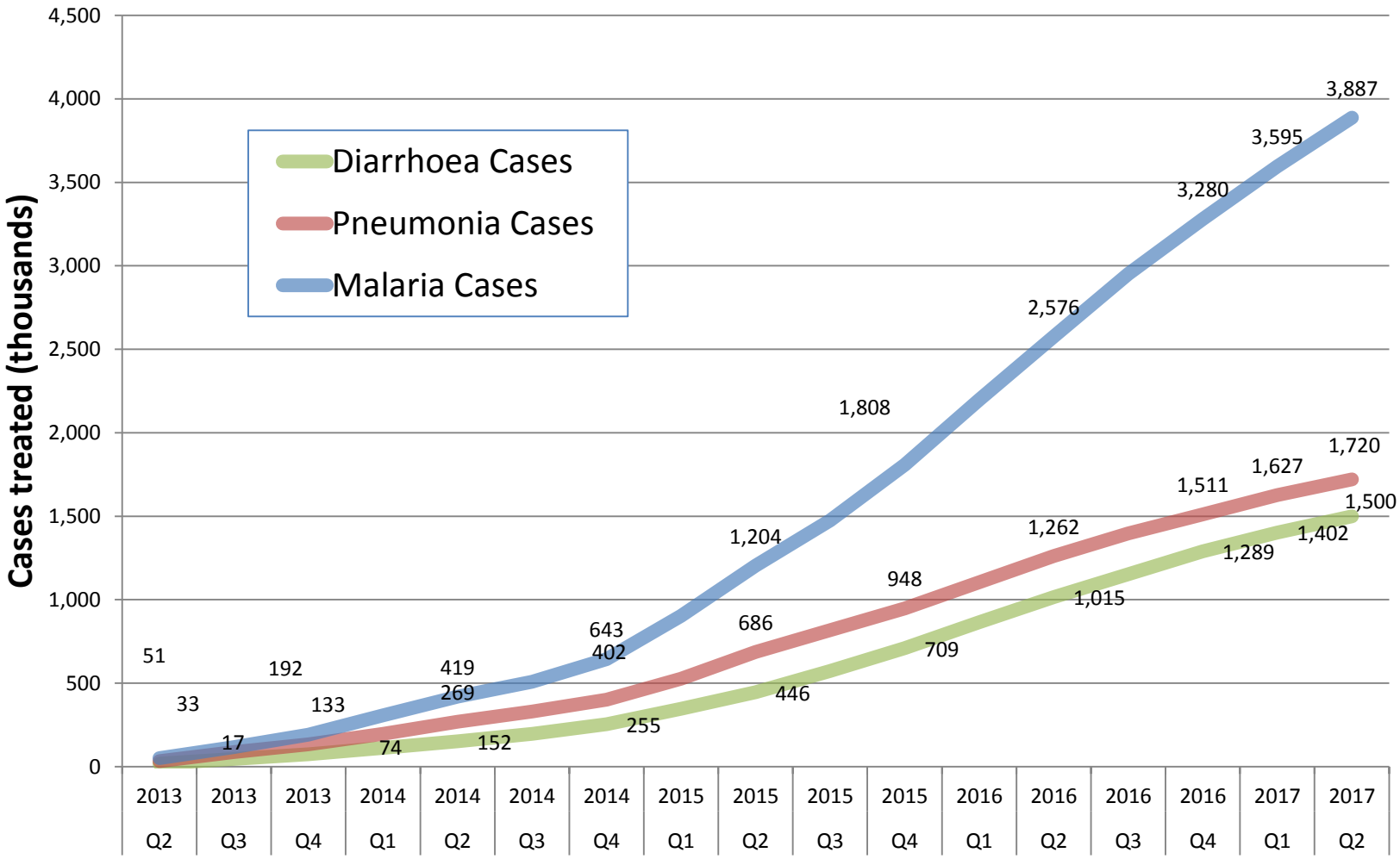
- **Country selection criteria:** high disease burden, enabling policy, commitment by MoH, potential for scale-up
- **NGO selection and review:** independent Project Review Panel
- Access to malaria (RDTs, ACT), pneumonia (ARI timers, amoxicllin), and diarrhea (ORS, zinc) case management extended to 1.5 million children

Country	NGO Partner	Number of Children Covered
Democratic Republic of the Congo	International Rescue Committee	150 000
Malawi	Save the Children	386 802
Mozambique	Save the Children	319 250
Niger	World Vision	230 833
Nigeria – Abia State	Society for Family Health	407 057
Nigeria – Niger State	Malaria Consortium	

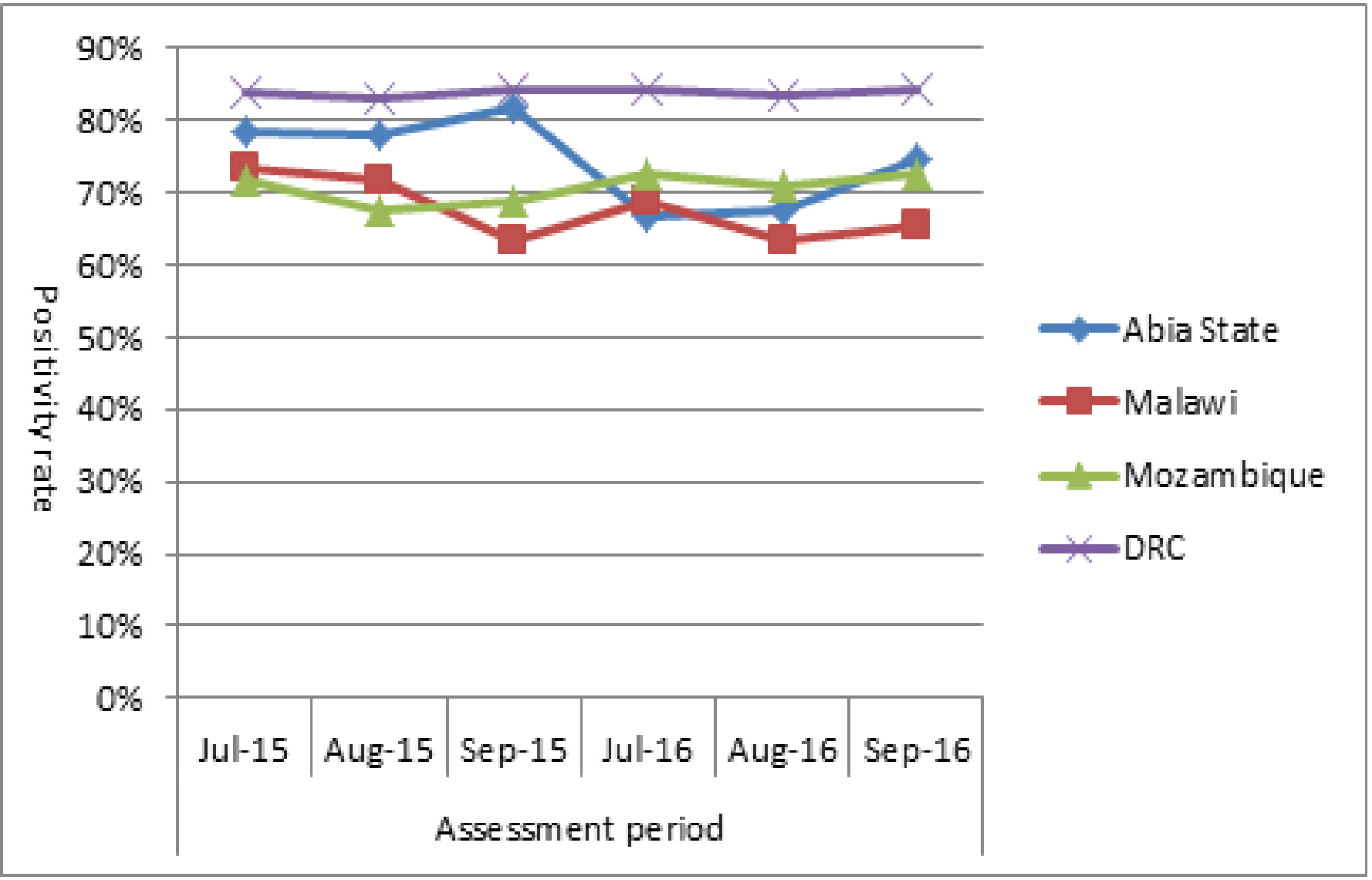
Characteristics of community health workers in RAcE sites

Country	Community health worker	Trained
Democratic Republic of the Congo	*Relais communautaires* (ReCos): volunteers selected by community members	1671
Malawi	*Health Surveillance Agents* (HSAs): paid MOH employees	1121
Mozambique	*Agentes polivalentes elementares* (APEs): : MOH , incentivized by partners	1470
Niger	*Relais communautaires*: volunteers selected by community members	1426
Nigeria	*Community-oriented resource persons* (CORPs) : volunteers selected by community members	Abia State – 1351 Niger State - 1320

RAcE-supported CHWs have treated more than 7 million cases



Malaria positivity rates in RAcE sites



Results

1. Household survey – care seeking and treatment coverage
2. Evaluation - plausible contribution of RAcE on < 5 mortality

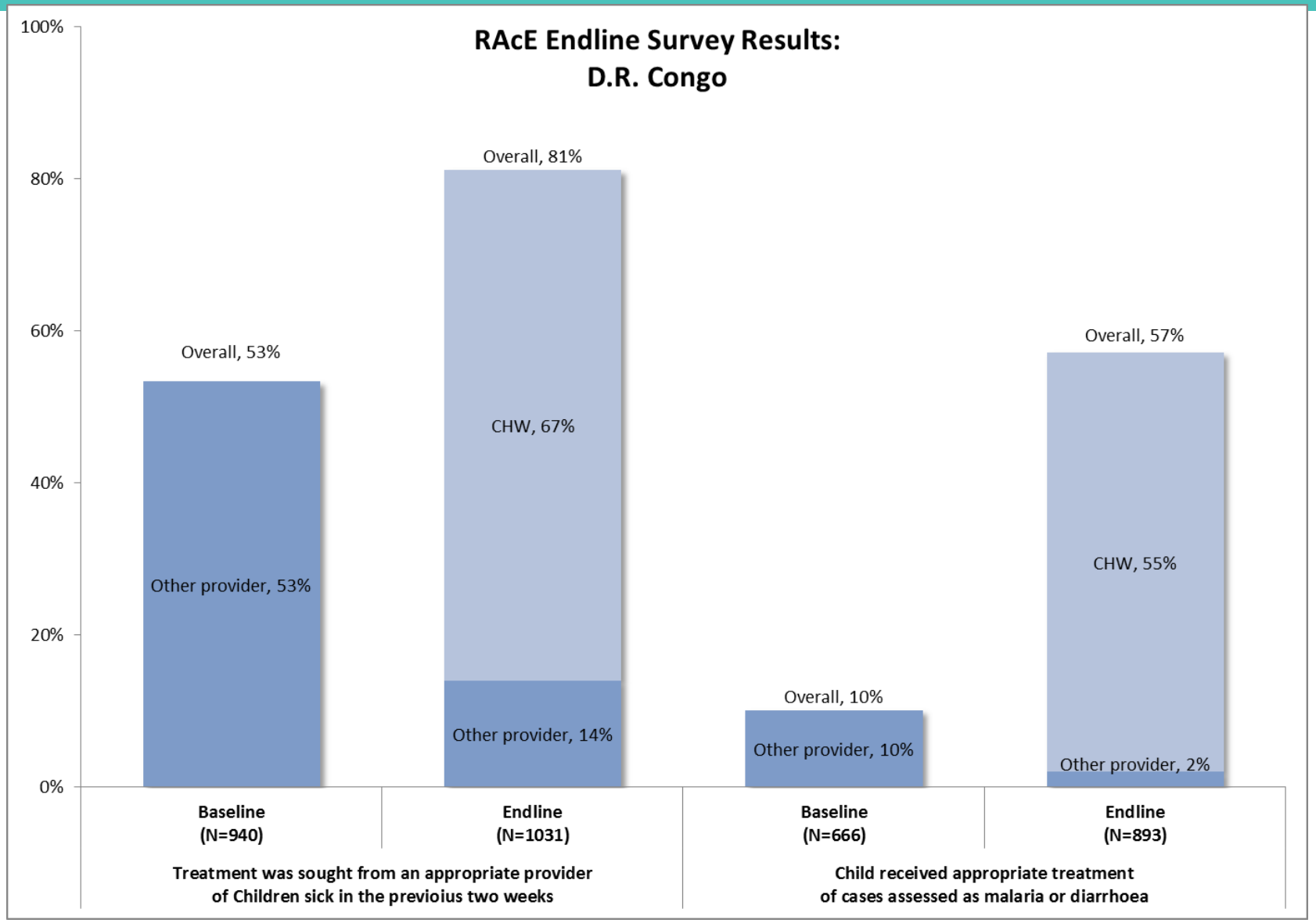
Household survey objectives

- The objective of the RAcE endline household survey was to assess caregiver knowledge, attitudes, and practices related to pneumonia, diarrhea, and malaria in the RAcE intervention areas.
- The household survey collected 21 key indicators related to caregiver knowledge of CHWs and child illnesses; caregiver perceptions of CHWs; and sick child care-seeking, assessment, treatment, referral adherence, and follow-up.
- The survey also collected information on household and caregiver characteristics and household decision-making.

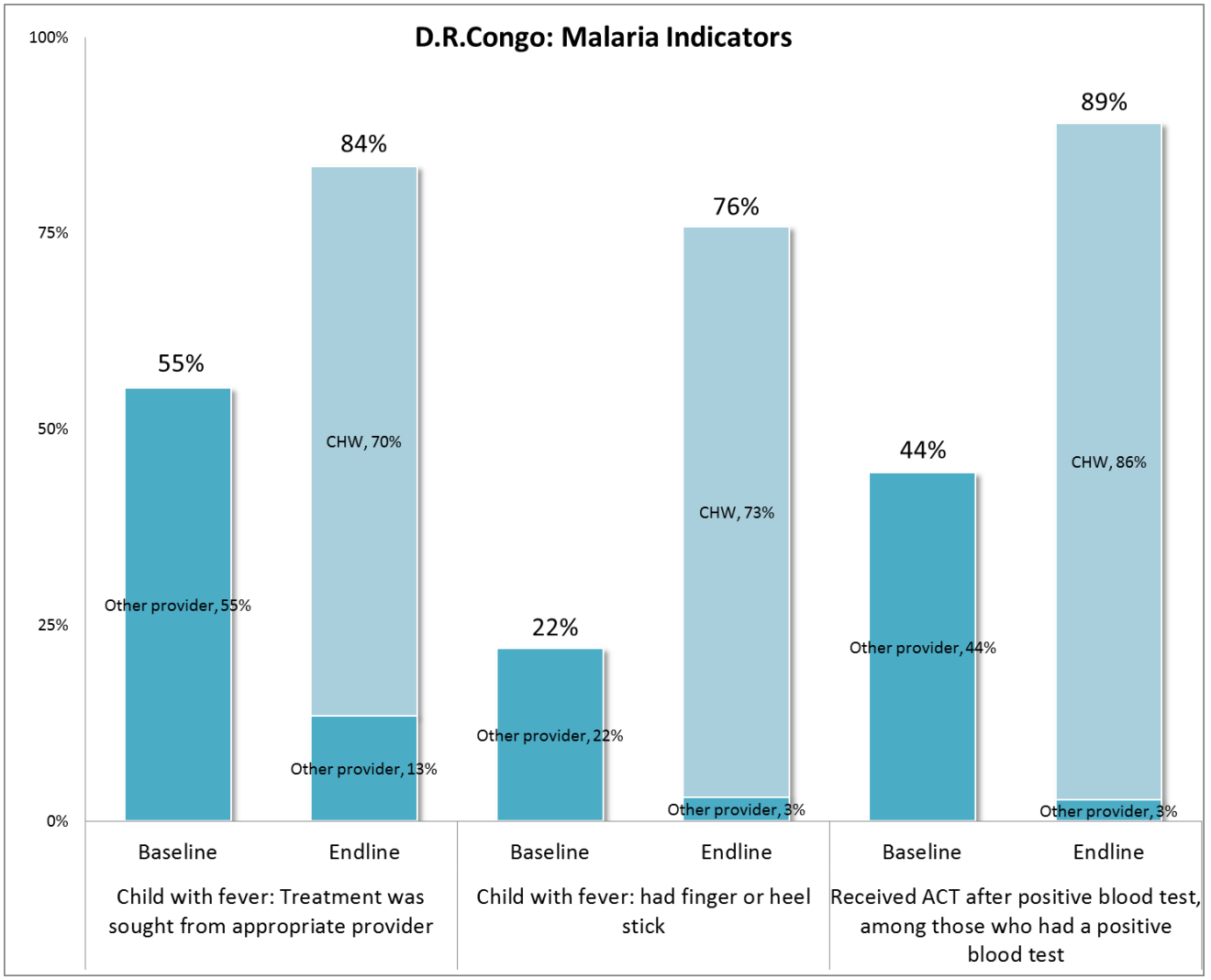
Survey design – overview

- Cross-sectional cluster survey: 30 clusters
- Sample size: 900 illness cases total - 30 sick child cases per cluster (10 per illness)
- Sampling Frame
  - Entire RAcE project area = iCCM-eligible areas located ≥ 5 km from a health facility
- Target population
  - Primary caregivers of children who were sick with diarrhea, fever, or cough with rapid breathing in the two weeks preceding the survey.
- Multi-stage cluster sampling to obtain a sample representative of the project area. Three stages:
  - Randomly selected clusters using probability proportional to size sampling
  - Randomly select the first house in each cluster
  - Randomly select respondents in each household (if multiple eligible)

Democratic Republic of the Congo

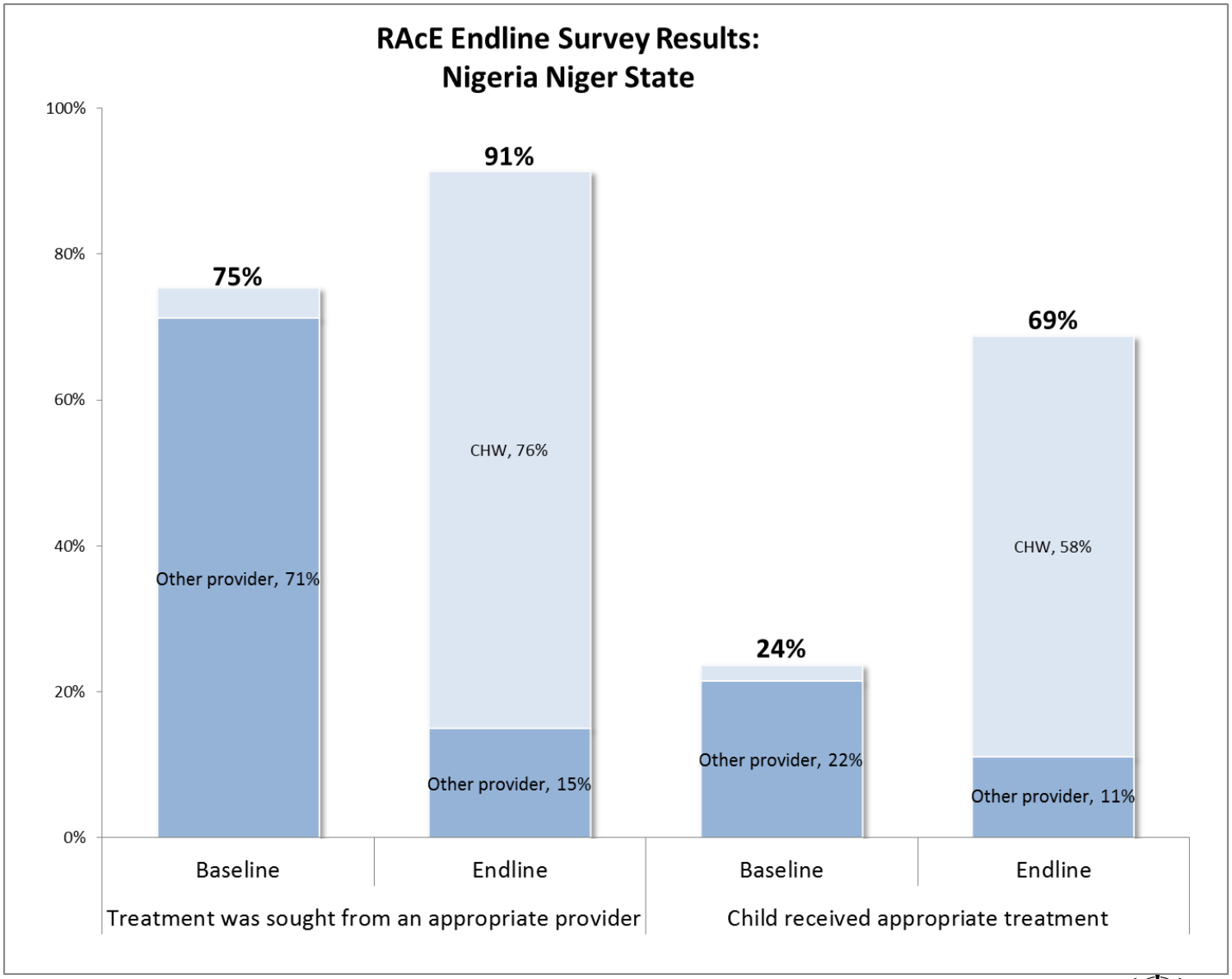


Democratic Republic of the Congo: malaria

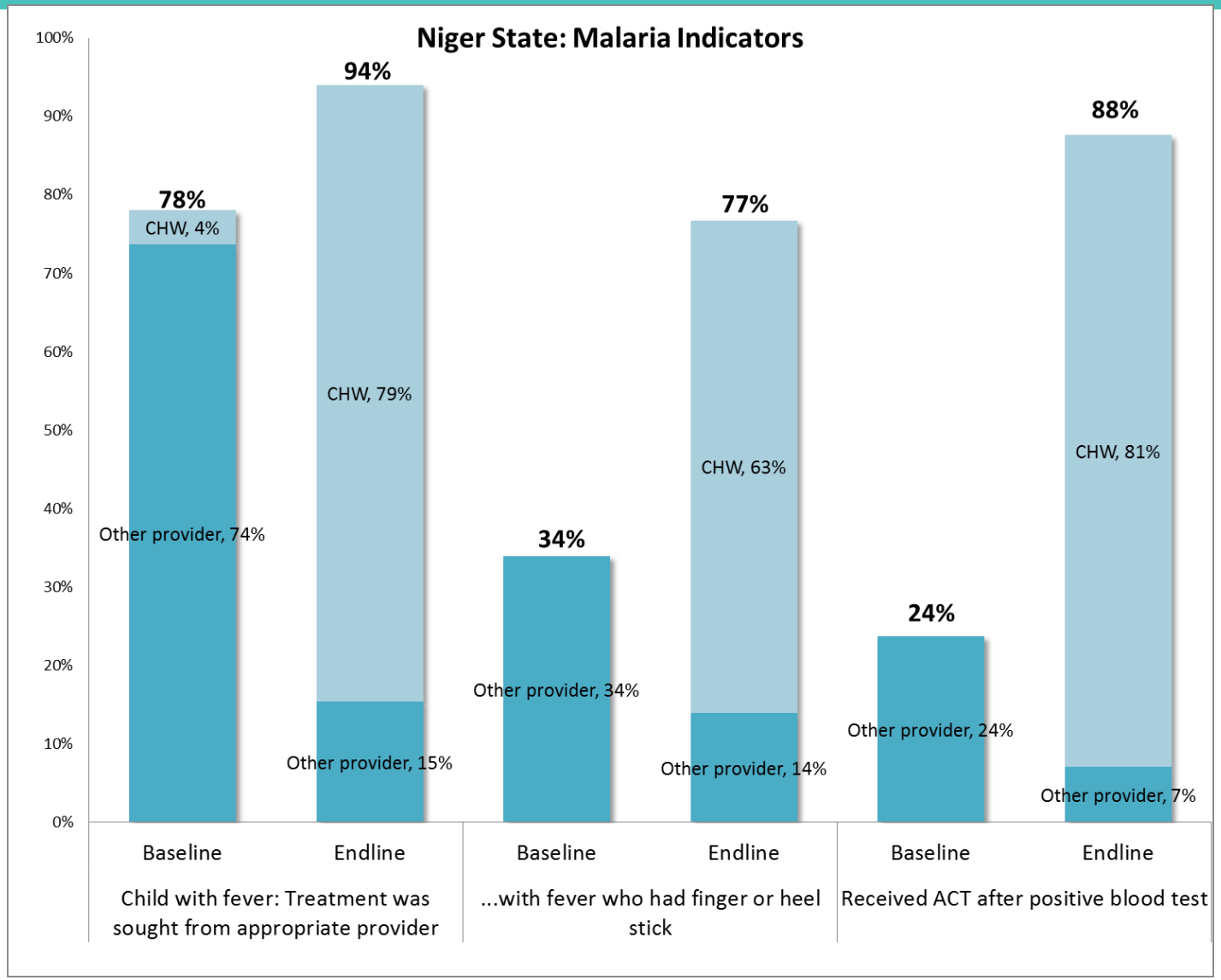


Of those who received an ACT, 97% received it from a community health worker

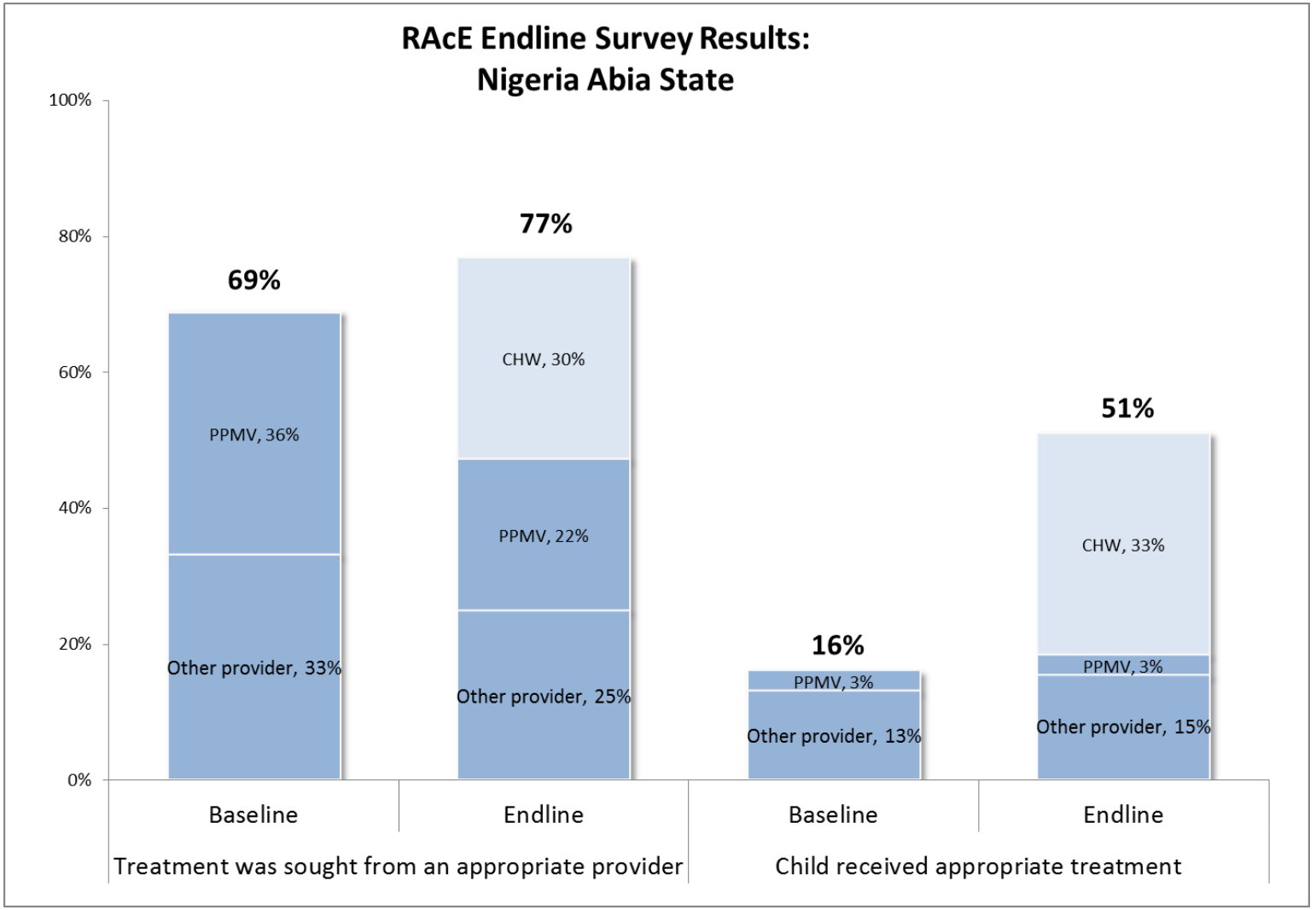
Nigeria - Niger State



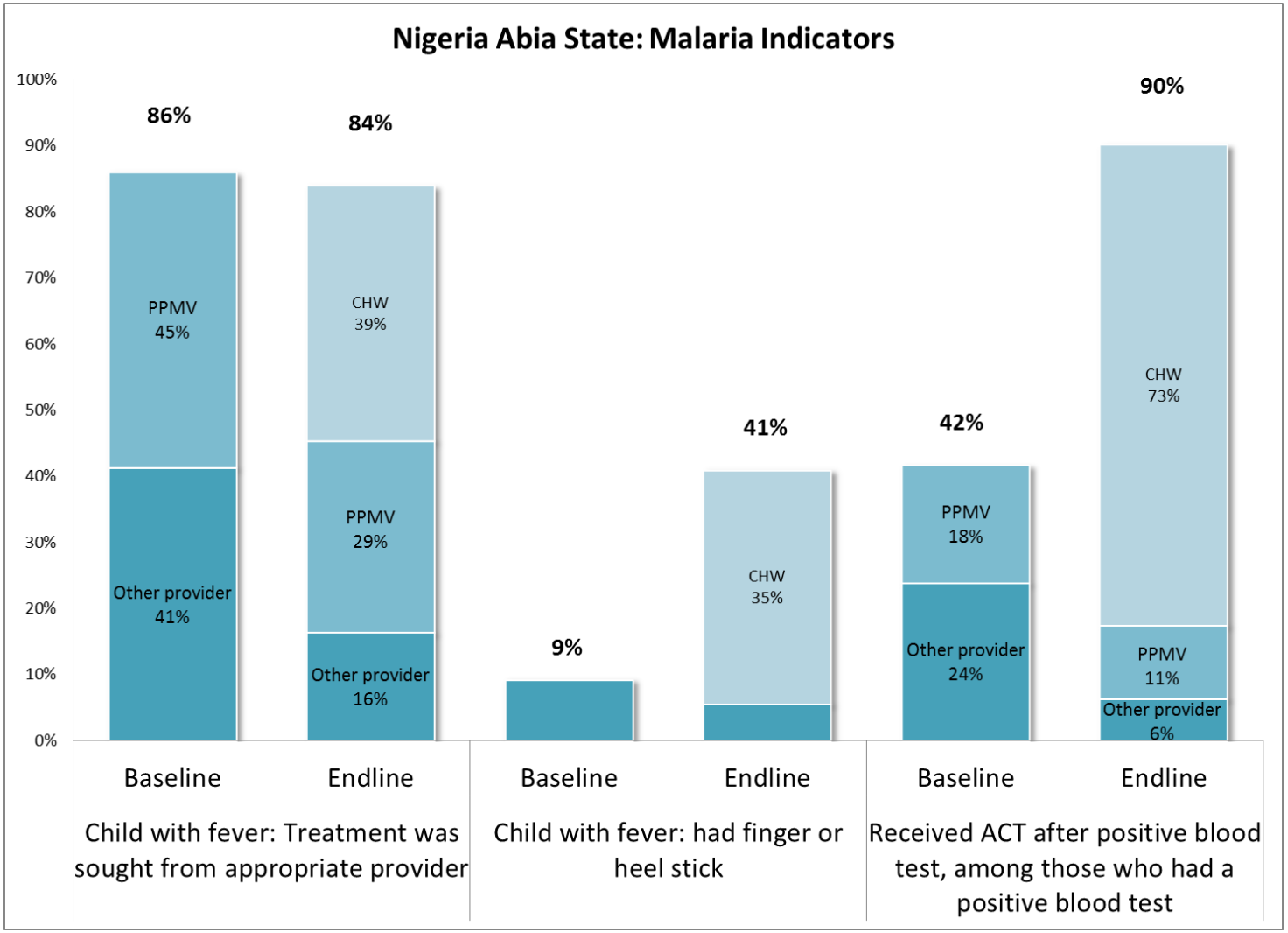
Nigeria - Niger State: malaria



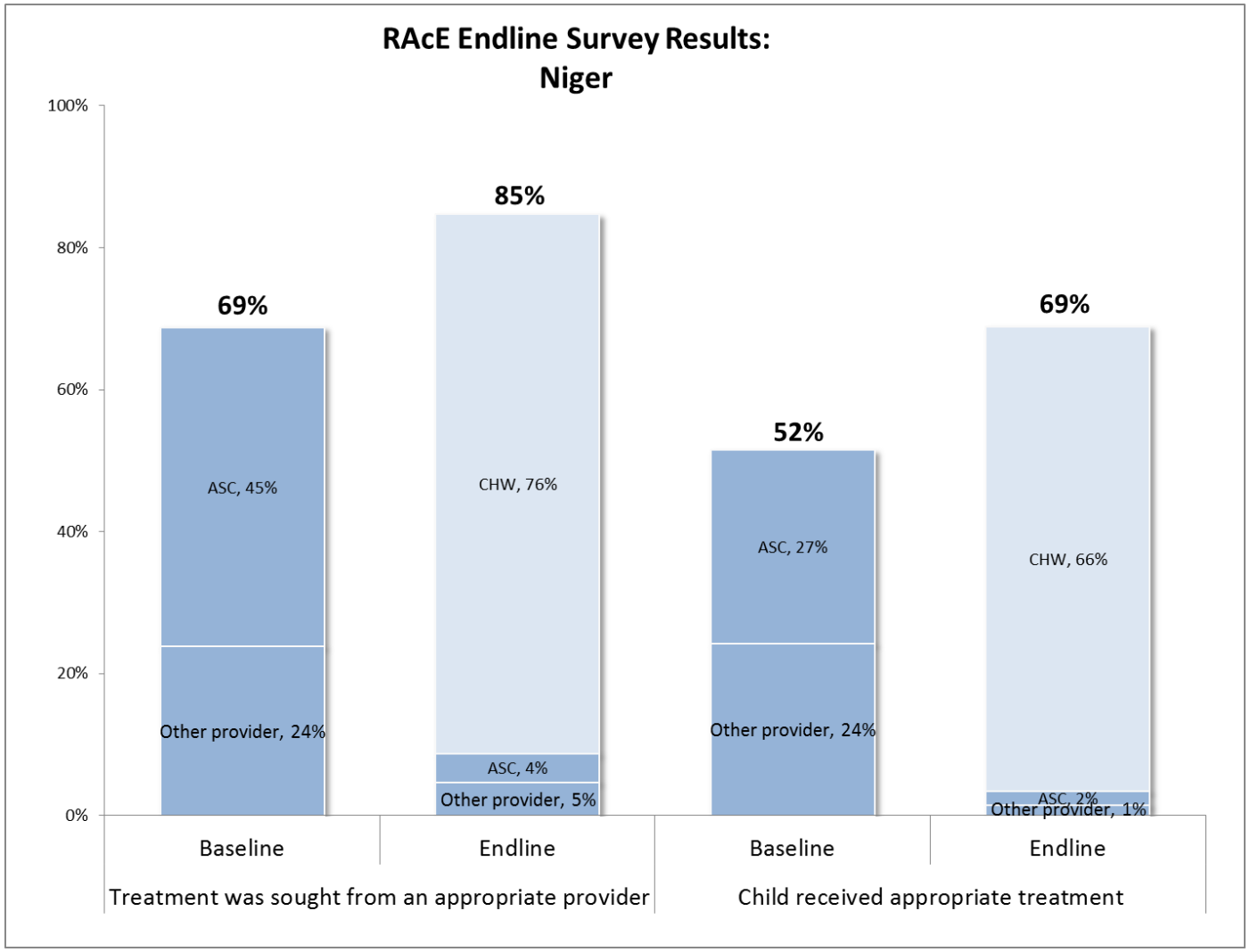
Nigeria - Abia State



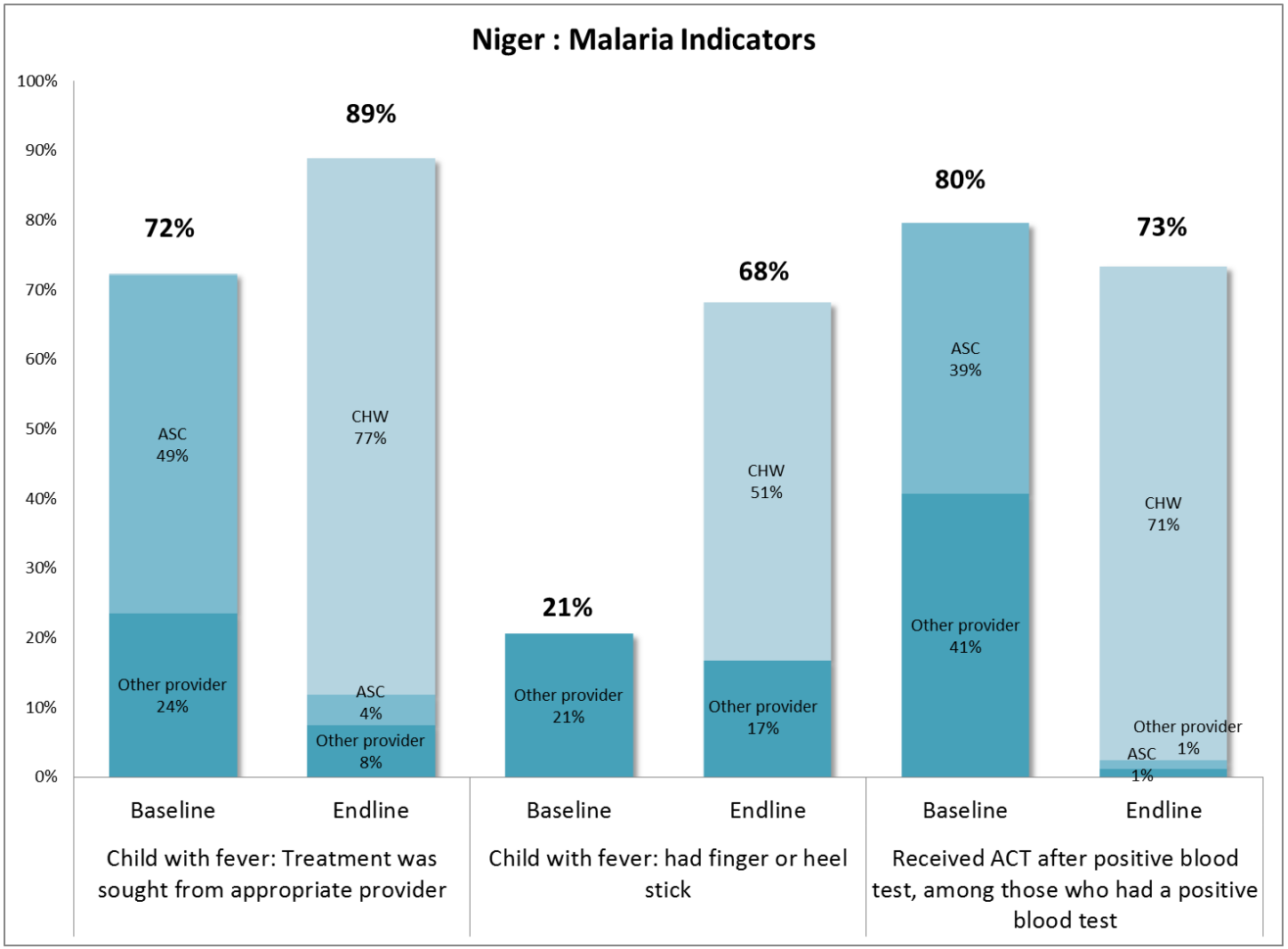
Nigeria – Abia State: malaria



Niger


RAcE Endline Survey Results:
Niger
100%
80%
60%
40%
20%
0%
69%
85%
52%
69%
ASC, 45%
Other provider, 24%
CHW, 76%
ASC, 4%
Other provider, 5%
ASC, 27%
Other provider, 24%
CHW, 66%
ASC, 2%
Other provider, 1%
Baseline
Endline
Baseline
Endline
Treatment was sought from an appropriate provider
Child received appropriate treatment

Niger: malaria



Evaluation of the plausible contribution on RAcE on child mortality

- Objectives
- Method
- Initial Results: Niger, Nigeria, DRC

Evaluation objectives

- Determine whether the project goal of improved diagnostic and treatment coverage has been reached in RAcE project areas; and
- Demonstrate the plausible contribution of RAcE to any changes in treatment coverage and estimated mortality change

Estimate the change in child mortality using the Lives Saved Tool (LiST) (1)

- Computer-based software for modeling maternal and child mortality
- LiST calculates impact using an algorithm that combines change in intervention coverage, effectiveness of the intervention, and the affected fraction
  - Effectiveness is the percent of deaths due to a specific case that are reduced by the intervention
  - Affected fraction is proportion of cause-specific deaths that can be averted by the specific intervention
- Effectiveness and affected fractions are determined by the Child Health Epidemiology Reference Group

Estimate the change in child mortality using LiST (2)

- The baseline RAcE model was created in the LiST using:
  - The total population in the RAcE project areas at baseline (start of project)
  - DHS and/or HMIS data
  - RAcE baseline household survey data for treatment of pneumonia, fever with ACT within 48 hours, treatment of diarrhea with ORS, and treatment of diarrhea with zinc
- Endline (2016) data points inputs were:
  - RAcE endline household survey data
  - DHS, projected DHS, or HMIS data
- Values were linearly interpolated from 2013 to 2016 for each indicator.
- The model considers the coverage increase (difference) from baseline to endline in the algorithm to estimate impact on mortality

Estimate the change in child mortality using LiST (3)

- Model outputs:
  - Under-five mortality rates for each year.
  - Number of lives saved per year, among children under 5 years of age
  - Number of lives saved per year by intervention
- Lives saved by malaria, pneumonia, and diarrhea treatment were adjusted proportionally to the percentage of cases treated by CHWs

Estimated child lives saved per year by interventions

Intervention	2013	2014	2015	2016	Total
	Estimated lives saved				
Preventive					
Vitamin A supplementation	0	-8	-17	-27	-52
Improved water source	0	-3	-6	-9	-18
Improved sanitation—Utilization of latrines or toilets	0	1	2	3	6
Hygienic disposal of children's stools	0	1	3	5	9
Insecticide-treated net/indoor residual spraying—Households protected from malaria	0	-17	-34	-52	-103
Complementary feeding to prevent wasting	0	0	0	0	0
Vaccines					
H. influenzae b vaccine	0	64	88	102	254
Pneumococcal vaccine	0	0	18	46	64
Measles vaccine	0	3	9	11	23
Curative after birth					
Case management of premature babies	0	0	-1	-1	-2
Case management of neonatal sepsis/pneumonia	0	-1	-2	-3	-6
ORS	0	60	119	178	357
Antibiotics for treatment of dysentery	0	1	2	4	7
Zinc for treatment of diarrhea	0	16	33	49	98
Oral antibiotics for pneumonia	0	81	158	233	472
Vitamin A for treatment of measles	0	-13	-26	-39	-78
ACTs for treatment of malaria	0	77	158	245	480
Cotrimoxazole (HIV)	0	0	0	1	1
ART	0	0	0	0	0

Estimated lives saved (LiST analysis)

RAcE sites	Under 5 mortality rate (deaths per 1,000 live births) 2013 and 2016	% change between 2013 and 2016	Lives saved through increases in intervention coverage	Estimated lives saved by CHW-provided treatment	% lives saved by CHW treatment	Under 5 mortality reduction attributable to iCCM
DRC	121 to 103	18%	2182	1,728	79%	**14%**
Niger	137 to 120	14%	2290	965	38%	**6%**
Nigeria Abia	131 to 115	14%	1815	967	53%	**7%**
Nigeria Niger	100 to 86	17%	1649	1,062	64%	**11%**

Conclusions

- RAcE has contributed to the evidence that iCCM is an effective strategy to save lives
- Effective iCCM is an integral part of the primary health system
- The strength of the intervention lies in the availability of a trained CHW in the village when a child falls ill
- Caregivers, communities and peripheral health staff place a high value on the intervention
- The LiST tool provides valuable information on the impact in a certain context, but must be interpreted carefully
- Quality of care is a major benefit, but not measured by the LiST tool

Malaria Threats Map

Malaria Policy Advisory Committee Meeting

Geneva, Switzerland

18 October 2017

Global **Malaria** Programme

World Health Organization

Overview

1. Scope
2. Progress
3. Status
4. Data overview
5. Demonstration
6. Plans

Scope

Biological challenges to malaria control and elimination

Vector insecticide resistance
(bioassays, mechanisms)

hrp2/3 gene deletions
(single and mixed)

Antimalarial drug efficacy and drug resistance
(therapeutic efficacy studies (TES), molecular markers)

Progress

Updates since MPAC March 2017

- Extra data ie. 2016/2017
- Significant refinement of:
  - Data filters
  - Dynamic legends
  - Symbols ie. toggle for country/site data
  - Popup content ie. text, tables and figures
  - Geographies navigator
- Formulated explanatory text
- Translated all content ie. French, Spanish

Status

As of 18 October 2017

- 98% completed
- Pending: minor updates to functionality and aesthetics
- Launch: anticipated by end October 2017

Data overview

GMP Databases

Vector insecticide resistance
1949 – 2017
bioassays (all), mechanisms
91 countries = 29,137 tests

***hrp2/3* gene deletions**
1996 – 2017
suspected, confirmed
26 countries = 131 survey areas

Drug efficacy & drug resistance
2004 – 2017
TES results, molecular markers
78 countries = 2,133 studies

Malaria Threats Map

Vector insecticide resistance
2010 – 2017
bioassays (standard), mechanisms
83 countries = 18,712 tests

***hrp2/3* gene deletions**
1998 – 2017
confirmed
24 countries = 125 survey areas

Drug efficacy & drug resistance
2010 – 2017
TES results, molecular markers
71 countries = 1,006 studies

- **Bioassays** (standard only)
  - discriminating concentration
  - intensity concentration
- **Mechanisms** (biochemical, molecular, synergist-insecticide assays)
  - metabolic - mono oxygenases, esterases, GSTs
  - target-site mutations - *kdr* , *Ace1R*

Data overview

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- **Type of deletion**
  - *pfhrp2*
  - *pfhrp2 and 3*
- **Clinical status**
  - symptomatic
  - asymptomatic
  - mixed or unknown

- **Survey type**
  - Cross sectional
  - Convenience/screening
  - Case report
  - DHS

Across surveys, the criteria for selecting samples to test for *pfhrp2/3* deletions varies. Percentage of samples tested with deletions is presented

Data overview

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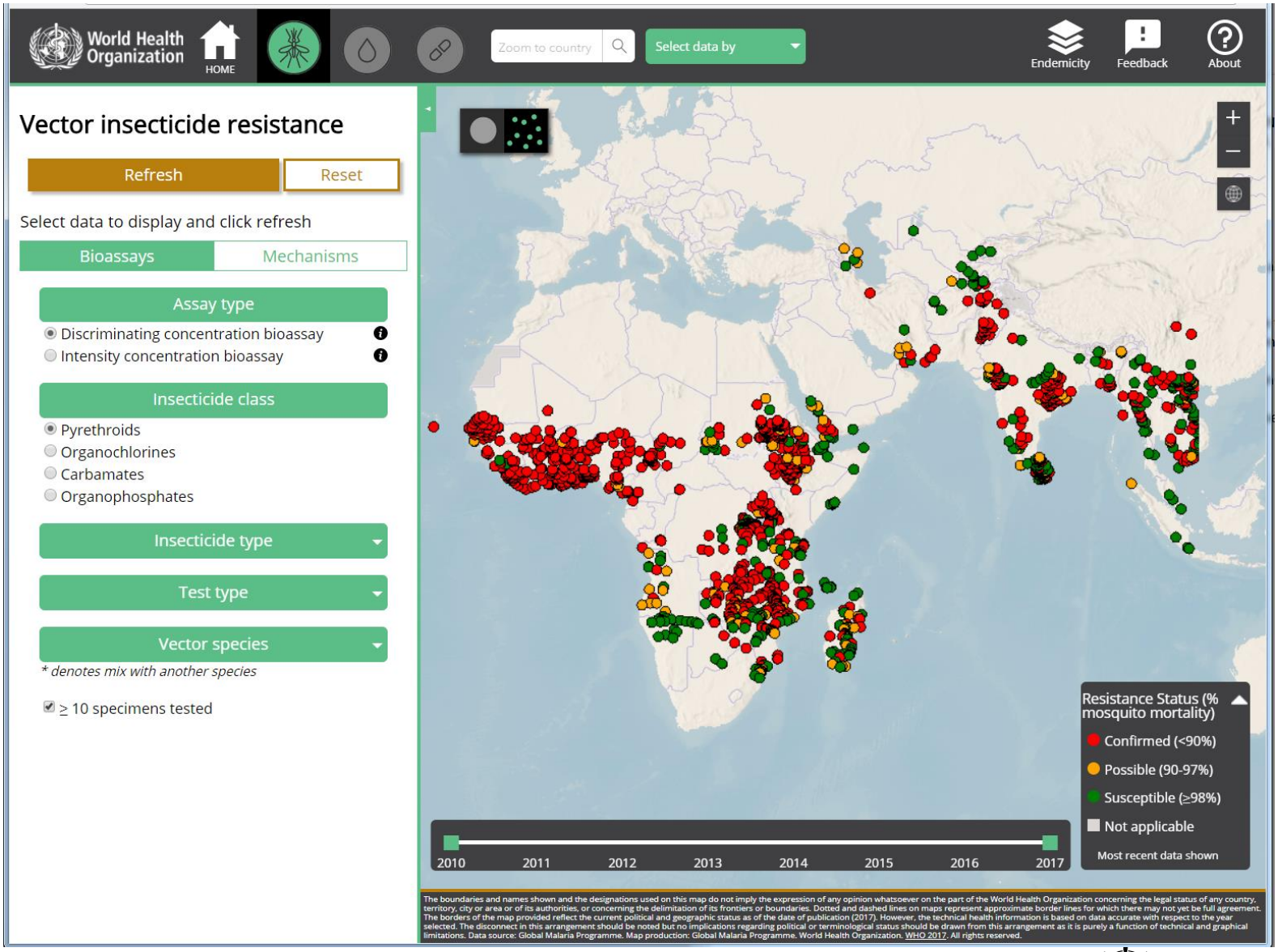
71 countries = 1,006 studies

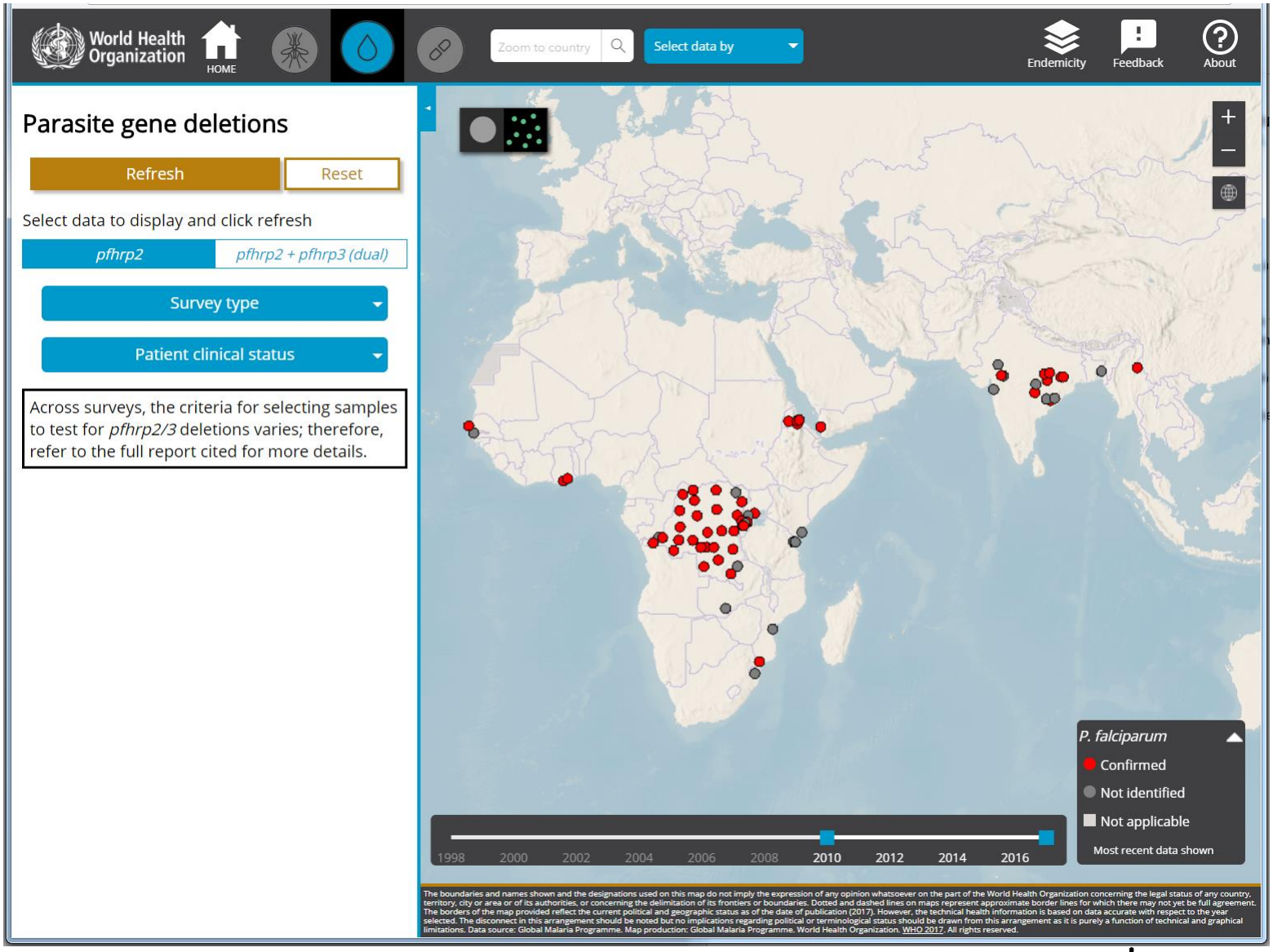
- **Therapeutic efficacy studies**
  - *P. falciparum*
  - *P. vivax*
- **Molecular marker studies**
  - K13
  - *Pfcrt* (next version)

Live demonstration

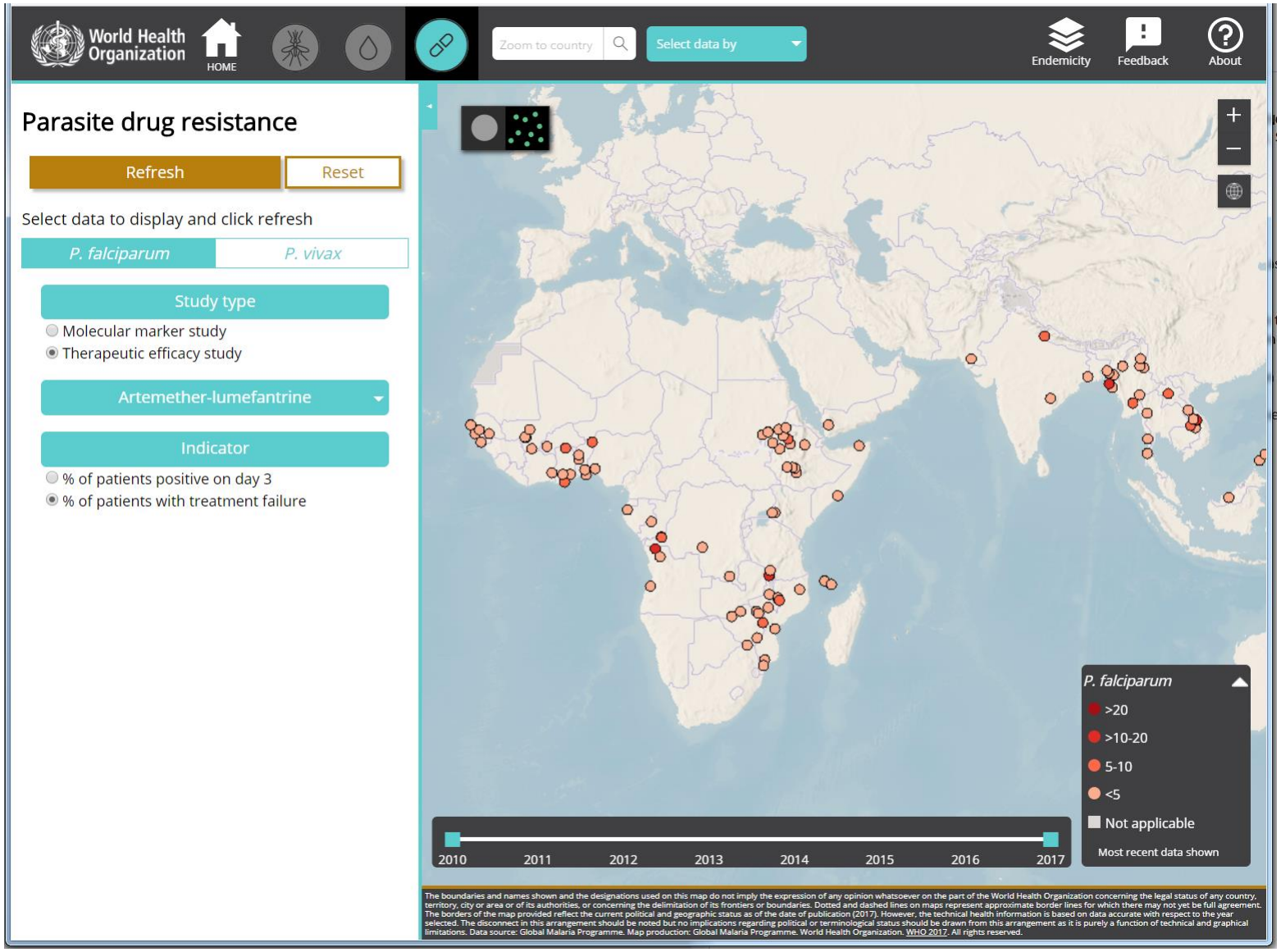
Live demonstration



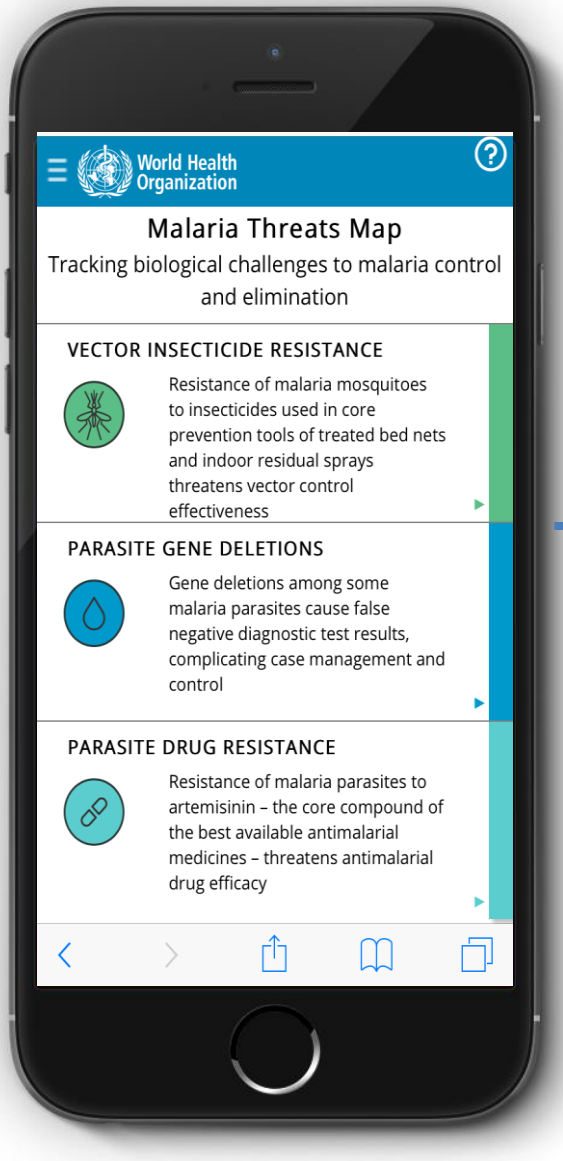
Live demonstration

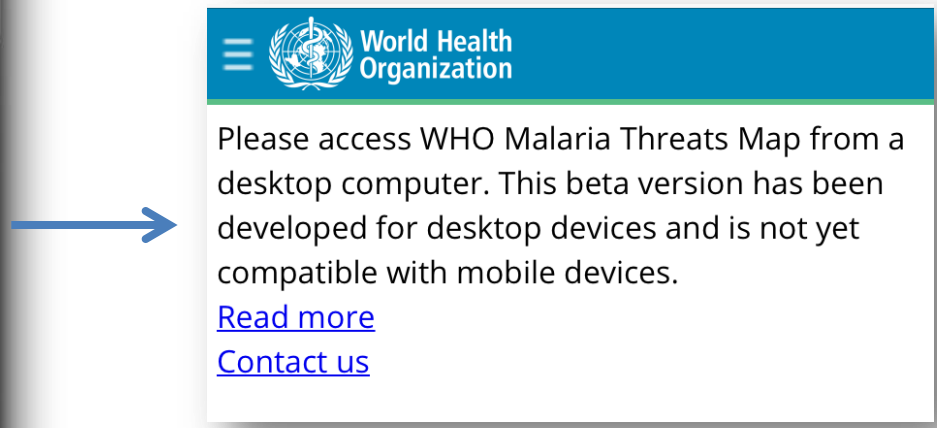


Live demonstration



Mobile compatibility: pending





Plans

Interim

- Finalise pending updates
- Shift to WHO server and launch
- Beta test and address arising issues (eg. bugs)
- Conduct consultations to define priorities for optimising / expanding

Phase II development

Potential options:

- Regional symbols and pop-ups (to compare across countries)
- Data upload / download
- Automated summary report
- Print functionality
- Mobile compatibility

Thank you

For further information:

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Jane Cunningham: cunninghamj@who.int

Amy Barrette: barrettea@who.int

- The URL to the Malaria Threats Map *beta application* will be circulated widely upon launch

Malaria Threats Map

Tracking biological challenges to malaria control and elimination

Drug efficacy and response (DER)

Malaria Policy Advisory Committee Meeting

Geneva, Switzerland

18 October 2017

Global **Malaria** Programme

World Health Organization

Introduction to the drug resistance threat maps

1. Feature stories (4)
2. Customized maps using filters

Feature stories (1)

World Health Organization

HOME

1 2 3 4

Malaria parasites repeatedly develop resistance to antimalarial treatment

For decades, drug resistance has been one of the main obstacles in the fight against malaria.

Continuous global monitoring and reporting of drug efficacy and parasite resistance is critical to ensure patients receive effective treatment. WHO supports national malaria control programmes to monitor antimalarial treatment efficacy and to track the genetic changes linked to drug resistance in malaria parasites.

The critical role of monitoring drug efficacy has been observed worldwide. Resistance has been a persistent challenge in the Greater Mekong Subregion. The region has been very active in monitoring drug efficacy.

Feature stories (2)

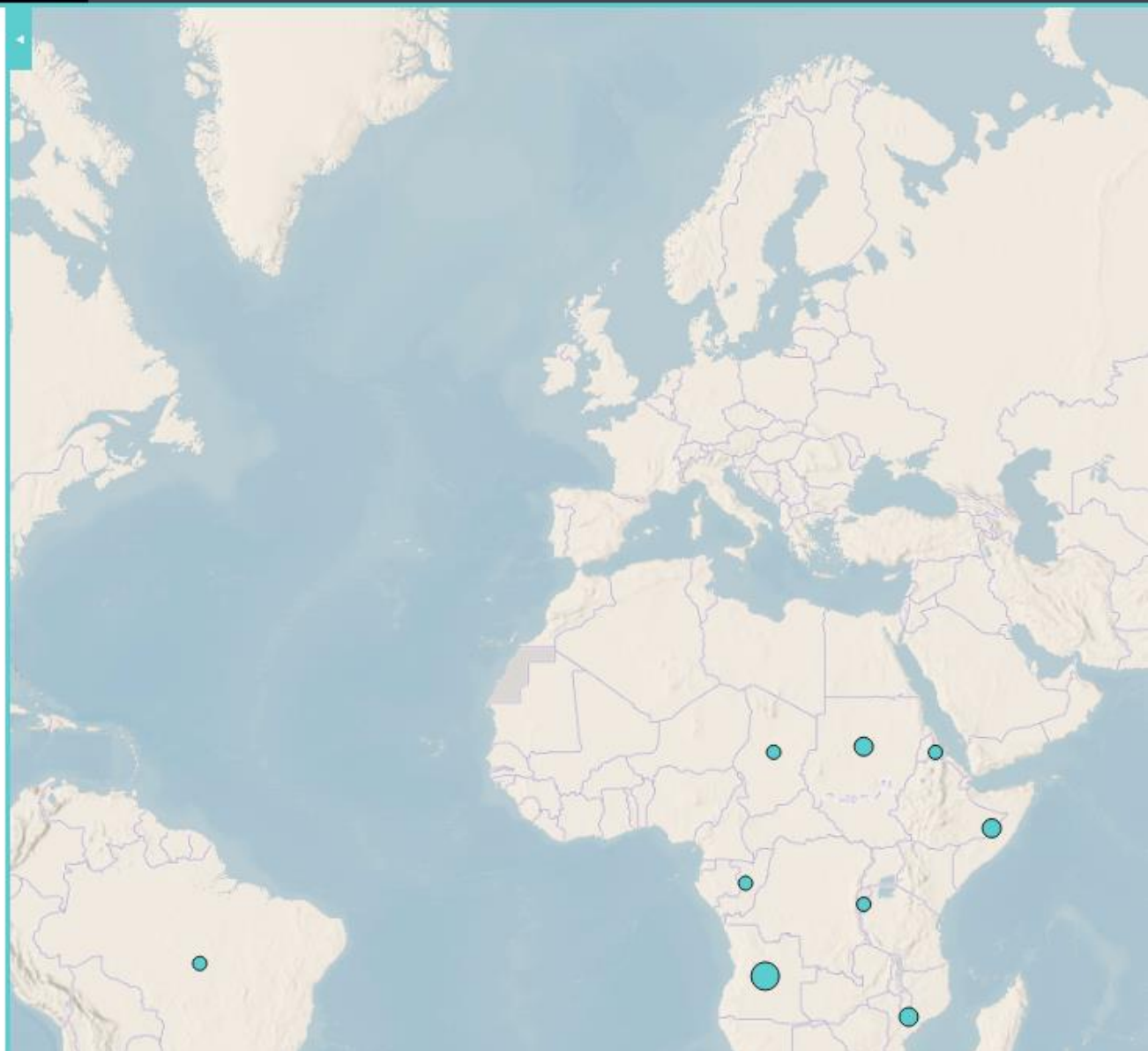
World Health Organization HOME

1 2 3 4

Routine monitoring of the efficacy of artemisinin-based combination therapies (ACTs) is essential to ensure that patients receive effective treatment

WHO recommends that all malaria endemic countries conduct therapeutic efficacy studies at least once every two years to inform treatment policy.

The selection of the recommended antimalarial drug is based on the medicine's efficacy against the malaria parasite. As such, monitoring the therapeutic efficacy of antimalarial medicine is a fundamental component of malaria treatment strategies. WHO has developed a standard protocol for monitoring the treatment efficacy of antimalarial medicine.



Feature stories (3)

World Health Organization HOME

1 2 3 4

Studies of molecular markers provide essential data for detecting and tracking antimalarial drug resistance

Molecular markers for drug resistance are genetic changes in the malaria parasite found to be associated with resistance.

Compared to efficacy studies, studies of molecular markers have several practical advantages. For example, a large number of samples can be collected and rapidly analysed. Molecular markers of drug resistance have been identified for different drugs, including *P. falciparum* resistance to chloroquine and to artemisinins.

For artemisinins, many mutations in the Kelch 13 (K13)-propeller domain have been found to be associated with delayed parasite clearance. This is an evolving field as more K13 mutations are discovered and we develop a better understanding of which mutations are of greatest influence.

Feature stories (4)

World Health Organization HOME

1 2 3 4

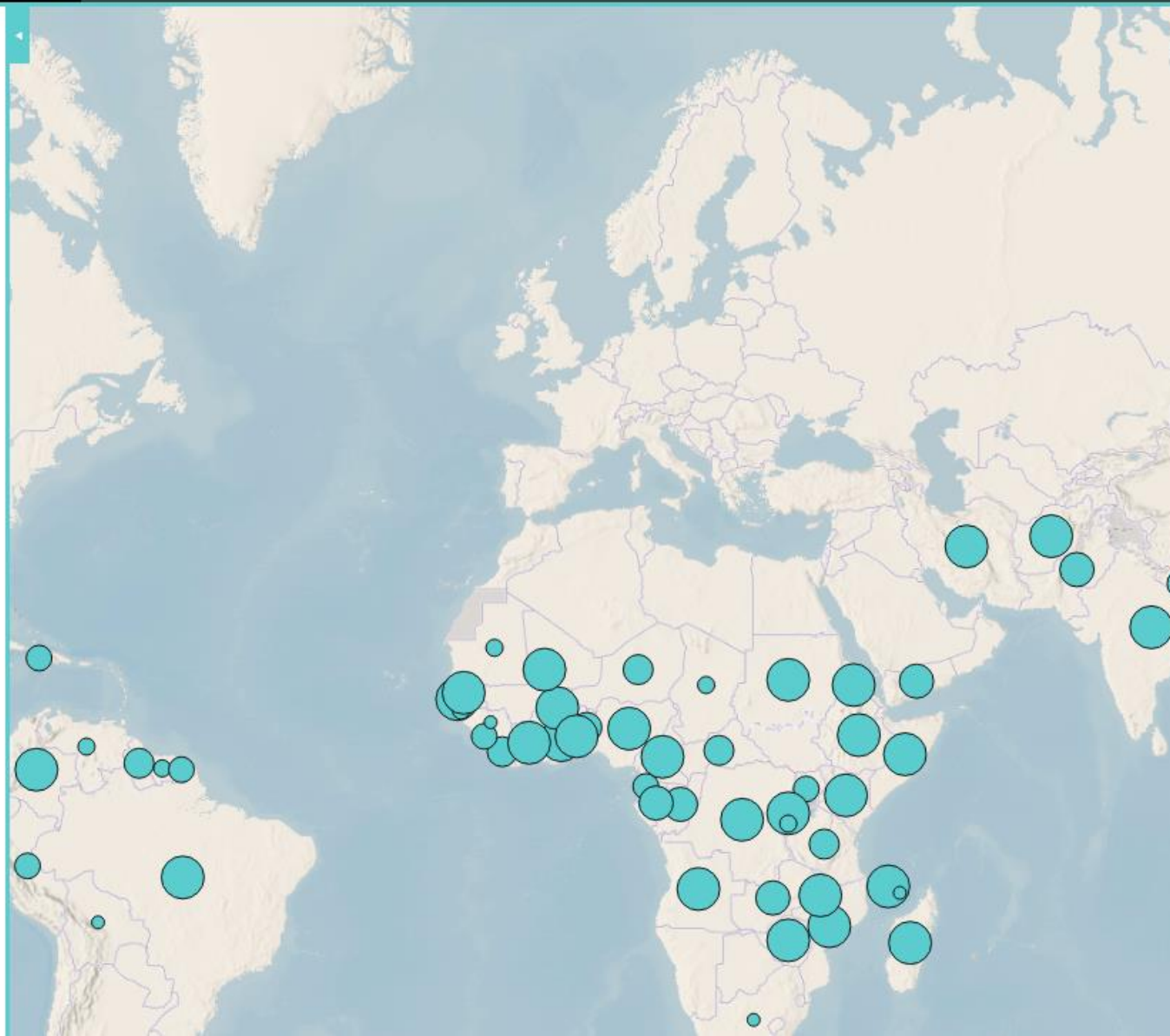
Drug resistance is a challenge in both *P. vivax* and *P. falciparum*, the two most common human malaria parasite species

Up-to-date information on drug resistance for both *P. vivax* and *P. falciparum* malaria is critical.

Artemisinin-based combination therapies (ACTs) are the recommended treatment for the most deadly malaria parasite, *P. falciparum*. There are two key outcome measures for monitoring the efficacy of ACTs: (1) the proportion of treatment failures and, (2) the proportion of patients with parasites on the third day after starting treatment. An increase in the proportion of patients with parasites on day 3 is a warning sign of artemisinin resistance.

Chloroquine is still used in many places to treat *P. vivax* malaria. However, as chloroquine resistance is also developing in *P. vivax* parasites, some countries have shifted to ACTs for treating *P. vivax* malaria.

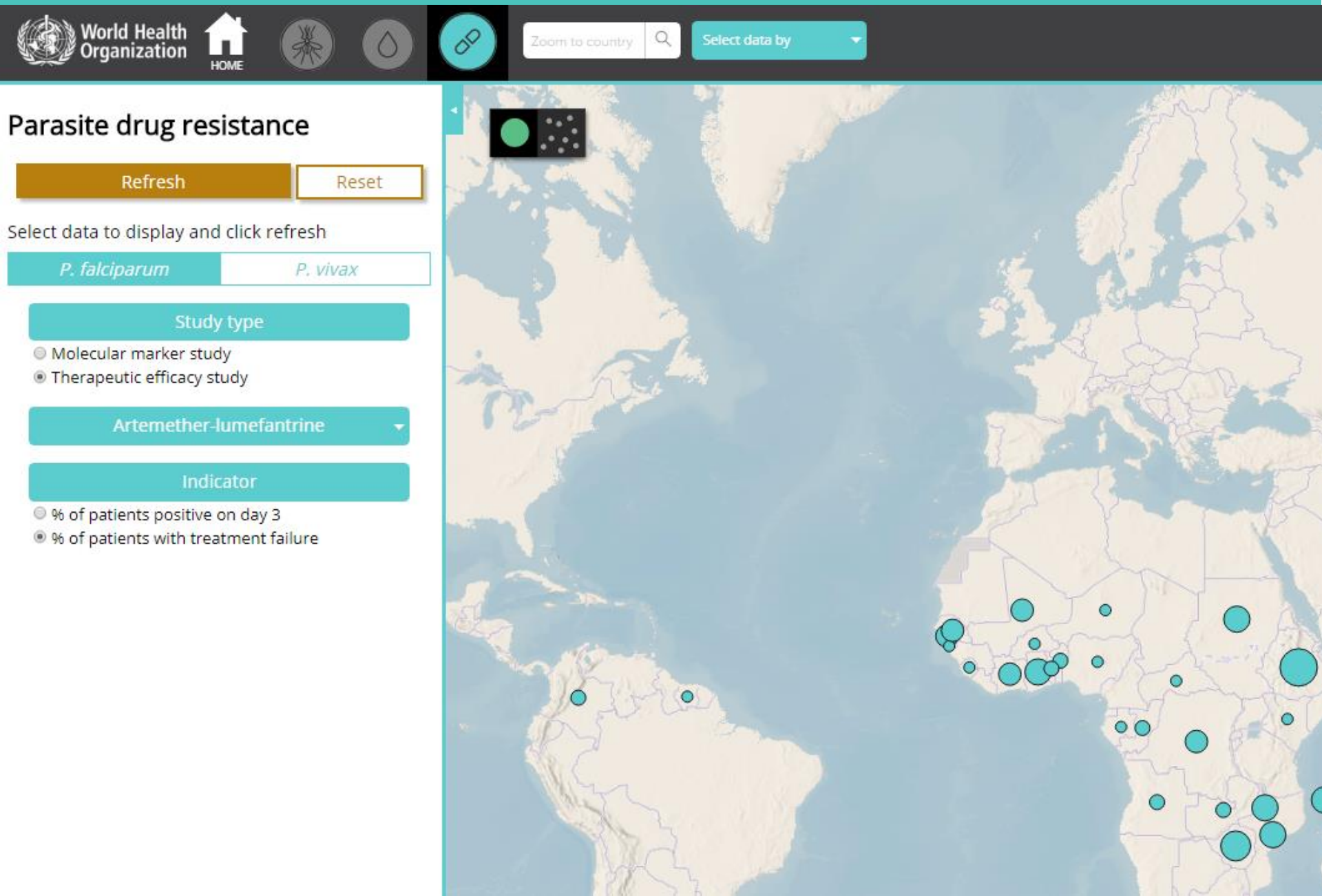
The WHO database contains 320 studies on *P. vivax* and 1600 studies on *P. falciparum* (including data from both therapeutic efficacy studies and molecular marker studies).



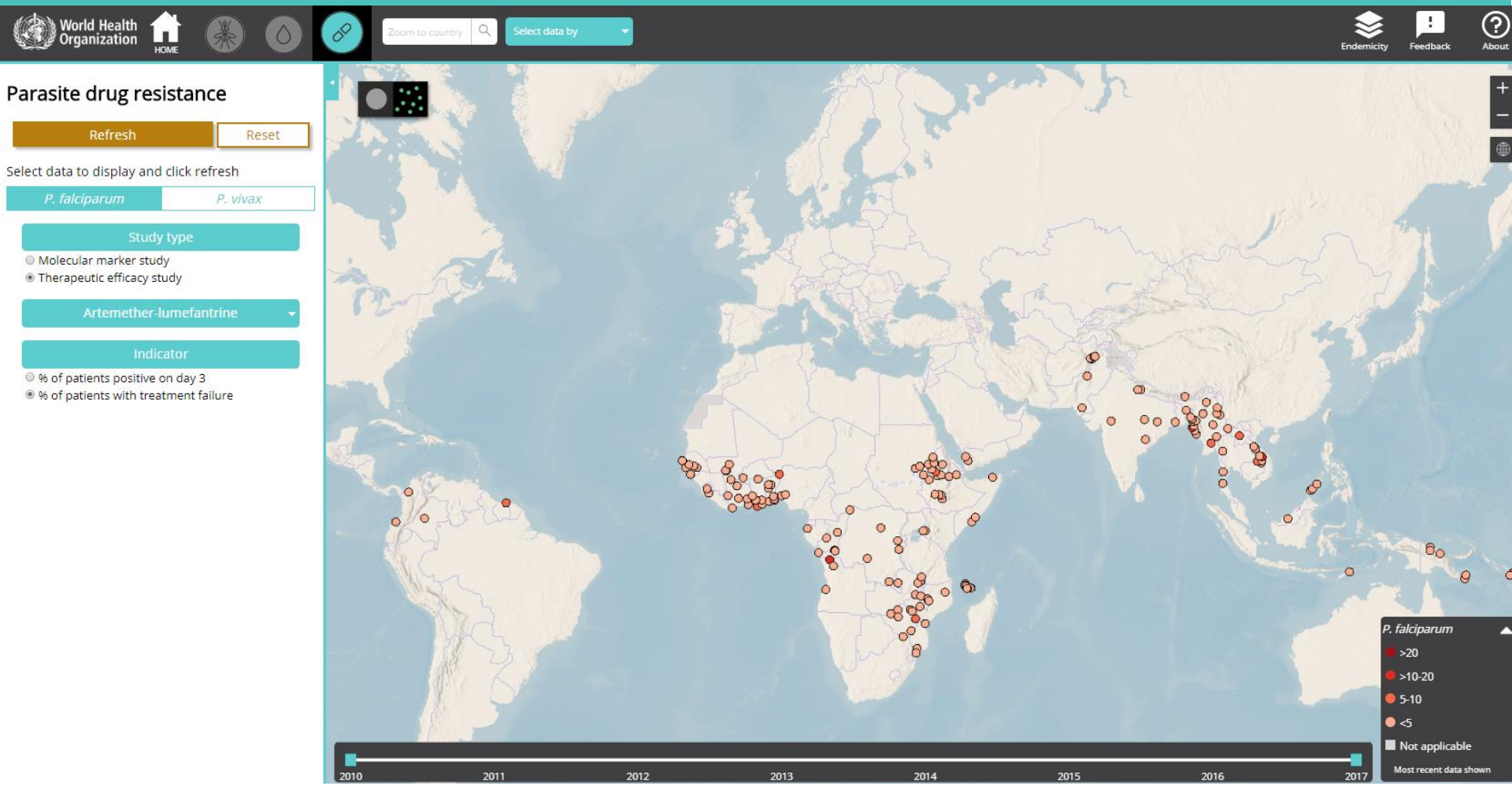
Customized maps using filters

- By species
  - *P. falciparum*
  - *P. vivax*
- By study type
  - molecular marker study
  - therapeutic efficacy study
- By treatment
  - By ACT
  - chloroquine (for *P. vivax* studies)
- By indicator

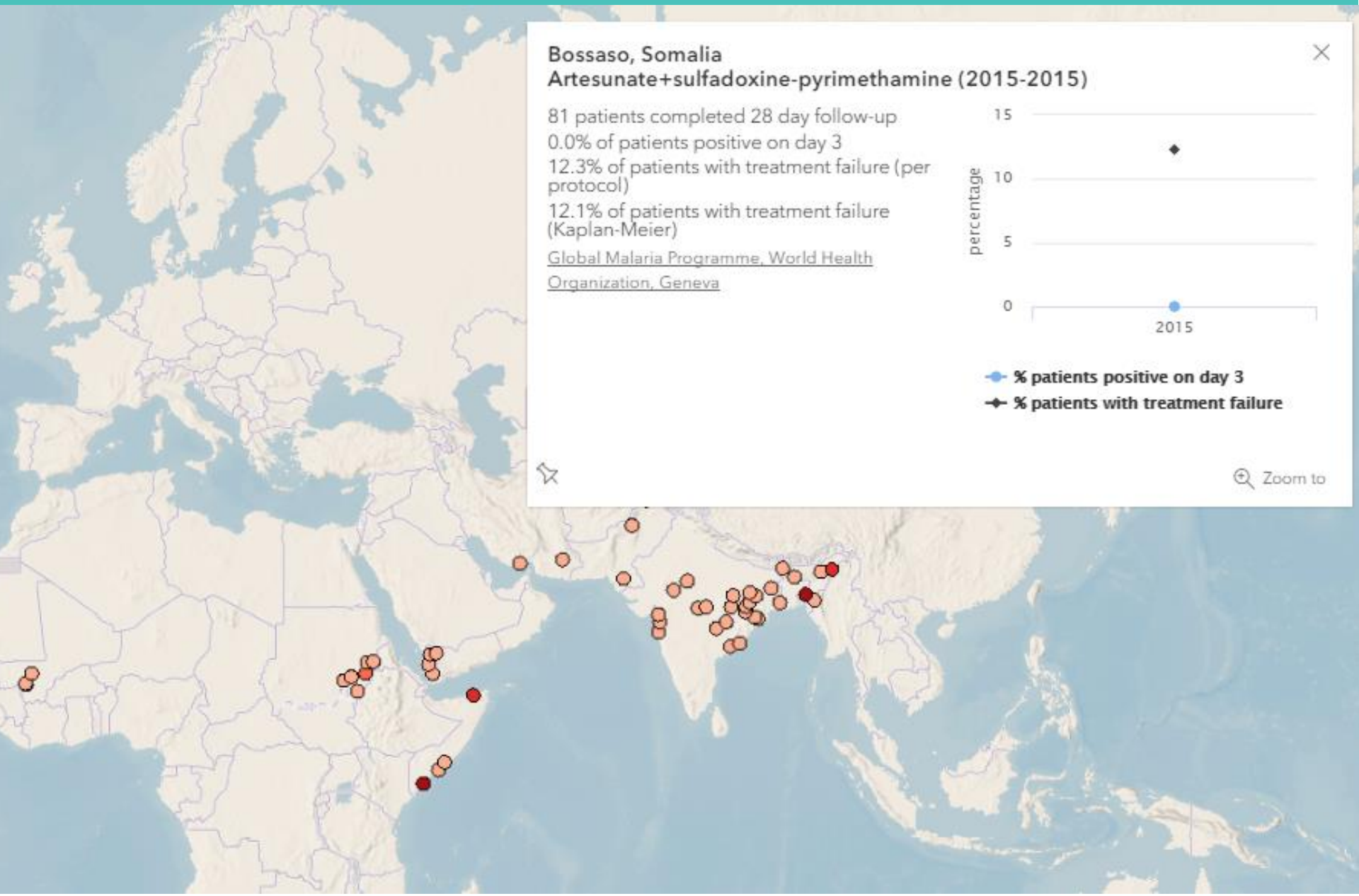
Customized maps: by country



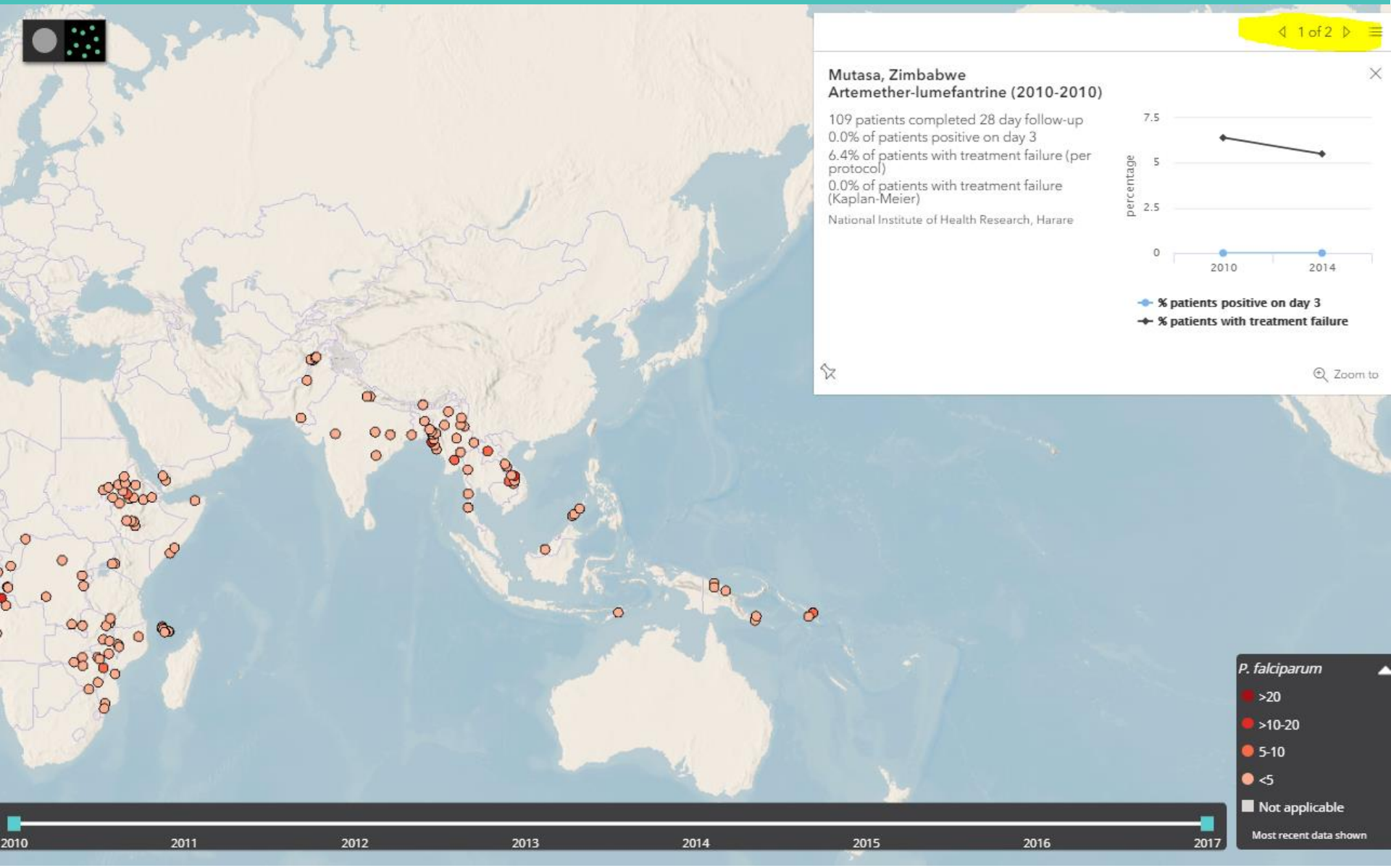
Customized maps: by study site



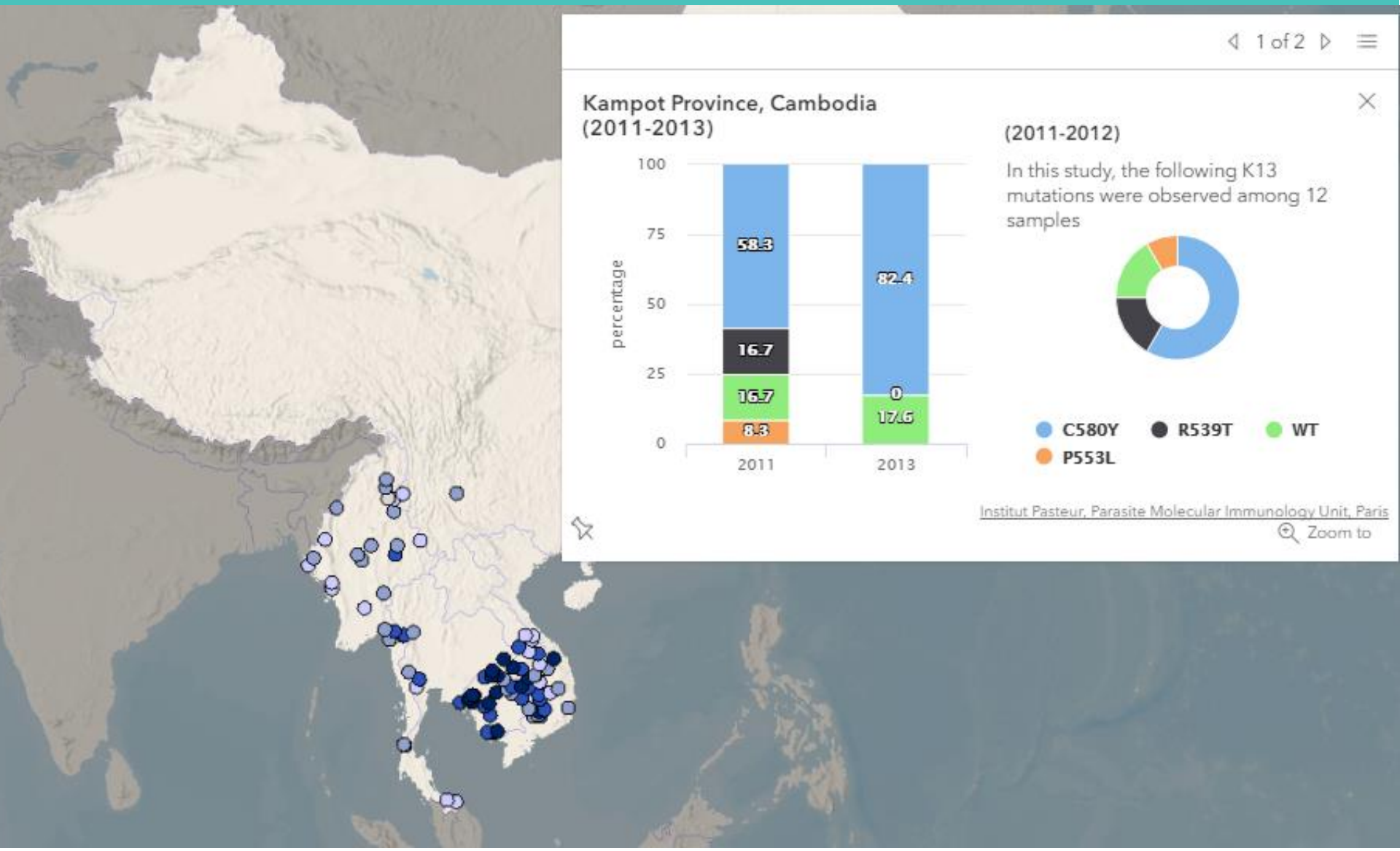
Customized maps: study site pop-up for TES



Customized maps: study site pop-up for TES +



Customized maps: study site pop-up for K13



Malaria Policy Advisory Committee Meeting
17–19 October 2017, Geneva, Switzerland
Background document for Session 8

Meeting report of the WHO Evidence Review Group on Malaria in Pregnancy

12–14 July 2017, Geneva, Switzerland

Summary

Malaria in pregnancy adversely affects maternal and infant health outcomes. The effects of *Plasmodium falciparum* infection and disease in sub-Saharan Africa have been well documented. However, the incidence and impact of *P. vivax* infection in pregnant women mainly outside Africa is less well known. Recently, different malaria control strategies among pregnant women – such as intermittent preventive treatment in pregnancy (IPTp), intermittent screening and treatment in pregnancy, and single screening and treatment – have been evaluated in Asia and the Pacific, in areas with both vivax and falciparum transmission.

WHO convened a group of experts to develop draft recommendations based on the review of recent evidence derived from malaria in pregnancy studies conducted in Africa, the Americas and Asia. Other studies reviewed also included evaluations on antimalarial drug pharmacokinetics in pregnant women, impact of maternal use of azithromycin added to IPTp-sulfadoxine-pyrimethamine on birth outcomes and sexually transmitted infections and reproductive tract infections, and the interactions between HIV infection and malaria in pregnancy.

The following conclusions and recommendations were proposed by the WHO Evidence Review Group for consideration by the WHO malaria Policy Advisory Committee.

Proposed conclusions and recommendations

1. Recent information indicates that although the overall incidence of *Plasmodium vivax* infection in pregnancy is low, it is associated with maternal anaemia, fetal loss, small for gestational age and preterm births, particularly in symptomatic pregnant women. Overall, the evidence reviewed does not support a change in the current recommendations on prevention, early diagnosis and treatment of clinical malaria followed by chloroquine prophylaxis to prevent parasitaemia following relapses.

2. Further research is needed on the effects of *P. falciparum* and *P. vivax* coinfection in pregnancy.

3. Evidence of pharmacokinetic (PK) and pharmacodynamics evaluations indicate that PK effects of pregnancy vary substantially among the different studies and antimalarial medicines. Given the inconsistency of the findings it is not entirely

WHO/HTM/GMP/MPAC/2017.18

clear whether dosage adjustment is required during pregnancy. Importantly, the clinical relevance of PK changes needs to be established before any dosage modification in pregnant women is suggested.

4. A cluster-randomized controlled trial compared monthly intermittent preventive treatment in pregnancy (IPTp) with dihydroartemisinin-piperaquine (DHA-PPQ) with intermittent screening and treatment (IST) and single screening and treatment (SST) conducted in two sites in Indonesia. Preliminary results indicate that IPTp halved the risk of malaria during pregnancy and at delivery compared with SST, but only on the higher transmission site in Papua Indonesia. Study findings were not consistent across sites and study outcomes, and there was no consistent positive impact on birth outcomes. IST did not result in the detection of significantly more malaria infections than the existing SST strategy. Based on the current level of evidence, IPTp-DHA-PPQ is not currently recommended for malaria prevention in pregnant women.

5. The provision of SP through IPTp does not cure sexually transmitted infections (STIs) and reproductive tract infections (RTIs). Also, the impact of adding azithromycin to IPTp with sulfadoxine-pyrimethamine (SP) on STIs or RTIs and adverse birth outcomes requires further research, since current evidence of improved outcomes is limited. Additionally, the risk of increases in antimicrobial resistance associated with azithromycin use also requires further assessment.

6. Studies evaluating the additional benefit of azithromycin added to IPTp-SP for preventing adverse birth outcomes in Malawi and Papua New Guinea have yielded contradictory results. Low birth weight and preterm birth rates were reduced in two studies but not in one of the largest studies. Since study designs differed across sites, further research is needed to evaluate the impact of adding azithromycin to IPTp-SP on adverse birth outcomes.

7. HIV-infected pregnant women are particularly vulnerable to malaria. Co-trimoxazole (CTX) prophylaxis provides only partial protection against malaria during pregnancy. Research is needed to evaluate new strategies, including alternative medicines for IPTp to be safely administered concomitantly with CTX prophylaxis.

Abbreviations

A	artemether
ACT	artemisinin-based combination therapy
AE	adverse event
AL	artemether lumefantrine
ANC	antenatal care
AQ	amodiaquine
ART	antiretroviral therapy
ARV	antiretroviral drug
AS	artesunate
AZ	azithromycin
CEA	cost–effectiveness analysis
CQ	chloroquine
CI	confidence interval
CTX	co-trimoxazole
DALY	disability-adjusted life year
DHA	dihydroartemisinin
DHA-PPQ	dihydroartemisinin-piperaquine
EFV	efavirenz
ERG	Evidence Review Group
Hb	haemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
IPT	intermittent preventive treatment
IPTp	intermittent preventive treatment in pregnancy
IRS	indoor residual spraying
IRR	incidence rate ratio
IST	intermittent screening and treatment in pregnancy
ITN	insecticide-treated mosquito net
L	lumefantrine
LAMP	loop mediated isothermal DNA amplification
LBW	low birth weight
LLIN	long-lasting insecticidal mosquito net
msec	millisecond
MTCT	mother-to-child transmission
MQ	mefloquine
OR	odds ratio
PCD	passive case detection
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetics
PPQ	piperaquine
py	person-years
RCT	randomized controlled trial
RDT	rapid diagnostic test
RR	relative risk
RTI	reproductive tract infection
SAE	serious adverse event
SGA	small for gestational age
SMRU	Shoklo malaria Research Unit
SP	sulfadoxine-pyrimethamine
SST	single screening and treatment
SSTp	single screening and treatment in pregnancy
STI	sexually transmitted infection
WHO	World Health Organization

1. Introduction

1.1. Background

Recent mapping estimates of the number of pregnancies at risk of malaria indicate that the number of pregnancies in areas outside Africa with low malaria transmission or with *Plasmodium vivax* exceed the number of pregnancies occurring in areas with stable *P. falciparum* malaria, yet there is limited information on the burden of malaria in pregnancy (malaria in pregnancy) in these endemic areas *(1)*. In these regions outside Africa, with the exception of Papua New Guinea and Papua Indonesia, the incidence of falciparum malaria in pregnant women is lower but infections are more likely to cause symptomatic and severe disease in the mothers, as well as preterm births and fetal loss *(2)*.

P. vivax is common in the Americas and Asia. Unlike *P. falciparum, P. vivax* does not cytoadhere to placental structures; nonetheless, vivax malaria during pregnancy is also associated with maternal anaemia and low birth weight (LBW) *(2)*. malaria prevention guidelines in pregnancy do not include endemic regions outside Africa, except Papua New Guinea where intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) is recommended. In these regions, control of malaria in pregnancy relies mainly on case management, although some countries recommend chloroquine (CQ) chemoprophylaxis, passive case detection (PCD), strategies for single screening and treatment (SST) and insecticide-treated mosquito nets (ITNs) *(3)*.

WHO convened a group of experts to develop recommendations based on new evidence derived from recent pregnancy studies conducted in Africa, the Americas and Asia. The studies reviewed also included evaluations on the pharmacokinetics (PK) of antimalarial medicines in pregnant women, the impact of maternal use of azithromycin (AZ) plus IPTp-SP on birth outcomes and sexually transmitted infections (STIs) and reproductive tract infections (RTIs), and the interactions between HIV infection and malaria in pregnancy.

1.2. Objectives

1. To review the burden of vivax malaria in pregnant women, including impact on maternal and birth outcomes.

2. To review the efficacy and safety of medicines to treat uncomplicated falciparum and vivax malaria in pregnancy in Asia and Latin America.

3. To review the efficacy and safety of intermittent screening and treatment in pregnancy (IST) and intermittent preventive treatment (IPT) of malaria in pregnancy in Asia.

4. To review the effects of SP and AZ protection against adverse birth outcomes related to STIs and RTIs.

5. To review the PK of dihydroartemisinin (DHA), piperaquine (PPQ), artesunate (AS), artemether (A), lumefantrine (L), amodiaquine (AQ) and mefloquine (MQ) during pregnancy, and implications for dose adjustments.

6. To review key challenges and knowledge gaps for malaria in pregnancy in HIV-infected women including:

    - the efficacy and effectiveness of co-trimoxazole (CTX) prophylaxis for prevention of malaria and its adverse consequences;
    - the efficacy and effectiveness of IPTp; and
    - the PK of antimalarial medicines in these women, including their interactions with antiretroviral medicines (ARVs).

1.3. Process

Data were presented as pre-reads and oral presentations for each of the following topics:

- burden of *P. vivax* in pregnancy;
- treatment of falciparum and vivax malaria in pregnancy;
- prevention of falciparum and vivax malaria in pregnancy;
- SP and AZ against STIs and RTIs; and
- HIV and malaria in pregnancy.

2. Evidence reviewed

2.1. Burden of *P. vivax* in pregnancy

2.1.1. Prevalence and clinical impact of P. vivax *infection in pregnant women: findings from a prospective multicentre project*

The results of a multicentre prospective facility-based study (the Pregvax study) to determine the burden and clinical impact of *P. vivax* in pregnant women from Brazil (BR), Colombia (CO), Guatemala (GT), India (IN) and Papua New Guinea (PNG) were presented and reviewed *(4)*.

Between 2008 and 2011, a total of 9388 women were enrolled at antenatal care (ANC) clinics of study sites; of these, 53% (4957) were followed until delivery. Prevalence of *P. vivax* mono-infection in maternal blood at delivery was 0.4% (20/4461) by microscopy (BR 0.1%, CO 0.5%, GT 0.1%, IN 0.2% and PNG 1.2%) and 7% (104/1488) by polymerase chain reaction (PCR). *P. falciparum* mono-infection was found in 0.5% (22/4463) of the women by microscopy (BR 0%, CO 0.5%, GT 0%, IN 0% and PNG 2%) and 2% by PCR (24/1191; performed in a subsample).

P. vivax infection was observed in 0.4% (14/3725) of placentas examined by microscopy and in 3.7% (19/508) by PCR. *P. vivax* in newborn blood was detected in 0.02% (1/4302) of samples examined by microscopy, and it was found in 0.05% (2/4040) of cord blood examined by microscopy, and 2.6% (13/497) by PCR. Only 0.5% of the study participants took CQ chemoprophylaxis during pregnancy.

Clinical *P. vivax* infection was associated with increased risk of maternal anaemia (odds ratio [OR] 5.48, 95% confidence interval [CI]: 1.83±16.41, p=0.009). Submicroscopic vivax infection (defined as an infection with a PCR positive for *P. vivax* and negative for *P. falciparum*, and a concomitant blood film negative by microscopy) was not associated with increased risk of moderate to severe anaemia (haemoglobin [Hb] <8 g/dL) (OR 1.16, 95% CI: 0.52–2.59, p=0.717), or LBW (<2500 g) (OR 0.52, 95% CI: 0.23–1.16, p=0.110) in the adjusted multivariate analysis. No impact of *P. vivax* infection was observed on other fetal or neonatal outcomes (e.g. prematurity or stillbirth). The impact of *P. vivax* and *P. falciparum* malaria on maternal anaemia and LBW is presented in Table 1.

TABLE 1.
Impact of *P. vivax* and *P. falciparum* malaria on maternal anaemia and LBW

	P. vivax						*P. falciparum*					
	Maternal anaemia *			Low birth weight			Maternal anaemia *			Low birth weight		
	Adjusted OR †	(95% CI)	p-value	Adjusted OR †	(95% CI)	p-value	Adjusted OR †	(95% CI)	p-value	Adjusted OR †	(95% CI)	p-value
At enrolment												
Non-infected	1		**0.009**	1		0.350	1		**0.001**	1		0.092
Asymptomatic malaria infection	0.96	(0.37-2.44)		0.92	(0.21-4.14)		4.01	(1.59-10.11)		2.03	(1.07-3.85)	
Clinical malaria	5.48	(1.83-16.41)		2.29	(0.74-7.04)		5.57	(1.22-25.34)		1.39	(0.16-12.03)	
At delivery												
Non-infected	1		0.754	1		0.298	1		0.122	1		**0.004**
Asymptomatic malaria infection	0.66	(0.22-1.96)		1.01	(0.22-4.63)		8.19	(1.08-62.38)		4.52	(1.63-12.49)	
Clinical malaria	1.05	(0.07-15.58)		9.39	(0.56-158.25)		1.29	(0.23-7.18)		4.29	(0.70-26-24)	
Non-infected	1		0.384	1		0.895	1		**<0.001**	1		**0.001**
Microscopic infection	0.62	(0.22-1.81)		0.90	(0.20-4.10)		4.07	(1.93-8.58)		4.28	(1.75-10.44)	
Non-infected	1		0.717	1		0.110	1		0.402	1		0.359
Sub-microscopic infection ‡	1.16	(0.52-2.59)		0.52	(0.23-1.16)		2.93	(0.24-36.23.16)		1.97	(0.46-8.46)	

* Maternal anaemia: Hb<11 g/dL
† Adjusted Odds Ratio (OR) for site and previous malaria episodes
‡ Neste case-control study

CI, confidence interval; LBW, low birth weight; OR, odds ratio
Source: Bardají et al. 2017 *(4).*

The incidence rate during pregnancy of *P. vivax* infection detected by microscopy was not associated with parity (incidence rate ratio [IRR] for multigravidae women with four or more pregnancies 1.14, 95% CI: 0.70±1.87, p=0.619). In contrast, the incidence rate of *P. falciparum* infection detected by microscopy decreased with parity (compared to primigravida, IRR for multigravidae 0.39, 95% CI: 0.25±0.62, p<0.001).

Studies on the humoral and cellular responses to *P. vivax* infection during pregnancy within the frame of the Pregvax study showed that naturally acquired binding-inhibitory antibodies to *P. vivax* Duffy binding protein in pregnant women were associated with higher birth weight *(5)*. Also, the virulence (VIR) antigens were shown to induce the natural acquisition of antibody and T cell memory responses that may be important in immunity to *P. vivax* during pregnancy in diverse geographical settings *(6)*.

With regard to the genotyping studies of *P. vivax* and *P. falciparum* isolates from pregnant women, *P. vivax* population diversity was higher in all sites than their sympatric *P. falciparum* populations *(7)*. *P. vivax* was associated with placental infection. However, placental inflammation was not observed in *P. vivax* mono-infections, suggesting other

causes of poor delivery outcomes associated with vivax infection *(8)*. Furthermore, *P. vivax* peripheral isolates from pregnant women did not exhibit a prominent adhesion to placental chondroitin sulfate A (CSA). Finally, in studies conducted in Brazil, rosetting was found to be a frequent cytoadhesive phenotype in peripheral blood *P. vivax* infections associated with anaemia *(9)*.

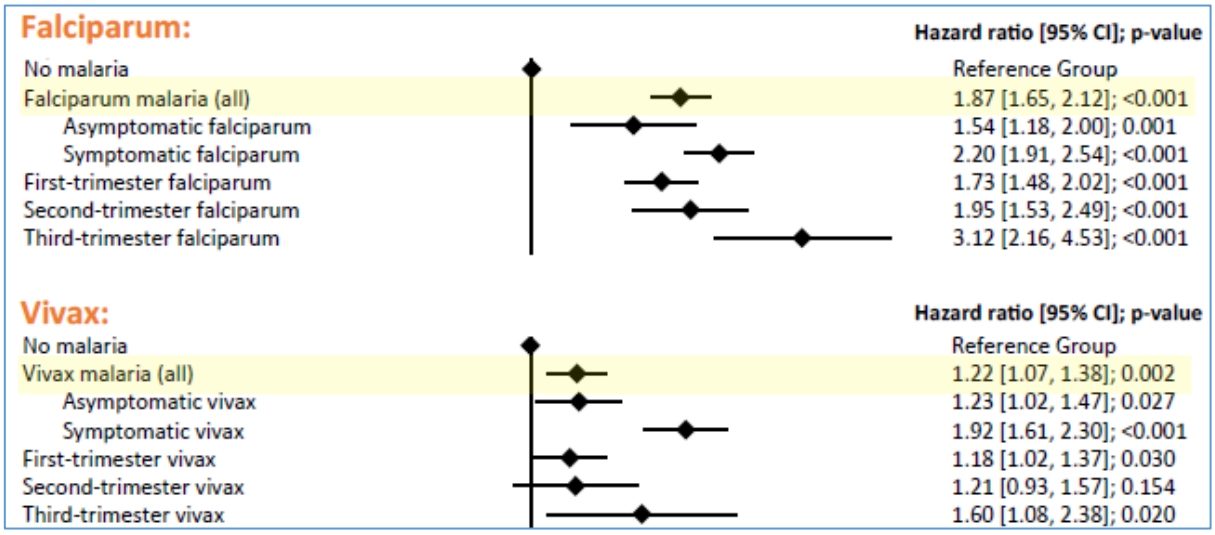
Costs associated with malaria in pregnancy in areas where *P. vivax* predominates constitute a substantial economic burden *(10)*. For instance, for a clinical malaria episode in pregnancy in Brazil, patients' costs reached up to 3.4% of the local average annual per capita income, while in Colombia, median inpatient costs represented 18% of the monthly minimum salary in the country. In Bikaner district, India, the economic costs of one hospital admission was over 12 times higher than the monthly average per capita income of the district. Therefore, a reduction of the burden of malaria in pregnancy is likely to have a significant economic benefit to households and might help to improve economic growth in endemic areas.

2.1.2. Association between vivax and falciparum malaria in pregnancy and adverse pregnancy outcomes in an area of low transmission

Two analyses of prospective observational data routinely collected at ANC clinics from the Shoklo malaria Research Unit (SMRU), in the Thai–Myanmar border area between 1986 and 2015 were presented and reviewed *(11, 12)*.

The effect of falciparum and vivax malaria in pregnancy on antepartum (death in utero) and intrapartum (death during labour) stillbirth and neonatal mortality was analysed in 61 836 women *(11)*. *Stillbirth* was defined as a baby born dead from 28 weeks' gestation, *malaria* as the presence of asexual parasites in the peripheral blood, and *symptomatic malaria* as parasitaemia plus a temperature ≥37.5 °C or a history of fever in the past 48 hours. A total of 9350 women (15%) had malaria in pregnancy detected by microscopy, and 526 (0.8%) had stillbirths (49% [260/526] antepartum, 34% [178/526] intrapartum and 17% [88/526] uncertain). In a subset of 9090 liveborn singletons followed from birth there were 153 (1.7%) neonatal deaths. Fig. 1 shows the observed association between falciparum and vivax malaria in pregnancy and fetal loss (miscarriage or stillbirth) in the study. Associations between malaria and fetal loss in the first and second trimester were driven by miscarriages, while associations in the third trimester were due to stillbirths.

FIG. 1.
Association between malaria in pregnancy and fetal loss (miscarriage or stillbirth)



CI, confidence interval
Source: Moore et al., 2017 *(11)*

The hazard of antepartum stillbirth increased 2.24-fold (95% CI: 1.47–3.41) following falciparum malaria, with 42% mediated through small for gestational age (SGA) status and anaemia. This was driven by symptomatic falciparum malaria (hazard ratio [HR] 2.99 [1.83–4.89]) rather than asymptomatic falciparum malaria infections (HR 1.35 [0.61–2.96]).

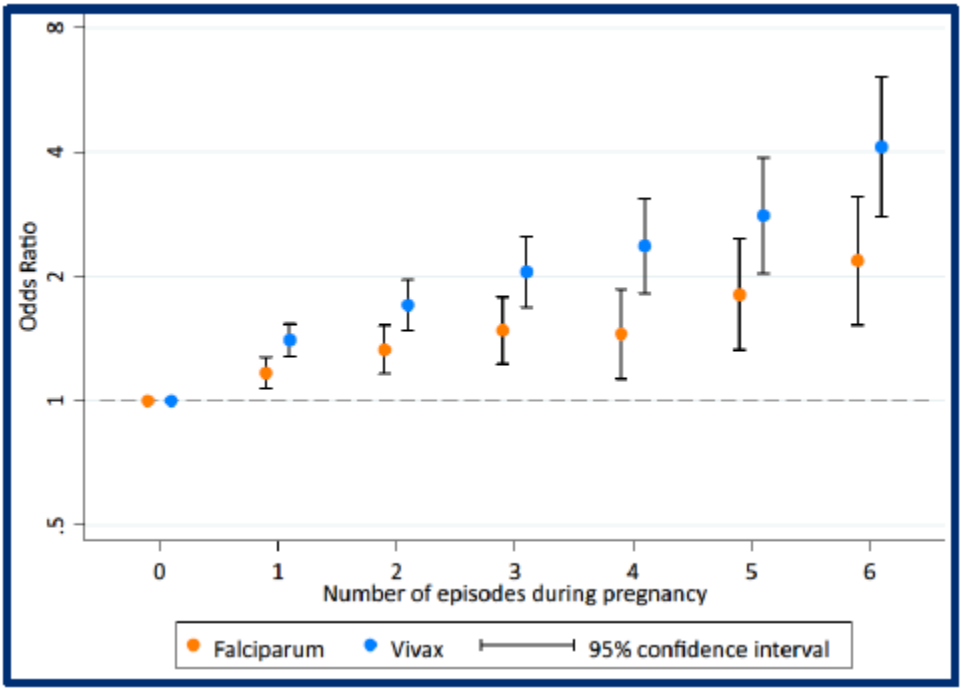
The hazard of antepartum stillbirth increased 2.21-fold (1.12–4.33) following symptomatic vivax malaria (24% mediated through SGA status and anaemia). Similar to falciparum malaria, asymptomatic vivax malaria infection was not associated with stillbirth (HR 0.54 [0.20–1.45]). The association between malaria and miscarriage was greater after a recurrence, whether the recurrence was due to a novel infection, recrudescence or relapse in the case of vivax infection. The hazard of miscarriage increased 3.24-fold following falciparum recurrence (2.24–4.68, p<0.0001), and 2.44-fold (1.01–5.88, p=0.0473) following recurrent symptomatic vivax malaria *(13)*.

There was no association between falciparum or vivax malaria in pregnancy and intrapartum stillbirth (falciparum HR 1.03 [0.58–1.83]; vivax HR 1.18 [0.66–2.11]). Overall, falciparum and vivax malaria in pregnancy increased the hazard of neonatal death 2.55-fold (1.54–4.22) and 1.98-fold (1.10–3.57), respectively (40% and 50%, respectively, mediated through SGA status and preterm birth).

The second analysis on the effects of the total number of malaria episodes in pregnancy on SGA and of the effects of malaria in pregnancy on SGA by the gestational age at malaria detection and treatment included 50 060 pregnant women enrolled at the SMRU ANC clinics between 1985 and 2015 *(12)*. A total of 8221 (16%) of them had malaria during their pregnancy. The analysis used WHO definitions of very preterm birth (≥28 and <32 weeks) and late preterm birth (≥32 and <37 weeks) and international SGA standards (INTERGROWTH-21st). Of the 50 060 neonates, 10 005 (21%) were SGA, 540 (1%) were very preterm and 4331 (9%) were late preterm. The rates of falciparum and vivax malaria were highest at 6 and 5 weeks' gestation, respectively.

The odds of SGA increased linearly by 1.13-fold (95% CI: 1.09–1.17) and 1.27-fold (95% CI: 1.21–1.33) per episode of falciparum and vivax malaria, respectively. Falciparum malaria at any gestation period after 12–16 weeks, and vivax malaria after 20–24 weeks, were associated with SGA (falciparum OR range: 1.15–1.63 [p range: <0.001–0.094] and vivax OR range: 1.12–1.54 [p range: <0.001–0.138]). The association between the number of malaria episodes and SGA is shown in Fig. 2.

FIG. 2.
Association between the number of malaria episodes and SGA



SGA, small for gestational age
Source: Moore et al., 2017 *(12)*

Falciparum malaria at any gestation period after 24–28 weeks was associated with either very or late preterm birth (OR range: 1.44–2.53; p range: <0.001–0.001). Vivax malaria at 24–28 weeks was associated with very preterm birth (OR 1.79 [1.11–2.90]), and vivax malaria at 28–32 weeks was associated with late preterm birth (OR 1.23 [1.01–1.50]). Many of these associations held for asymptomatic malaria (defined as clinically asymptomatic infections detected by microscopy).

Finally, we reviewed the results of a systematic review and meta-analysis on the association between malaria in pregnancy and stillbirth including 59 studies conducted in areas of different malaria endemicity (Moore et al., in press). The association between falciparum malaria and stillbirth was almost 2-fold greater in areas of low-to-intermediate endemicity than in areas of high endemicity, but few studies (18%) from areas of low transmission contributed to this analysis. Vivax malaria detected and treated at delivery, but not during pregnancy, was also associated with stillbirth. However, only seven studies of vivax malaria were included, resulting in wide confidence intervals. Additionally, no information about mixed infections (falciparum and vivax) was available.

Key conclusions on burden of *P. vivax* in pregnancy

- The incidence of *P. vivax* infection in pregnancy was low (<2%) across different endemic settings in a multicentre health facility-based prospective cohort study conducted between 2008 and 2011 in Brazil, Colombia, Guatemala, India and Papua New Guinea. Additionally:
  - *P. vivax* malaria was associated with anaemia in symptomatic women;
  - most *P. vivax* infections were of low density and were undetected with routine microscopy; and
  - *P. vivax* was associated with placental infection; however, placental inflammation was not observed in *P. vivax* mono-infections, suggesting other causes of poor delivery outcomes associated with vivax infection.
- Analyses of data routinely collected at ANC clinics between 1986 and 2015 in the Thai–Myanmar border area indicate that both treated falciparum and vivax malaria were associated with fetal loss, SGA and preterm birth. In these analyses, the associations between malaria in pregnancy and miscarriage and SGA were stronger following recurrence, whether that recurrence was due to a novel infection, treatment failure or relapse in the case of vivax malaria.

2.2. Treatment of falciparum and vivax malaria in pregnancy

2.2.1. Efficacy and safety of artesunate plus sulphadoxine-pyrimethamine (AS-SP) and artesunate plus mefloquine (AS-MQ) to treat uncomplicated falciparum malaria in pregnancy in India

The results of an open-label clinical trial evaluating the efficacy and safety of AS-SP and AS-MQ for treatment of falciparum malaria in pregnant women in India were presented and reviewed (Anvikar et al., unpublished).

Between 2010 and 2013, a total of 7064 pregnant women were screened for participation in the trial, which was conducted in the states of Jharkhand and Odisha (India). Of these women, 248 (3.5%) with uncomplicated *P. falciparum* mono-infection were enrolled in the trial, of whom 123 received AS-MQ and 125 received AS-SP. The prevalence of malaria was low in the study sites and this compromised the recruitment rate (it was not possible to reach the target sample size of 300).

A total of 239 women (121 in the AS-SP arm and 118 in the AS-MQ arm) completed the day 63 follow-up (per protocol). Among these women, the adequate clinical and parasite response was 100% in the AS-SP group and 99.2% (95% CI: 95.4–99.97) in the AS-MQ group.

There were five serious adverse events (SAEs) among pregnant women (four in AS-SP and one in AS-MQ) and 13 fetal or neonatal SAEs (seven in AS-SP and six in AS-MQ), but none of them were considered related to the study medicines. A higher proportion of women in the AS-MQ arm reported vomiting within 7 days post-treatment than in the AS-SP arm (12.2% versus 1.6%, p=0.001). The prevalence of LBW was found to be higher in the AS-SP group

than in the AS-MQ group (28.3% versus 16.8%, p=0.037). Placental biopsy sample was available for 181 women (73%), and none of the biopsies showed evidence of active placental malaria.

Both treatments were efficacious and safe, but AS-MQ appeared to be less well tolerated than AS-SP.

2.2.2 Safety, tolerability and pharmacokinetic (PK) properties of co-administered azithromycin and piperaquine in pregnant women from PNG

A recently published study evaluated the safety, tolerability and PK properties of co-administered AZ and PPQ in 30 pregnant women from Papua New Guinea attending their first ANC visit (median gestational age of 26) *(14)*. Participants were given three daily doses of 1 g AZ plus 960 mg PPQ tetraphosphate, with detailed monitoring and blood sampling over 42 days.

The treatment was found to be well tolerated. The median (interquartile range) increase in the rate-corrected electrocardiographic QT interval 4 hours post-dose (12 [6–26] $msec^{0.5}$) was similar to that found in previous studies in pregnancy with DHA-PPQ or SP-PPQ. Electrocardiographic changes were assessed at multiple intervals (4, 12 and 24 hours) after the first dose of PPQ, but not at the predicted maximum concentration (about 52 hours).

Six women with asymptomatic malaria cleared their parasitaemias within 72 hours. Two aparasitaemic women developed late uncomplicated *P. falciparum* infections on days 42 and 83; these infections were treated with a 3-day course of artemether-lumefantrine (AL). The remaining pregnant women were uninfected throughout the study.

Compared with previous studies among pregnant women, the area under the concentration-time curve ($AUC_{0-\infty}$) for PPQ (38 818 [24 354–52 299] µg h l^{-1}) was similar to published values, but there was a 52% increase in relative bioavailability with each subsequent dose.

The $AUC_{0-\infty}$ for AZ (46 799 [43 526–49 462] µg h l^{-1}) was at least as high as that reported for higher dose regimens, suggesting saturable absorption or concentration-dependent tissue uptake and clearance from the central compartment (or both).

2.2.3. K/PD analysis of dihydroartemisinin, piperaquine, artesunate, artemether, lumefantrine, amodiaquine and mefloquine during pregnancy and possible implications for dose adjustments

A comprehensive literature review on the pharmacokinetics (PK) and pharmacodynamics (PD) properties of different antimalarial medicines used in pregnancy was presented and reviewed at the meeting. The main findings are summarized in the tables below.

TABLE 2.
Summary of PK properties of artemisinin derivatives found in studies conducted among pregnant women

Antimalarial	Study patients	Country	Pregnancy effects
Artesunate	Pregnant women (n=24)	Thailand	Decreased exposure to DHA compared to historical controls.
	Pregnant and postpartum women (n=20/15)	Thailand	23% decreased exposure to DHA compared with postpartum women.
	Pregnant, postpartum and non-pregnant women (n=26/26/25)	DRC	42% decreased exposure to DHA compared with non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Burkina Faso	No difference in exposure to DHA compared non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Artemether	Pregnant and non-pregnant women (n=30/30)	Uganda	No difference in exposure to DHA compared non-pregnant women.
	Pregnant and non-pregnant women (n=33/22)	Tanzania	No difference in exposure to DHA compared non-pregnant women.
	Pregnant women (n=21)	Uganda	Decreased exposure to DHA compared to historical controls.
	Pregnant women (n=13)	Thailand	Decreased exposure to DHA compared to historical controls.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
DHA	Pregnant and non-pregnant women (n=32/33)	PNG	No difference in exposure to DHA compared to non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Thailand	38% decreased exposure to DHA compared to non-pregnant women.
	Pregnant and non-pregnant women (n=31/30)	Uganda	47% decreased exposure to DHA compared to non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		

DHA, dihydroartemisinin; DRC, Democratic Republic of the Congo; PK, pharmacokinetics; PNG, Papua New Guinea; Tanzania, United Republic of Tanzania
Source: Tarning et al., unpublished
Studies showing an effect of pregnancy on antimalarial medicines PK properties are highlighted in red.

Overall, PK studies of artemisinin derivatives in pregnant women showed contradictory results. However, most studies showed a lower drug exposure to artemisinins in pregnant women than in non-pregnant women.

TABLE 3.
Summary of PK properties of 4-amino-quinolones derivatives and quinolone methanols in studies conducted among pregnant women

Antimalarial	Study patients	Country	Pregnancy effects
Chloroquine	Pregnant and non-pregnant women (n=30/30)	PNG	34% decreased exposure to chloroquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=12/15)	Thailand	No difference in exposure to chloroquine compared to non-pregnant women.
	Pregnant women (n=49)	Tanzania	Decreased exposure to chloroquine compared to historical controls.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Amodiaquine	Pregnant and postpartum women (n=24/18)	Thailand	No difference in exposure to amodiaquine and desethylamodiaquine compared to postpartum women.
	No difference in exposure reported in pregnant women.		
Piperaquine	Pregnant and non-pregnant women (n=32/33)	PNG	42% decreased exposure to piperaquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Thailand	No difference in exposure to piperaquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=12/12)	Sudan	No difference in exposure to piperaquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=31/30)	Uganda	40% decreased exposure to piperaquine compared to non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Mefloquine	Pregnant and non-pregnant women (n=24/24)	Burkina Faso	No difference in exposure to MQ compared to non-pregnant women.
	Pregnant and non-pregnant women (n=9/8)	Burkina Faso	No difference in exposure to MQ compared to non-pregnant women.
	Pregnant women (n=20)	Thailand	Decreased exposure to MQ compared to historical controls.

Antimalarial	Study patients	Country	Pregnancy effects
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Quinine	Pregnant women (n=22)	Uganda	Decreased exposure to quinine women compared to historical controls.
	Pregnant and non-pregnant women (n=8/8)	Sudan	No difference in exposure to quinine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=9/8)	Sudan	No difference in exposure to quinine compared to non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Lumefantrine	Pregnant and non-pregnant women (n=30/30)	Uganda	No difference in exposure to L compared to non-pregnant women.
	Pregnant and non-pregnant women (n=33/22)	Tanzania	34% decreased exposure to L compared to non-pregnant women.
	Pregnant and non-pregnant women (n=26/17)	Uganda	No difference in exposure to L compared to non-pregnant women.
	Pregnant women (n=13)	Thailand	Decreased exposure to L compared to historical controls.
	Pregnant and non-pregnant women (n=116/17)	Uganda	No difference in exposure to L compared to non-pregnant women.
	Pregnant women (n=103)	Thailand	Decreased exposure to L compared to historical controls.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		

L, lumefantrine; MQ, mefloquine; PK, pharmacokinetics; PNG, Papua New Guinea; Tanzania, United Republic of Tanzania

Source: Tarning et al., unpublished

Studies showing an effect of pregnancy on antimalarial medicines PK properties are highlighted in red.

The efficacy of the standard six-dose AL regimen given over 3 days for treatment of falciparum malaria was shown to be unacceptably low (82%) in one small study in pregnant women in a low malaria intensity transmission setting in the Thai–Myanmar border area *(15)*. This high treatment failure rate may have been due to the low concentrations of A and of L. Decreased AL concentrations were also seen in high malaria transmission areas in Uganda and the United Republic of Tanzania, but without significant increases in treatment failure rates, possibly as a result of partial immunity or lower levels of antimalarial resistance (or both). A recent study on a small sample of pregnant women (n=48)

conducted in the Democratic Republic of the Congo prolonged treatment by adding a twice daily 80/480 mg AL dose on days 4 and 5 to the standard AL dosage regimen. This prolonged treatment ensured that pregnant women safely achieved antimalarial drug exposure equivalent to that of non-pregnant women given the standard six-dose AL regimen given over 3 days (Onyamboko et al., unpublished). No differences were observed in the therapeutic efficacy of AL between the 3-day standard regimen and the 5-day experimental treatment, which again may reflect higher levels of partial immunity or lower levels of antimalarial resistance in the African study site.

Regarding DHA-PPQ (DHA-PPQ), although there is no evidence of higher DHA-PPQ treatment failure rates in pregnancy, lower terminal drug concentrations may shorten the post-treatment prophylactic period of PPQ in pregnant women. Pharmacometrics modelling (i.e. science that quantifies drug, disease and trial information to aid efficient drug development or regulatory decisions *(16)*) is ongoing to determine the optimal DHA-PPQ dosage regimens for prospective testing in pregnant women.

Overall, the clinical significance of the PK changes of antimalarial medicines in pregnancy needs to be established before taking decisions on dose adjustments.

Key conclusions on treatment of falciparum and vivax malaria in pregnancy

- The prevalence of falciparum mono-infection among Indian pregnant women from Jharkhand and Odisha states was low (<3.5%).
- A recent study in India has shown that both AS-SP and AS-MQ are efficacious and safe for the treatment of falciparum malaria in pregnant women, but AS-MQ was less well tolerated than AS-SP, with a higher frequency of vomiting.
- A small study in Papua New Guinea has shown the combination of AZ-PPQ to be safe and well tolerated among pregnant women.
- The systematic review of antimalarial drug PK properties in studies among pregnant women found:
  - generally lower drug exposure to artemisinins, L, PPQ and SP in pregnant women compared with non-pregnant women;
  - contradictory results reported for CQ and pyrimethamine in pregnant women compared with non-pregnant women;
  - no difference in drug exposure to AQ, MQ and quinine in pregnant women compared to postpartum women; and
  - that the clinical impact of the reported PK changes and dose optimization need to be established.

2.3. Prevention of falciparum and vivax malaria in pregnancy

2.3.1. RCT on the efficacy and safety of intermittent screening and treatment (IST) with AS-SP versus passive case detection in India.

Between 2012 and 2015, a two-arm, cluster-randomized controlled trial (RCT) comparing the effectiveness of IST with the current policy of PCD for malaria during ANC visits was conducted in four districts of Jharkhand, India (Kuepfer et al., unpublished). A total of 3300 pregnant women in 46 clusters were enrolled in the IST arm, and 3568 women in 41 clusters in the PCD arm. Women in the IST group were screened with a rapid diagnostic test (RDT) for malaria at each ANC visit, and those in the PCD arm were screened only if they had a symptom or sign suggestive of malaria. Women in either arm who had a positive RDT for malaria were treated with AS-SP.

The proportion of women in whom RDT positive malaria was detected at least once during an ANC visit was significantly higher in the IST arm (4.8%) (157/3300) than in the PCD arm (0.6%) (22/3568) ($p<0.001$). However, there was no difference in the risk of placental malaria (active or past) between the IST and PCD arms (6.0% versus 4.5%, $p=0.29$). Most cases of placenta malaria were not detected by RDT (88.5%; 77/87). There was no significant difference in any of the secondary endpoints (birth weight, gestational age, vital status at birth and maternal anaemia) between the two groups. However, there were 30 maternal deaths (14 in the IST arm and 16 in the PCD arm; four of these deaths were attributable to malaria [2 in each arm]), representing an exceptionally high maternal mortality ratio of 437/100 000 live births for the study area.

Overall, IST detected a significantly higher number of women with malaria in pregnancy compared with PCD, indicating that malaria in pregnancy is mostly asymptomatic, even in this very low transmission setting. However, this intervention did not reduce the risk of placental malaria or adverse birth outcomes compared to PCD.

2.3.2. Evaluation of implementation of IST for control of malaria in pregnancy in Jharkhand, India

A study to evaluate implementation of IST in health facilities from Jharkhand (India) along with the previously presented RCT was conducted between 2013 and 2014 (Webster et al., unpublished). The study methods included two cross-sectional household surveys conducted before and after implementation of the intervention, in-depth interviews with health workers delivering the intervention and focus group discussions with pregnant women eligible to receive the intervention.

A total of 1087 questionnaires were completed – 553 before and 534 after the implementation of IST. In-depth interviews were conducted with 29 health providers, and 13 focus group discussions were conducted with currently and recently pregnant women. The proportion of pregnant women who received an RDT for malaria at ANC at least once during their current or recent pregnancy increased from 19.2% (95% CI: 14.9–24.3) before implementation to 42.5% (95% CI: 36.6–48.7) after implementation ($p<0.0001$), and the proportion of women who had more than one RDT during their current or recent pregnancy also increased ($p<0.0001$). Health workers were positive about IST, mainly due to their perception that many pregnant women with malaria were asymptomatic. Health workers perceived pregnant women to have reservations about IST due to dislike of frequent blood taking, but the pregnant women themselves were more positive.

The study concluded that the proportion of pregnant women tested for malaria at least once during their pregnancy increased with implementation of IST. However, if IST is implemented, efforts would need to be made to further increase the proportion of women tested because, overall, less than half of women were reached.

2.3. Intermittent preventive treatment (IPT) or intermittent screening and treatment (IST) with dihydroartemisinin-piperaquine for malaria in pregnancy: an open label cluster-randomized controlled trial in Indonesia

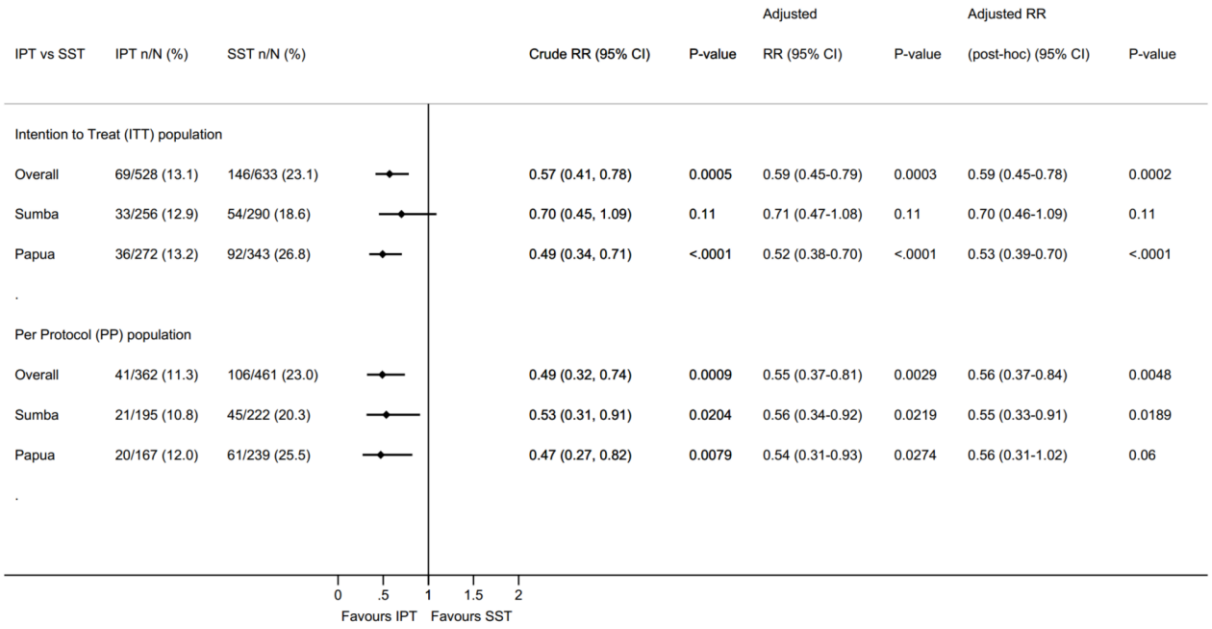
The preliminary results of a recently completed open-label three-arm cluster-RCT in Indonesia comparing the safety and efficacy of monthly IPT with DHA-PPQ, monthly IST with DHA-PPQ, and SST with DHA-PPQ was presented and reviewed (Ahmed et al., unpublished, STOPmalaria in pregnancy project). The trial was carried out in two sites in Indonesia with low (Sumba) and moderate year-round transmission (Papua), and enrolled a total of 2279 pregnant women (Sumba=989; Papua=1290) between 2013 and 2016. Patent *Plasmodium* infection was defined as microscopy or RDT positive and PCR-confirmed loop mediated isothermal DNA amplification (LAMP) positive (where PCR-confirmed LAMP is a LAMP positive sample that was subsequently confirmed as positive by quantitative PCR or nested PCR). Subpatent infection was defined as PCR-confirmed LAMP positive, but microscopy or RDT negative.

At baseline, about 15% of the women were infected with malaria parasites; the level was similar in the SST and IPT arms (18.3% and 17.8%), but was significantly lower in the IST arm (10.4%). Most of these infections were subpatent and below the level of detection by RDT. Ultimately, 1874 (82.1%) women contributed to the primary endpoint at delivery (IST=83.5%, IPT=77.5% and SST=85.1%). Retention was significantly lower in the IPT arm than in the IST arm (relative risk [RR] 0.83, 95% CI: 0.73–0.95, p=0.0032) or SST arm (RR 0.77, 95% CI: 0.66–0.90, p=0.0002), because of a higher withdrawal of consent in two of the seven IPT clusters in Papua, a situation that did not occur in Sumba.

IPT versus SST comparison

At delivery, the prevalence of malaria infection was lower in the IPT than SST arm: 69/528 (13%) versus 146/633 (23%) (RR 0.57, 95% CI: 0.41–0.78, p=0.0005) (Fig. 3). IPT prevented 92% of patent infections in the peripheral blood (RR 0.08, 95% CI: 0.01–0.61, p=0.0147) and 38% of the subpatent infections (RR 0.62, 95% CI: 0.41–0.93, p=0.0192). The protective effect was seen in all gravidae, and was not modified by ITN use, season or socioeconomic status.

FIG. 3.
Malaria at delivery (primary endpoint) in the IPT and SST groups



CI, confidence interval; IPT, intermittent preventive treatment; RR, relative risk; SST, single screening and treatment

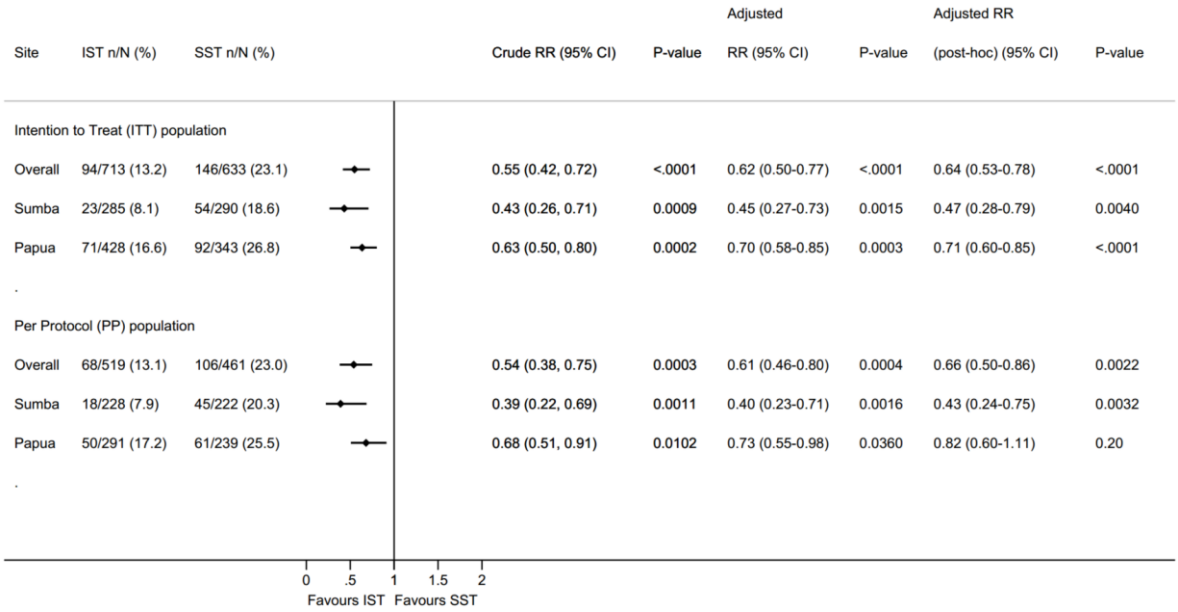
IPT was also associated with lower incidence rates of malaria infection during pregnancy (47.9 versus 91.4 events/100 person-years (py), incidence rate ratio (IRR) 0.56, 95% CI: 0.36–0.88, p=0.0125), but only in Papua Indonesia (higher transmission intensity) (IRR 0.22, 95% CI: 0.14–0.36, p=<0.0001), not in Sumba (low transmission intensity) (IRR 1.14, 95% CI: 0.73–1.77, p=0.57). IPT was also more effective than SST at reducing placental malaria detected by histology (RR 0.47, 95% CI: 0.23–0.95, p=0.0363), but again only in Papua (RR 0.32, 95% CI: 0.18–0.55, p<0.0001), not in Sumba (RR 1.31, 95% CI: 0.50–3.44, p=0.58). In Papua, IPTp-DHA-PPQ reduced the risk of maternal Hb <9 g/dL (RR 0.64, 95% CI: 0.44–0.92, p=0.0157), but not in Sumba (RR 0.91, 95% CI: 0.68–1.23, p=0.55).

The beneficial impact of IPTp with DHA-PPQ on maternal parasites at delivery – and placental malaria – did not translate into benefits for the newborn at birth. Relative to SST, there were no differences in adverse pregnancy outcomes (composite of fetal loss, SGA, LBW or preterm birth, or neonatal death) overall (IPT: RR 1.16, 95% CI: 0.88–1.54, p=0.29). The risk was higher in Sumba (RR 1.44, 95% CI: 1.15–1.81, p=0.0016), but not in Papua (RR 0.88, 95% CI: 0.59–1.30, p=0.52).

IST versus SST comparison

Compared with SST, IST was associated with a lower prevalence of malaria infection at delivery (any measure: 94/713 [13%] versus 146/633 [23%]; RR 0.55, 95% CI: 0.42–0.72, p<0.0001) (Fig. 4), in both sites, but not for placental malaria detected by histology (RR 0.98, 95% CI: 0.57–1.68, p=0.94), and IST was also not associated with a lower incidence of malaria infection during pregnancy (IRR 0.92, 95% CI: 0.64–1.33, p=0.67). There were also no differences in adverse pregnancy outcomes (composite of fetal loss, SGA, LBW or preterm birth, or neonatal death) (RR 1.00, 95% CI: 0.75–1.33, p=0.99).

FIG. 4.
Malaria at delivery (primary endpoint) in the IST and SST groups



CI, confidence interval; IST, intermittent screening and treatment in pregnancy; RR, relative risk; SST, single screening and treatment

IPT versus IST comparison

Overall, only five infections were detected by RDT during 2886 visits in the IST arm, compared to 18 in 2392 visits in the SST arm (all 18 in Papua). Compared with IST, IPT was more effective at reducing the incidence of malaria infection (IRR 0.61, 95% CI: 0.39–0.95, p=0.0303), but only in Papua (IRR 0.33, 95% CI: 0.22–0.49, p<0.0001), not in Sumba (IRR 0.96, 95% CI: 0.62–1.49, p=0.85). IPT was also more effective than IST at reducing placental malaria detected by histology (RR 0.48, 95% CI: 0.25–0.92, p<0.0261), but again only in Papua (RR 0.34, 95% CI: 0.20–0.58, p<0.0001), not in Sumba (RR 1.25, 95% CI: 0.49–3.17, p=0.65). IPT was not associated with less adverse pregnancy outcomes compared with IST (RR 1.16, 95% CI: 0.82–1.65, p=0.39).

Summary of effectiveness of IPT

Compared with SST, IPTp-DHA-PPQ was associated with substantial reductions in multiple malaria infection incidence and prevalence measures during pregnancy and at delivery, but this effect was only observed in the higher transmission intensity study site (where the incidence of malaria infections detected by microscopy during pregnancy was 46/100 py) and not in the lower transmission site (6/100 py). This reduction in malaria in the higher transmission sites was not associated with a lower risk of adverse pregnancy outcomes. Regarding IST, at the current levels of RDT sensitivity, monthly screening with RDTs did not result in the detection of more malaria infections than the existing SST strategy.

The study has several limitations and some of the results (e.g. differences between sites and the observed increased risk of LBW associated with IPT in Sumba) are difficult to interpret. The possibility that DHA-PPQ reduced intrauterine growth in Sumba was explored in two analyses of the per-protocol population. Importantly, there was no evidence of a dose–response effect of DHA-PPQ on either mean birth weights or mean birth weight-for-

age Z-scores, in analyses that included women receiving between two and six doses of the drug. Therefore, it remains unexplained why, in Sumba, compared with SST, exposure to IPTp-DHA-PPQ reduced birth weights, probably owing to intrauterine growth restriction.

The cardiac safety of monthly doses of DHA-PPQ was evaluated in 33 pregnant women from Papua Indonesia (ter Kuile et al., unpublished). Statistically significant increases of the QT interval corrected using the Fridericia method (QTcF) following the final dose of each course were observed (mean 20 msec range –20 to 71). The mean increases in QTcF following DHA-PPQ declined with subsequent doses, suggesting an absence of cumulative effects of DHA-PPQ on QTcF. There were no cardiac events and no QTcF values above 500 msec.

2.3.4. Evaluation of the implementation of single screening and treatment (SST) for the malaria in pregnancy in Eastern Indonesia

The Asia-Pacific region has no standardized and widely recognized strategy for prevention of malaria in pregnancy, and the most common strategy currently in practice for malaria in pregnancyis passive case detection (PCD). However, in 2010–2011, in malaria endemic areas of Indonesia, SST on first visit to ANC followed by PCD at all subsequent visits was introduced, together with provision of a long-lasting insecticidal mosquito net (LLIN).

The preliminary results of a study evaluating the implementation of SST for prevention of malaria in pregnancy in two islands of eastern Indonesia, as per the national guidelines, were presented (Webster et al., unpublished). This study was conducted within the frame of the STOPmalaria in pregnancy project 2013 (in Mimika, Papua) and 2014 (in Sumba). Mixed methods were used, including cross-sectional surveys at hospitals, health centres and health posts in the two study sites. Observations and exit interviews of the ANC visit were conducted to assess compliance with SST guidelines.

A total of 865 ANC visits in Mimika and 895 in West Sumba were included in the study across seven and 10 health facilities, respectively. The study was conducted in hospitals, health centres and health posts. Adherence to malaria screening at first ANC visits among pregnant women varied by level of health facility. In Mimika, among pregnant women attending health centres for their first visit, adherence to screening was high at 94.8% (95% CI: 81.1–98.7), whereas among those attending hospitals it was lower at 60.0% (95% CI: 32.6–82.3) and it was lowest among those attending health posts at 3.8% (95% CI: 1.6–8.8). In West Sumba, corresponding estimates for adherence to screening at first ANC visit for pregnant women attending health centres, hospitals and health posts were 60.0% (95% CI: 32.6–82.3), 0.0% and 9.8% (95% CI: 4.4–20.5), respectively. Most screening conducted at first ANC visit in both sites was by microscopy. In Mimika, 1.1% (2/185) of first ANC visits were screened by RDT, and in West Sumba 1.2% (2/161).

Screening for malaria at first ANC visit in health centres was highly feasible in Mimika, and feasible in West Sumba. The success of the strategy at this level of health facility was due to screening by microscopy. However, in the health posts of both Mimika and West Sumba, where the strategy relies on the use of RDTs, the findings suggest that screening at first ANC visit is not feasible.

2.3.5. *Cost–effectiveness of intermittent preventive treatment (IPT) or intermittent screening and treatment (IST) with DHA-PPQ versus single screening and treatment (SST) for malaria in pregnancy: analysis from a superiority trial in Indonesia*

The preliminary results of the cost–effectiveness analysis (CEA) of the cluster-randomized trial evaluating IPTp, IST and SST in two sites in Indonesia were presented and reviewed (Paintain et al., unpublished). Disability-adjusted life years (DALYs) were calculated using disability weights from the 2015, 2010 and 2004 global burden of disease studies, local life expectancies, no age weighting, and 3% discounting for each trial arm and four outcomes (fetal loss or infant death by 6–8 weeks, LBW, maternal anaemia and malaria infection during pregnancy).

In addition to the costs of the intervention, the provider costs of the consequences of malaria in pregnancymalaria in pregnancy were also calculated per event for each of the four trial outcomes. Step-down costing was used to estimate the unit cost per outpatient consultation, per adult inpatient day and per paediatric inpatient day. The incremental cost–effectiveness ratio (ICER) was calculated for a hypothetical cohort of 1000 women by dividing the incremental cost of the intervention by the incremental DALYs averted.

Provider costs were considerably higher in the Papua health facilities than in the Sumba health facilities, due to a greater number of personnel and therefore higher salary commitments:

- the cost of delivering the current strategy of SST-DHA-PPQ per pregnant woman is US$ 1.64 in Sumba and US$ 2.06 in Papua;
- the cost of delivering IPTp-DHA-PPQ per pregnant woman is US$ 11.54 in Sumba and US$ 10.70 in Papua; and
- the cost of delivering IST-DHA-PPQ per pregnant woman is US$ 7.01 in Sumba and US$ 8.82 in Papua.

Different results for the CEA were found by site:

- in Sumba, the current strategy of SST in pregnancy (SSTp) with DHA-PPQ incurred lower costs (for intervention delivery and cost of consequences) and resulted in fewer DALYs compared with IPTp with DHA-PPQ or IST with DHA-PPQ; and
- in the higher malaria transmission setting of Papua, IPTp-DHA-PPQ and IST-DHA-PPQ were both incrementally more cost effective than the current strategy of SSTp-DHA-PPQ; although IPTp-DHA-PPQ and IST-DHA-PPQ incurred higher incremental costs than SSTp-DHA-PPQ, they resulted in incrementally fewer DALYs.

2.3.6. *Health provider acceptability of intermittent preventive treatment (IPT) or intermittent screening and treatment (IST) versus current policy (single screening and treatment (SST) with DHA-PPQ) in Indonesia*

Within the frame of the STOPmalaria in pregnancy project, health provider acceptance of the current (SSTp) strategy was assessed compared with IPTp and IST in Indonesia (Hoyt et al., unpublished). Between 2015 and 2016, qualitative data were collected through individual in-depth interviews with 121 health providers working in the provision of ANC (midwives, doctors, laboratory staff, pharmacists and heads of drug stores), heads of health

facilities and District Health Office staff. Staff involved in the clinical trial in south-west Sumba and Mimika districts were also interviewed. Health providers were receptive to screening pregnant women at every ANC visit because it provided an increased frequency to detect asymptomatic infections, thereby providing more comprehensive care for mother and baby than the current policy of screening at first ANC visit only. A primary concern was the accuracy and availability of RDTs used for screening; the RDTs were considered less accurate than microscopy. Providers expressed serious reservations about giving antimalarial medicines presumptively as IPTp, because of concerns of causing potential harm to mother and baby, and of contributing to drug resistance.

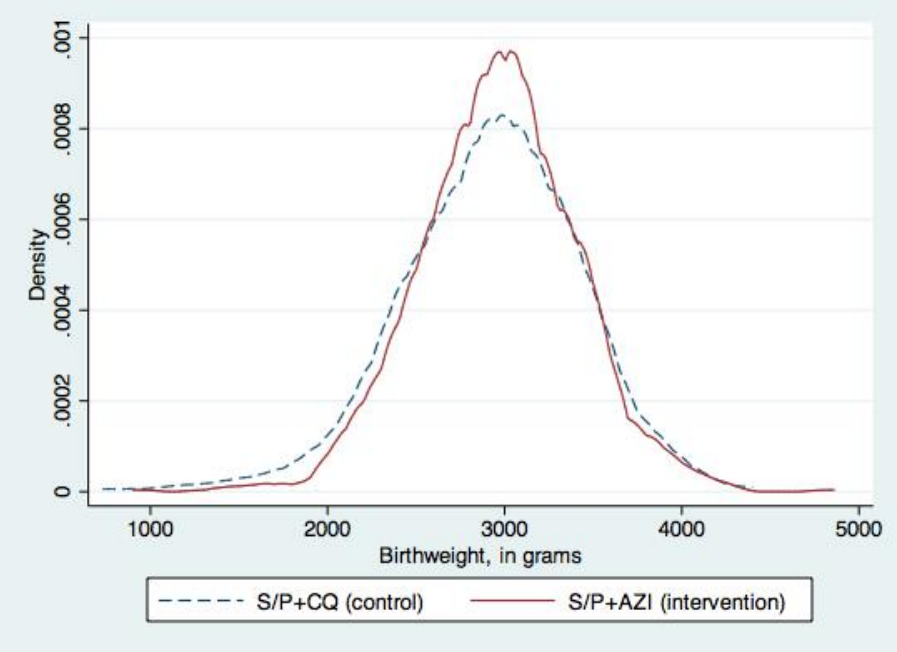
Within the trial context, screening women at every ANC visit (IST) was thus considered an acceptable strategy among health providers owing to an existing culture of screening women at ANC and providing treatment based on positive test results. In contrast, adoption of IPTp would require a considerable shift in health provider attitudes.

2.3.7 IPTp of three courses of SP plus AZ twice daily for 2 days compared to an initial course of SP plus CQ (3 days) followed by placebo for the prevention of LBW: a randomised controlled trial in Papua New Guinea

An RCT conducted between 2009 and 2013 in Papua New Guinea compared IPTp-SP plus AZ (1 g twice daily for 2 days) (SP-AZ) three times from the second trimester (intervention) against SP-CQ (450–600 mg daily for 3 days) given once, followed by SP-CQ placebo (control) *(17)*. Participants were blinded to assignments.

Of the 2793 women randomized, 2021 (72.4%) were included in the primary outcome analysis of LBW (SP-CQ: 1008; SP-AZ: 1013). Overall, the prevalence of LBW was 15.1% (305/2021). SP-AZ reduced LBW (RR 0.74, 95% CI: 0.60–0.91, p=0.005; absolute risk reduction 4.5%, 95% CI: 1.4–7.6), and preterm delivery (RR 0.62, 95% CI: 0.43–0.89, p=0.010); it also increased mean birthweight (41.9 g, 95% CI: 0.2–83.6, p=0.049), as shown in Fig. 5.

FIG. 5.
Distribution of birth weights by treatment arm



AZI, azithromycin; CQ, chloroquine; S/P, sulfadoxine-pyrimethamine

Additionally, SP-AZ reduced maternal parasitaemia (RR 0.57, 95% CI: 0.35–0.95, p=0.029) and active placental malaria (RR 0.68, 95% CI: 0.47–0.98, p=0.037), and reduced carriage of *Neisseria gonorrhoeae* (RR 0.66, 95% CI: 0.44–0.99, p=0.041) at second visit. A reduction in preterm birth in the intervention arm was noted (RR 0.62, 95% CI: 0.43–0.89, p=0.010; absolute risk reduction 4.0%, 95% CI: 1.0–7.0). There were no treatment-related SAEs, and the number of SAEs (intervention 13.1% [181/1378], control 12.7% [174/1374], p=0.712) and adverse events (AEs) (intervention 10.5% [144/1378], control 10.8% [149/1374], p=0.737) was similar. A major limitation of the study was the high loss to follow-up for birthweight.

Compared to a single dose of SP-CQ, three-dose IPTp with SP-AZ was thus efficacious and safe in reducing LBW, possibly acting through multiple mechanisms, including the effect on malaria and on STIs. However, caution is required when interpreting these results because the trial compared three-dose IPTp-SP-AZ with a single dose of SP-CQ, and therefore it is not possible to attribute the benefits observed specifically to AZ or to increased number of SP doses.

The study also assessed the effect on maternal nasopharyngeal carriage and antibiotic susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* at delivery among a subsample of 854 women *(18)*. Nasopharyngeal carriage at delivery was significantly reduced among women who had received SP-AZ for *S. pneumoniae* (SP-AZ, 7.2% [30/418] versus SP-CQ, 19.3% [84/436], p<0.001) and *H. influenzae* (2.9% [12/418] versus 6.0% [26/436], p=0.028), but not for *S. aureus*.

Key conclusions on prevention of falciparum and vivax malaria in pregnancy

- IST did not reduce the risk of placental malaria or adverse birth outcomes compared with PCD in a trial conducted in India. In this trial, most cases of placenta malaria were not detected by RDT.
- The proportion of pregnant women tested for malaria at least once during their pregnancy increased with implementation of IST (compared with PCD) in India.
- Preliminary results of a cluster randomized trial comparing monthly IPTp-DHA-PPQ with IST and SST conducted in two sites in Indonesia indicate that IPTp halved the risk of malaria during pregnancy and at delivery compared with SST, but only in the higher transmission site, and study findings on IPTp were not consistent across sites. IST did not result in the detection of more malaria infections than the existing SST strategy. Based on the current level of evidence, which is inconclusive, additional evaluation and research is needed to determine the potential of IPTp-DHA-PPQ as a malaria control strategy in areas of high transmission in Asia. Further research on IST using highly sensitive RDTs is also required.
- Three doses of IPTp with SP-AZ compared with a single dose of SP-CQ reduced the prevalence of LBW and preterm birth in a trial in Papua New Guinea. Because this effect could at least partly be explained by more frequent SP-dosing in the AP-AZ arm, the impact of adding AZ to IPTp-SP on adverse birth outcomes requires further research.
- IPTp with SP-AZ reduced nasopharyngeal carriage at delivery of S. pneumoniae and *H. influenzae*, but not of *S. aureus*.

2.4 SP and AZ against sexually transmitted and reproductive tract infections

2.4.1 Impact of SP and AZ against sexually transmitted and reproductive tract infections

Curable sexually transmitted and reproductive tract infections (STIs and RTIs include infections by *Treponema pallidum, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis* and bacterial vaginosis, and have been associated with increased risk of adverse birth outcomes such as stillbirths, preterm, intrauterine growth restriction (IUGR) and LBW *(19)*. AZ-based therapies have been suggested as potential candidates to replace SP for IPTp, since they may offer important public health benefits by also reducing the burden of curable STIs and RTIs in pregnancy *(19)*.

A systematic review and meta-analysis of malaria and STI and RTI prevalence estimates in sub-Saharan Africa indicates that such infections impose a considerable burden on pregnant women attending ANC facilities *(20)*. In a cohort study conducted among Zambian pregnant women between 2013 and 2014, 38.7% (95% CI: 35.7–41.6) were coinfected with malaria parasites and at least one STI or RTI *(21)*. Importantly, HIV-infected women had a higher risk of being coinfected than HIV-uninfected women (OR 3.59, 95% CI: 1.73–7.48, p<0.001) *(21)*.

A prospective observational cohort study conducted between 2013 and 2014 in Zambia analysed the incidence of malaria infection and curable STIs and RTIs, maternal exposure to IPTp-SP during the antenatal period (0–1 doses versus ≥2 doses and, separately, 2 doses versus ≥3 doses), and the resulting incidence of stillbirth, LBW, preterm delivery and IUGR *(22)*. In this study, the presence of curable STIs or RTIs by *T. pallidum*, *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* and bacterial vaginosis was diagnosed at study enrolment only.

No significant differences in baseline prevalence of infection across IPTp-SP exposure groups were found. However, among women given two doses compared to no or one dose, the odds of any adverse birth outcome were reduced by 45% (OR 0.55, 95% CI: 0.36–0.86) and 13% further with at least three doses (OR 0.43, 95% CI: 0.27–0.68). Two or more doses compared to no or one dose reduced preterm delivery by 58% (OR 0.42, 95% CI: 0.27–0.67) and 21% further with at least three doses (OR 0.21, 95% CI: 0.13–0.35).

Women with malaria at enrolment who received at least two doses versus no or one dose had 76% lower odds of any adverse birth outcome (OR 0.24, 95% CI: 0.09–0.66), whereas women who had *N. gonorrhoeae* or *C. trachomatis* (or both) at enrolment and were provided with at least two doses versus no or one dose had 92% lower odds of any adverse birth outcome (OR 0.08, 95% CI: 0.01–0.64). Women with neither a malaria infection nor an STI or RTI who received at least two doses had 73% fewer adverse birth outcomes (OR 0.27, 95% CI: 0.11–0.68).

The study was limited by its observational methodology, the effect of unmeasured potential confounders, and the lack of information on whether women were treated for STIs or RTIs. Importantly, available evidence on the pathogens responsible for STIs and RTIs suggests that it is unlikely that intermittent administration of multiple doses of SP given 1 month apart might cure any of these infections.

2.4.2. Efficacy and safety of azithromycin-chloroquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of P. falciparum *malaria infection in pregnant women in Africa*

A multicentre open-label RCT evaluated the efficacy, tolerability and safety of a fixed-dose combination of AZCQ (250 mg AZ/155 mg CQ base) for IPTp compared with IPTp-SP between 2010 and 2013 in Benin, Kenya, Malawi, Uganda and the United Republic of Tanzania *(23)*.

Pregnant women received three IPTp courses with AZCQ (each course: 1000/620 mg AZCQ QD for 3 days) or SP (each course: 1500/75 mg SP QD for 1 day) at 4- to 8-week intervals during the second and third trimester. Study participants were followed up until day 28 post-delivery (time window: day 28–42). The primary endpoint was the proportion of participants with suboptimal pregnancy outcomes – a composite endpoint comprising liveborn neonates with LBW (<2500 g), premature birth (<37 weeks), stillbirth (>28 weeks), abortion (≤28 weeks), lost to follow-up before observation of pregnancy outcome or missing birth weight. The study was terminated early after recruitment of 2891 of the planned 5044 participants, due to futility observed in a pre-specified 35% interim analysis of the primary endpoint of suboptimal pregnancy outcome.

In the final intent-to-treat dataset, 378/1445 (26.2%) participants in the AZCQ and 342/1445 (23.7%) in the SP group had suboptimal pregnancy outcomes, with an estimated RR of 1.11 (95% CI: 0.97–1.25, p=0.12). There was no significant difference in the incidence

of LBW between treatment groups (57/1138 [5.0%] in the AZCQ group, 68/1188 [5.7%] in the SP group, RR 0.87, 95% CI: 0.62–1.23, p=0.44). IPTp-AZCQ was less well tolerated in mothers than IPTp-SP. Occurrences of congenital anomalies, deaths and SAE were similar in both groups. The limitation of the open-label design may have influenced the reported low tolerability of the AZCQ combination treatment.

2.4.3. Impact of intermittent AZ in addition to IPTp with SP in Malawi

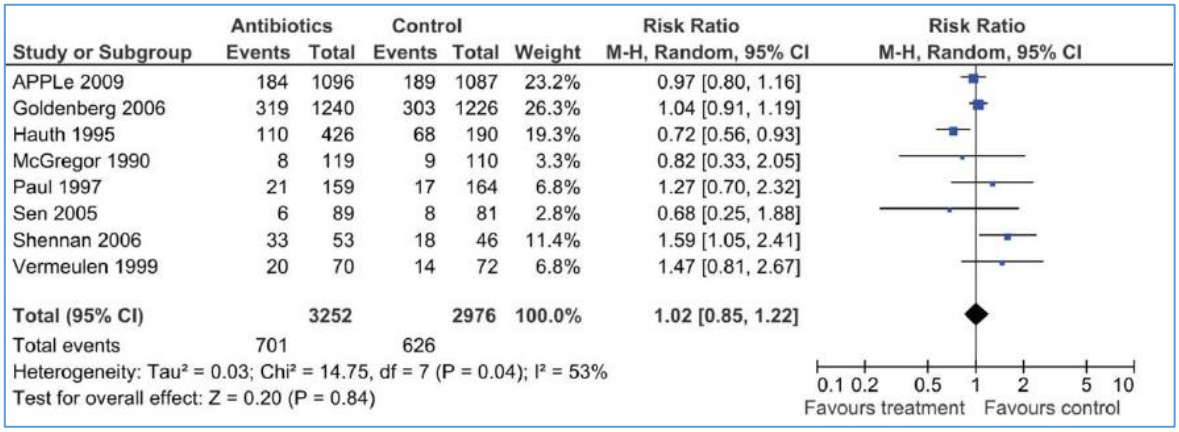
Results from the APPLe placebo-controlled trial conducted in southern Malawi between 2004 and 2005 were presented and reviewed *(24)*. The study evaluated the impact of routine prophylaxis with AZ as directly observed, single-dose therapy at two gestational windows on the incidence of preterm birth.

A total of 2297 pregnant women attending three rural and one periurban health centres were randomized to either 1 g AZ or placebo given at both 16–24 and 28–32 weeks gestational windows. Additionally, all women received two-dose IPTp-SP, as per the national guidelines. Women and their infants were followed up until 6 weeks post-delivery. The primary outcome was incidence of preterm delivery, defined as less than 37 weeks. Secondary outcomes were mean gestational age at delivery, perinatal mortality, birthweight, maternal malaria and anaemia.

There were no significant differences in study outcome between the azithromycin group (n=1096) and the placebo group (n=1087) with regard to preterm birth (16.8% versus 17.4%), OR 0.96 (95% CI: 0.76–1.21); mean gestational age at delivery (38.5 weeks versus 38.4 weeks), mean difference 0.16 (95% CI: 20.08–0.40); mean birthweight (3.03 kg versus 2.99 kg), mean difference in birthweight (0.04 kg, 95% CI: –0.005–0.08); perinatal deaths (95% CI: 4.3% versus 5.0%), OR 0.85 (95% CI: 0.53–1.38); or maternal malarial parasitaemia (11.5% versus 10.1%), OR 1.11 (95% CI: 0.84–1.49) and anaemia (44.1% versus 41.3%) at 28–32 weeks, OR 1.07 (95% CI: 0.88–1.30).

Of note, meta-analysis of seven additional studies of routine antibiotic prophylaxis in pregnancy (>6200 pregnancies) shows no effect on preterm birth (RR 1.02, 95% CI: 0.86–1.22), as shown in Fig. 6 *(24)*.

FIG. 6.
Meta-analysis of trials of routine antibiotic prophylaxis in pregnancy that report preterm birth as outcome



Source: van den Broek et al., 2009 (24)

These findings are in contrast with those of a single-centre, randomized, partially placebo-controlled trial conducted in another region from Malawi *(25)*. A total of 1320 pregnant women were enrolled and received either two-dose IPTp-SP (controls), monthly SP, or monthly SP and two doses of 1 g AZ (AZ-SP).

The incidence of preterm delivery was 17.9% in controls, 15.4% in the monthly SP group (p=0.32), and 11.8% in AZ-SP group (RR 0.66, p=0.01). Moreover, compared with controls, those in AZ-SP group had an RR of 0.61 (95% CI: 0.40–0.93, p=0.02) for LBW. Incidence of SAEs was low and similar in all groups.

Infant follow-up also revealed beneficial effects of AZ-SP. Babies in the AZ-SP group were on average 140 g (95% CI: 70–200 g) heavier at birth and 0.6 cm (0.2–0.9 cm) longer at 4 weeks of age than control group babies *(26)*. Additionally, they had an RR of 0.60 (0.44–0.81) for stunting and 0.48 (0.29–0.79) for underweight at 4 weeks of age compared with controls *(26)*. The analysis of the 5-year follow-up of children born to women who participated in the trial indicates that incidence of stunting and severe stunting was also reduced among children aged under 5 years born to women in the AZ-SP group (Hallamaa et al., unpublished).

2.4.4. Perspective from WHO reproductive health programme

Current WHO recommendations and guidelines for the treatment of STIs (including *T. pallidum*, *N. gonorrhoeae* and *C. trachomatis*) were presented and reviewed.

Syphilis screening is recommended at least once for all women during pregnancy (dual RDTs for HIV/syphilis are now available).

With regard to the potential use of maternal AZ for preventing adverse birth outcomes, the risk of contributing to the development of AZ resistance needs to be taken into account. Besides, it was pointed out that additional laboratory capacity at country level is needed to monitor the possible emergence of antimicrobial resistance to *N. gonorrhoeae*.

Key conclusions on SP and AZ against STIs and RTIs

- Evidence from an observational study conducted in Zambia suggests that, as noted previously in other studies and WHO recommendations, IPTp-SP provides dose-related protection against adverse birth outcomes related to malaria, provided at least three doses of SP are received. This dose–response protection extended to women coinfected with malaria and curable STIs or RTIs. The mechanisms by which sulfadoxine may protect against non-malaria causes of adverse birth outcomes requires more investigation. It is unlikely that multiple doses of SP given 1 month apart provides a cure for any of the major causes of STI or RTIs.
- IPTp-AZCQ was not superior to IPTp-SP in an open-label, multicentre RCT conducted in five sub-Saharan countries.
- Two trials conducted in Malawi evaluating AZ in addition to IPTp-SP in preventing preterm birth yielded conflicting results. The differences may be due to differences in the study population and frequency of SP-dosing in the study intervention. The risk of contributing to the development of AZ resistance needs to be taken into account when considering IPTp-AZCQ.

2.5. HIV and malaria in pregnancy

HIV-infected pregnant women in Africa are especially vulnerable to malaria infection. Paradoxically, these women have been described as the least protected against malaria due to fear of potential drug interactions between IPTp-SP and co-trimoxazole (CTX) prophylaxis and between some antimalarial and ARVs *(27)*.

It has been estimated that about one million pregnancies per year are complicated by the coinfection of malaria and HIV in sub-Saharan Africa *(28)*. Recently, in a randomized placebo-controlled trial, the addition of IPT with an efficacious antimalarial drug (mefloquine) to CTX prophylaxis in HIV-infected pregnant women improved malaria prevention, as evidenced by reductions in peripheral parasitaemia and placental infection, as well as improvement in overall maternal health through decreased hospital admissions *(29)*. However, MQ prophylaxis was not well tolerated, and it was associated with both an increased maternal HIV viral load at delivery and risk of mother-to-child transmission (MTCT) of HIV.

There is thus a need to evaluate antimalarial medicines that can be safely administered to HIV-infected pregnant women on antiretroviral therapy (ART) and CTX prophylaxis.

2.5.1. Effects of HIV infection on malaria in pregnancy: review of the literature

A review of the evidence of HIV and malaria interactions in pregnancy was presented and reviewed (González et al., unpublished).

Malaria and HIV coinfection in pregnant women leads to poorer health for the women and their babies, as well as to higher maternal mortality. This is particularly true in sub-Saharan Africa, which harbours the highest burden of both diseases. Malaria and HIV coinfection during pregnancy leads to a higher risk of poor birth outcomes in infants, including LBW and infant morbidity. Furthermore, treatment of malaria in HIV-infected pregnant women is complicated by HIV-induced immunosuppression and potential interaction with some antiretroviral (ARV) medicines and other medication given concomitantly. Tables 4 and 5 summarize the main evidence on the effects of HIV and malaria coinfection in pregnant women.

TABLE 4.
Main effects of HIV and malaria coinfection in pregnant women

Effect of HIV on malaria	• ↑ Risk of infection • ↑ Parasite density • ↓ Antibodies against placental-type parasites • Loss of parity-dependent malaria immunity
Effect of malaria on HIV	• ↑ HIV viral load • ↑ Production of IL-6, IFN-γ, TNF-α cytokines • Possible ↑ of MTCT of HIV (conflicting results, see Table 5)
Effect of dual infection	• ↑ Severity of illness • ↑ Maternal mortality • ↑ Adverse birth outcomes (LBW, FGR) • ↑ Neonatal mortality

FGR, fetal growth restriction; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; LBW, low birth weight; MTCT, mother-to-child transmission; TFN, tumour necrosis factor

Source: adapted from Hochman et al., 2009 (30)

TABLE 5.
Summary of studies reporting on the association between MTCT of HIV and malaria

Reference	Countries & years	Main results
Brahmbhatt et al., 2003	Uganda 1994–1999	Placental malaria associated with MTCT (RR 2.85, 95% CI: 1.53–5.32)
Inion et al., 2003	Kenya 1996–1999	No association was found between placental malaria and either maternal virus load
Ayisi et al., 2004	Kenya 1996–2000	Low-density placental malaria (<10 000 parasites/µL) was associated with reduced MTCT (absolute risk reduction 0.4). In women dually infected with malaria and HIV, high-density placental malaria (>10 000 parasites/µL) was associated with increased risk of MTCT (aRR 2.0), compared to low-density malaria.
Brahmbhatt et al., 2008	Uganda 1994–2000	Placental malaria associated with MTCT adjusted for maternal HIV viral load (RR 7.9, 95% CI: 1.4–58.5)
Naniche et al., 2008	Mozambique 2003–2006	Placental malaria was associated with a decrease in MTCT (aOR 0.23, 95% CI: 0.06–0.89, p=0.034)
Msamanga et al., 2009	Malawi, Tanzania, Zambia 2001–2003	Placental malaria was not associated with the infant HIV-1 infection status at birth (p=0.67)
Bulterys et al., 2011	Rwanda 1989–1994	Placental malaria associated with MTCT (aOR 6.3, 95% CI: 1.4–29.1), especially among primigravidae

Reference	Countries & years	Main results
Ezeama et al., 2014	Tanzania 2004–2008	HIV MTCT risk increased by 29% (95% CI: 4–58%) per malaria in pregnancy episode.
González et al., 2014	Kenya, Mozambique, Tanzania 2010–2013	Clinical malaria associated with MTCT in adjusted multivariate analysis (RR 4.76, 95% CI: 2.01–11.24)

aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; HIV, human immunodeficiency virus; malaria in pregnancy, malaria in pregnancy; MTCT, mother-to-child transmission; RR, relative risk; Tanzania, United Republic of Tanzania

Prevention of malaria in HIV-infected women remains a challenge since IPTp-SP cannot be co-administered with CTX prophylaxis. Alternative medicines to SP for IPTp have been evaluated in two trials that are summarized in Table 6.

TABLE 6.
Summary of trials evaluating alternative medicines for IPTp among HIV-infected women

Reference	Study design	Countries, years and sample size	Main results
González et al., 2014 *(29)*	Double-blinded, multicentre, placebo superiority trial comparing three-dose IPTp-MQ with placebo in women on CTX prophylaxis	Kenya, Tanzania and Mozambique 2010–2013 N=1071	IPTp-MQ reduced the risk of maternal parasitaemia at delivery, placental infection and hospital admissions in pregnancy. No differences were observed on adverse birth outcomes between groups. However, MQ was associated with transient vomiting, dizziness and an increased MTCT of HIV.
Natureeba et al., 2017 *(31)*	Double-blinded, single-centre, placebo-controlled trial comparing monthly IPTp-DHA-PPQ with placebo in women on CTX prophylaxis	Uganda 2014–2015 N=200	No differences were found between arms on placental malaria, secondary outcomes and frequency of AEs. The frequency of MTCT of HIV was not reported.

AE, adverse event; CTX, co-trimoxazole; DHA-PPQ, dihydroartemisinin-piperaquine; HIV, human immunodeficiency virus; IPTp, intermittent preventive treatment in pregnancy; MTCT, mother-to-child transmission; MQ, mefloquine

Most knowledge on drug interactions comes from in vitro studies or from studies conducted among healthy non-pregnant adults; the clinical relevance of the findings still needs to be assessed. Research is also limited since pregnant women, who constitute one of the most vulnerable populations to malaria and HIV, are generally systematically excluded from clinical trials.

2.5.2. *An assessment of mefloquine, co-trimoxazole and antiretroviral medicines interaction among HIV-infected pregnant women in Kenya*

In the context of the double-blinded placebo-controlled trial evaluating MQ for IPTp *(29)* in combination with CTX prophylaxis, a substudy was conducted in women from Kenya to determine the PK properties of MQ and its effect on the blood levels of CTX *(32)*.

CTX prophylaxis did not influence MQ half-life, observed clearance, and the area under the curve. Although trimethoprim steady-state levels were not significantly different between arms, sulfamethoxazole levels decreased significantly, by 53%, after MQ administration relative to the placebo group, and returned to pre-dose levels after 28 days *(32)*.

A recent analysis of ART concentrations in maternal and cord plasma samples of pregnant Kenyan women participating in the aforementioned IPTp-MQ trial found that women taking nevirapine who received MQ had reduced nevirapine concentrations compared with women who received placebo [Haaland et al., unpublished]. However, the clinical significance of this remains uncertain.

2.5.3. *Intermittent preventive treatment with DHA-PPQ for the prevention of malaria among HIV-infected pregnant women in Uganda*

A double-blinded, randomized, placebo-controlled trial recently published compared daily CTX prophylaxis plus monthly DHA-PPQ with daily CTX prophylaxis plus monthly placebo in HIV-infected pregnant women between 2014 and 2015 in an area of Uganda where indoor residual spraying (IRS) for malaria control had been implemented *(31)*.

A total of 200 pregnant women were enrolled between gestation weeks 12 and 28, and given an LLIN. All women were on ART. The primary outcome was detection of active or past placental malarial infection by histopathologic analysis. Secondary outcomes included incidence of malaria, parasite prevalence and adverse birth outcomes. Those enrolled were followed through delivery, and the primary outcome was assessed in 194 women. In this small study, there was no statistically significant difference in the risk of placental malarial infection between the daily CTX prophylaxis plus monthly DHA-PPQ arm, and the daily CTX prophylaxis plus monthly placebo arm (6.1% versus 3.1%; RR 1.96, 95% CI: 0.50–7.61, p=0.50). Similarly, there were no differences in secondary outcomes. The low prevalence of placental malaria in both arms may reflect the remarkable drop in malaria transmission observed following the introduction of IRS in the study district around the time study enrolment began. Vomiting occurred in less than 0.2% of women after administration of study medicines, with no differences between study arms.

In addition, a PK study was conducted within the frame of the RCT among HIV-infected, uninfected pregnant and non-pregnant women *(33)*. The study found that exposure to DHA and PPQ were lower among pregnant women, particularly in those on efavirenz (EFV)-based ART *(33)*. Additional data on pharmacodynamics and on the clinical impact of this PK study are needed to fully interpret the results. Cardiac monitoring did not suggest that PPQ-associated QTc prolongations were worse in HIV-infected women receiving CTX and EFV-based ARTs than in HIV-uninfected women receiving DHA-PPQ; also, they were not associated with pregnancy status, or the number of previous IPTp courses taken *(33)*.

2.5.4. Perspective from WHO HIV programme

Consolidated ARV 2016 guidelines for HIV-infected individuals living in malaria endemic areas were reviewed. The recommendation on the use of CTX prophylaxis in women and adolescents living with HIV is primarily for prophylaxis against *Pneumocystis* pneumonia, serious bacterial infection and toxoplasmosis. This is relevant to all contexts including malaria endemic settings. The need to avoid simultaneous IPT-SP use is retained in current guidelines, based on a systematic review showing that CTX prophylaxis is not inferior to IPTp with respect to mortality, LBW, placental malaria, maternal deaths and SAEs *(34)*. However, there are limited data on adherence to CTX prophylaxis, and there is a need for further evaluation of its effectiveness in preventing malaria.

Currently, more than 88% of 144 low- and middle-income countries use option B+ (lifelong ARV therapy, ART). Consequently, a high proportion of HIV-infected pregnant women receive ARVsmedicines. Adherence to lifelong treatment is a major objective of national and international efforts to reduce HIV burden and transmission.

First-line antiretroviral treatment is likely to be replaced in the short to medium term by dolutegravir-based ART. Dolutegravir is an integrase inhibitor that has a better profile in terms of drug–drug interactions, which are currently of particular concern with EFV-based ARVs.

Recent reports indicate that EFV-based ART significantly reduce exposure to both DHA-PPQAL and DHA-PPQ. Pharmacometric modelling is ongoing to determine the optimal AL and DHA-PPQ dosage regimens for pregnant women. Given their potential increased risk of treatment failure, full adherence and closer monitoring of their malaria treatment response is essential. However, available evidence does not support a specific dose adjustment in HIV-infected pregnant women.

Key conclusions on HIV and malaria in pregnancy

- HIV-infected pregnant women are particularly vulnerable to malaria and should be targeted in malaria in pregnancy control programmes with specific strategies and tools.
- Recent reports indicate a possible reduction in nevirapine exposure associated to MQ (which was associated with an increased risk of MTCT of HIV) and of DHA-PPQ in women receiving efavirenz (EFV).
- Results of a small RCT conducted in Uganda evaluating monthly DHA-PPQ in HIV-infected women on CTX prophylaxis did not find differences between study arms in placental malaria and birth outcomes. However, maternal and infant HIV-related parameters were not assessed.
- Use of CTX prophylaxis during pregnancy in HIV-infected women is recommended by the WHO HIV programme to prevent Pneumocystis pneumonia, serious bacterial infection, toxoplasmosis and malaria. In malaria endemic areas, CTX prophylaxis is recommended regardless of immunosuppression levels for malaria prevention.
- A large RCT found that an efficacious antimalarial as IPTp added to daily CTX prophylaxis is beneficial for optimal malaria control in HIV-infected pregnant women.
- There is a need to further study drug interactions between CTX, antimalarial and ARV medicines for use in pregnancy to find the best strategy to adequately control malaria during pregnancy in HIV-infected women.

Annex 1. List of meeting pre-reads

Publication	Countries	Description
Ahmed et al., unpublished	Indonesia, Papua Indonesia	Open-label three-arm cluster-randomized trial of SST, IPT and IST in pregnant women
Ahmed et al., 2015 *(35)*	Indonesia	Diagnostic study to compare the performance of four different RDTs in predominately asymptomatic pregnant women under field condition
Anvikar et al., unpublished	India	A Phase II/III randomized open-label two-arm clinical trial of the efficacy and safety of AS-SP and AS-MQ to treat uncomplicated falciparum malaria in pregnancy
Bardají et al., 2017 *(4)*	Brazil, Colombia, Guatemala, India, Papua New Guinea	Multicentre facility-based prospective study to determine the burden and clinical impact of *P. vivax* infection in pregnant women
Bôtto-Menezes et al., 2016 *(10)*	Brazil	Evaluation of the costs associated with malaria treatment among pregnant and postpartum women in a low endemic area of Brazil where *P. vivax* infection predominates
Chico et al., 2011 *(36)*	NA	Comprehensive review on the safety, tolerability and efficacy data of AZ and CQ, alone or in combination, when used to prevent or treat malaria and several curable STIs and RTIs
Chico et al., 2012 *(20)*	NA	Systematic review and meta-analysis of malaria and STI/RTI prevalence estimates among pregnant women attending antenatal care facilities in sub-Saharan Africa
Chico et al., 2013 *(19)*	NA	Systematic review on AZ and curable STIs
Chico et al., 2017 *(22)*	Zambia	Cohort study among pregnant women who received IPTp-SP that relates the incidence of malaria infection and curable STIs and RTIs
Ding et al., unpublished	NA	Pooled PK analysis to investigate the impact of pregnancy on the PK properties of PPQ to optimize the antimalarial dosing regimen
González et al., unpublished	Benin, Gabon, Kenya, Mozambique, Tanzania, Thailand	Cochrane review on the efficacy and safety of mefloquine for preventing malaria in pregnancy
González et al., 2016 *(27)*	NA	Essay on the challenges and way forward of malaria prevention in HIV-infected pregnant women
González et al., unpublished	NA	Literature review on HIV and malaria interactions in pregnancy
Green et al., 2016 *(32)*	Kenya	Study on the PK interactions of MQ, sulfamethoxazole and trimethoprim in pregnant, HIV-infected women

Hill et al., unpublished	Indonesia	Qualitative study on health providers' acceptability and perceptions on the feasibility of implementing the SST strategy in the context of the national programme in Indonesia
Hoyt et al., unpublished	Indonesia	Qualitative study on health provider acceptability of the current SST strategy compared to two potential alternative strategies – IPTp and IST – in the context of a cluster-randomized clinical trial
Kloprogge et al., unpublished	NA	Individual patient data meta-analysis of the PK and PD properties of lumefantrine and the PK properties of its metabolite, desbutyl-lumefantrine
Kuepfer et al., unpublished	India	Cluster-RCT comparing IST and PCD
Luntamo et al., 2010 *(25)*	Malawi	Single-centre RCT comparing two-dose IPTp-SP (controls), monthly SP or monthly SP and two doses of AZ (AZ-SP) on preterm rates (LAIS trial)
Luntamo et al., 2012 *(37)*	Malawi	PCR malaria analysis of samples collected at delivery of women participating in the LAIS trial (Luntamo et al., 2010)
Luntamo et al., 2013 *(26)*	Malawi	Single-centre RCT evaluating the effect of antenatal monthly SP, alone or with AZ, on fetal and neonatal growth (follow-up data of Luntamo et al., 2010)
Marin-Menendez et al., 2013 *(9)*	Brazil	Description of clinically relevant cytoadhesive phenotypes of *P. vivax* isolates
Mayor et al., 2012 *(8)*	PNG	Histopathologic examination of placental biopsies from pregnant women combined with quantitative PCR
Menegon et al., 2016 *(7)*	Brazil, Colombia, India, Papua New Guinea	Characterization of the genetic structure of *P. vivax* populations obtained from pregnant women from different malaria endemic settings
Moore et al., 2016 *(14)*	Papua New Guinea	Study on the safety, tolerability and pharmacokinetics of co-administered AZ and PPQ for treating malaria in pregnant women
Moore et al., 2016 *(13)*	Thailand	Analysis of data collected at ANC clinics between 1994 and 2013 on the safety of artemisinins in first trimester of pregnancy
Moore et al., 2017 *(11)*	Thailand	Analysis of data collected at ANC clinics between 1986 and 2015 on the effects of falciparum and vivax malaria in pregnancy on antepartum and intrapartum stillbirth and neonatal mortality

Moore et al., 2017 *(12)*	Thailand	Analysis of data collected at ANC clinics between 1986 and 2015 on the effects of the total number of malaria episodes in pregnancy on SGA and the effects of malaria in pregnancy on SGA and preterm birth, by the gestational age at malaria detection and treatment
Natureeba et al., 2017 *(31)*	Uganda	Double-blinded, single-centre, placebo-controlled trial comparing monthly IPTp-DHA-PPQ with placebo in HIV-infected women on ART and CTX prophylaxis
Paintain et al., unpublished	Indonesia	Cost–effectiveness analysis of IPTp or IST with DHA-PPQ versus SST for the control of malaria in pregnancy
Requena et al., 2014 *(38)*	Papua New Guinea, Spain	Study of the combined impact of high malaria exposure and pregnancy in B cell subpopulations, where peripheral blood mononuclear cells from pregnant and non-pregnant individuals from a malaria non-endemic country (Spain) and from a high malaria endemic country (Papua New Guinea) were analysed
Requena et al., 2017 *(5)*	Brazil, Colombia, Guatemala, India, Papua New Guinea	Analysis of IgG responses to *P. vivax* and *P. falciparum* antigens, and cellular immune responses to two *P. vivax* antigens, in a subset of 1056 pregnant women
ter Kuile et al., unpublished	Papua Indonesia	Cardiac safety study of monthly IPTp with DHA-PPQ in 33 pregnant women
Unger et al., 2015 *(17)*	Papua New Guinea	RCT that compared IPTp-SP plus AZ monthly from second trimester (intervention) against SP-CQ given once, followed by SP-CQ placebo (control)
van den Broek et al., 2009 *(25)*	Malawi	Placebo RCT that evaluated the impact of routine prophylaxis with AZ as directly observed, single-dose therapy at two gestational windows on the incidence of preterm birth
Webster et al., unpublished	Indonesia	Evaluation of the implementation of SST for the control of malaria in pregnancy
Webster et al., unpublished	India	Evaluation of the implementation of IST for control of malaria in pregnancy

ANC, antenatal care; ART, antiretroviral therapy; AS, artesunate; AZ, azithromycin; CQ, chloroquine; CTX, co-trimoxazole; DHA-PPQ, dihydroartemisinin-piperaquine; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IPT, intermittent preventive treatment; IPTp, intermittent preventive treatment in pregnancy; IST, intermittent screening and treatment in pregnancy; malaria in pregnancy, malaria in pregnancy; MQ, mefloquine; NA, not applicable; PCD, passive case detection; PCR, polymerase chain reaction; PD, pharmacodynamics; PK, pharmacokinetics; PPQ, piperaquine; RCT, randomized controlled trial; RDT, rapid diagnostic test; RTI, reproductive tract infection; SGA, small for gestational age; SP, sulfadoxine-pyrimethamine; SST, single screening and treatment; STI, sexually transmitted infection

Annex 2. Questions addressed and proposed responses to the Evidence Review Group panel

Q1 – What are the consequences of vivax malaria in pregnancy (malaria in pregnancy) in terms of birth outcomes and morbidity for the pregnant women?

With regard to maternal morbidity, the evidence reviewed indicates that vivax malaria in pregnancy increases the risk of maternal anaemia.

Additionally, analyses of data from the Thai–Myanmar border area indicate that vivax malaria is associated with fetal loss, small for gestational age (SGA) babies, preterm birth and neonatal mortality. Fetal loss was particularly relevant in pregnant women suffering malaria symptomatic episodes and SGA in those with recurrent infections.

Q2 – What are the consequences of falciparum and vivax coinfections in pregnancy in terms of birth outcomes and morbidity for the pregnant women?

No studies have yet been carried out to evaluate the consequences of falciparum and vivax coinfections on birth outcomes and maternal morbidity.

Q3 – Is there evidence from clinical trials or pharmacokinetics/pharmacodynamics (PK/PD) studies of specific PK changes in pregnancy of any of the following antimalarials: dihydroartemisinin (DHA), piperaquine (PPQ), artesunate (AS), artemether (AM), lumefantrine (L), amodiaquine (AQ) and mefloquine (MQ)? Is there evidence that these changes are affecting therapeutic efficacy or safety of antimalarial medicines for the treatment of uncomplicated falciparum malaria, so to require specific dose adjustments during pregnancy?

The PK effects of pregnancy vary substantially between the different studies and antimalarial medicines. Some prospective studies have shown a significantly decreased exposure to AS, DHA, L, PPQ and sulfadoxine during pregnancy, but these findings have not been consistent for all studies reported.

The limited prospective data available do not suggest pregnancy associated pharmacokinetic changes for AQ, AM, quinine and MQ. The findings on the effect of pregnancy on pyrimethamine exposure have been inconsistent, with decreased, unchanged and increased exposure reported.

Given the inconsistency of the above findings it is not entirely clear whether dosage adjustment is required during pregnancy.

Q4 – Is intermittent screening and treatment (IST) or intermittent preventive treatment (IPT) with dihydroartemisinin-piperaquine (DHA-PPQ) more effective in the prevention of the consequences of malaria in pregnancy compared to single screening and treatment (SST)?

The preliminary results of a randomized controlled trial (RCT) conducted in Indonesia comparing the three strategies do not allow conclusions to be drawn on which is the most

effective strategy, because the findings were not consistent across sites and study outcomes.

IST was superior to SST for the prevention of malaria at delivery, but did not improve birth outcomes, and the ability to interpret this comparison meaningfully was undermined by the very low (4/713) number of women in the IST arm that received DHA-PPQ. Therefore, based on the results from this study it is not possible to confirm or reject the potential efficacy of IST as a strategy.

Intermittent preventive treatment in pregnancy (IPTp) was superior to SST on the primary outcome, namely the prevention of malaria at delivery. Overall, IPTp reduced the risk of parasites at delivery by 41%. This effect was driven by the site in Papua (47% reduction), and was not significantly observed in Sumba (30% reduction). In Papua only, IPTp also reduced the risk of maternal haemoglobin (Hb) of below 9 (by 31%) and placental malaria (by 58%). Antenatal clinical malaria was rare in all arms; therefore, no strategy significantly prevented clinical malaria in mothers. However, these benefits on maternal parasites at delivery – and placental malaria – did not translate into benefits for the newborn.

Q5 – Is IST with AS plus sulfadoxine-pyrimethamine (SP) more effective in the prevention of the consequences of malaria in pregnancy than passive case detection (PCD)?

Results from a cluster-RCT conducted in India comparing IST-AS-SP with PCD found no difference in the risk of placental malaria (active or past) between study arms (6.0% versus 4.5%, p=0.29). In addition, prevalence was similar in the different arms in terms of adverse birth outcomes including preterm birth, stillbirth, low birth weight (LBW) and perinatal death. Therefore, in this setting, IST with AS-SP was not found to be more effective than PCD.

Q6 – Is IST with DHA-PPQ or with AS-SP feasible and cost effective in the context of the studies implemented in India and Indonesia?

In Indonesia, the acceptability of IST to providers was high owing to the existing clinical practices of screening women for malaria. However, the feasibility of IST in Indonesia is undermined by inconsistent supplies of rapid diagnostic tests (RDTs).

With regard to the cost–effectiveness analyses of IST-DHA-PPQ, IPTp-DHA-PPQ and SSTp-DHA-PPQ conducted within the frame of the RCT in Indonesia, different results were found by site. In Sumba, IPTp-DHA-PPQ and IST-DHA-PPQ resulted in higher costs and a greater number of disability-adjusted life years (DALYs) (for intervention delivery and cost of consequences) compared with the current strategy of SSTp-DHA-PPQ. In contrast, in the higher malaria transmission setting of Papua, IPTp-DHA-PPQ and IST-DHA-PPQ were both incrementally more cost effective than the current strategy of SSTp-DHA-PPQ; although IPTp-DHA-PPQ and IST-DHA-PPQ incurred higher incremental costs than SSTp-DHA-PPQ, they resulted in fewer DALYs.

Q7 – What is the impact of intermittent treatment for malaria in pregnancy with SP and azithromycin (AZ) on adverse birth outcomes?

Compared with IPTp with SP plus chloroquine (SP-CQ+) monthly placebo, IPTp-SP-AZ reduced the prevalence of LBW and preterm delivery in a trial in Papua New Guinea. The risk of placental malaria and maternal parasitaemia was also reduced.

Q8 – What is the additive impact of AZ when added to IPTp with SP on adverse birth outcomes?

Two trials conducted in Malawi evaluating AZ in addition to IPTp-SP in preventing preterm birth yielded opposite results. The difference can be explained by differences in prevalence of malaria and frequency of SP dosing in the study intervention.

Q9 – What is the additive impact of IPTp with SP and AZ on sexually transmitted diseases (STIs) and reproductive tract infections (RTIs)?

The trial comparing IPTp-SP-CQ plus monthly placebo with IPTp-SP-AZ conducted in Papua New Guinea found a reduced carriage of gonorrhoea (OR 0.66, 95% CI: 0.44–0.99, p=0.041) at the second antenatal care visit in the AZ arm.

The potential of IPTp-SP for reducing the burden and consequences of STIs and RTIs as suggested in a recent observational study is contrary to current knowledge that multiple doses of SP given 1 month apart do not cure STIs and RTIs caused by *Treponema pallidum, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis* and bacterial vaginosis mentioned in the study. More research is needed to determine whether sulfadoxine has an inhibitory effect on or other clinically important pathogens, or whether sulfadoxine reduces maternal inflammatory responses that might otherwise contribute to preterm delivery in the presence of maternal infection.

More research would be thus needed to establish the additive effect of AZ to IPTp-SP plus AZ on STIs and RTIs. The minimum dose of AZ to prevent the syphilis-related adverse pregnancy outcomes is 2 g. The impact of AZ on bacterial antibiotic resistance also requires further evaluation.

Q10 – Among pregnant women with malaria and HIV coinfections, what is the efficacy and effectiveness of co-trimoxazole (CTX) prophylaxis for prevention of malaria and its adverse consequences compared to the efficacy and effectiveness of IPTp using alternative medicines (MQ or DHA-PPQ)

Studies have evaluated the effect of adding MQ or DHA-PPQ as IPTp in HIV-infected women receiving CTX prophylaxis.

The multicentre placebo-controlled trial evaluating IPTp-MQ in HIV-infected women on CTX prophylaxis from Kenya, Mozambique and Tanzania (n=1071) showed three-dose IPTp-MQ reduced the risk of maternal parasitaemia at delivery, placental infection and hospital admissions in pregnancy. No differences were observed on adverse birth outcomes between groups. However, MQ was associated with vomiting, dizziness and an increased risk of mother-to-child transmission (MTCT) of HIV.

A recent placebo-controlled trial conducted in Uganda evaluated monthly IPTp-DHA-PPQ among 200 HIV-infected pregnant women receiving antiretroviral therapy (ART) and CTX prophylaxis in a setting where indoor residual spraying was practised. The study reported no significant differences between arms in pregnancy outcomes. The frequency of MTCT of HIV has not been reported.

Further research is needed on optimal malaria prevention in HIV-infected pregnant women.

Q11 – Is there evidence from clinical trials or PK/PD studies of specific changes in HIV-infected pregnant women affecting the therapeutic efficacy or safety of medicines for the treatment of uncomplicated falciparum malaria, so to require specific dose adjustments during pregnancy?

Recent reports indicate that efavirenz-based ART significantly reduces exposure to both DHA-PPQ and AL. Pharmacometric modelling is ongoing to determine the optimal AL and DHA-PPQ dosage regimens for pregnant women. Given their potential increased risk of treatment failure, full adherence and closer monitoring of their malaria treatment response is essential. However, current evidence does not support a specific dose adjustment in HIV-infected pregnant women.

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WHO Evidence Review Group (ERG) on malaria in pregnancy (MiP) outside of Africa

Dr L. Slutsker

Malaria Policy Advisory Committee (MPAC) Meeting

17-19 October 2017

Chateau de Penthes, Pregny-Chambésy, Switzerland

Global **Malaria** Programme

World Health Organization

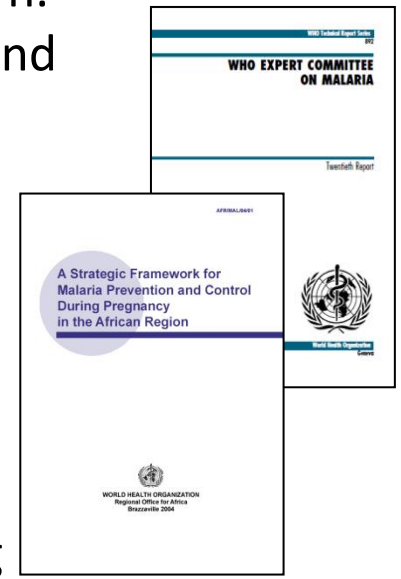
Background of the meeting

- Number of pregnancies outside Africa (low malaria transmission) or with *P. vivax* > number pregnancies in areas with stable *P. falciparum*
- Limited information on the burden of malaria in pregnancy in these endemic areas outside of Africa.
  - malaria infection rates lower, but associated with symptomatic and severe disease, preterm births, and fetal loss.
  - *P. vivax* common in Asia and the Americas, associated with maternal anaemia and LBW
- Generic prevention guidelines for MiP not available for regions outside Africa. Currently - mainly case management (some countries promote CQ chemoprophylaxis, single screen and treat strategies, and ITNs)
- Lack of guidance for malaria prevention for HIV-infected pregnant women (concern re: potential interactions ARVs and antimalarial drugs)

Current WHO recommendations

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the newborn. WHO recommends a package of interventions for preventing and controlling malaria during pregnancy, which includes:

1. promotion and use of insecticide-treated nets,
2. appropriate case management with prompt, effective treatment
3. in areas with moderate to high transmission of *P. falciparum*, administration of IPTp-SP.



Meta-analysis of 32 national cross-sectional datasets assessing the effectiveness of IPTp or ITNs showed that the use of IPTp or ITNs decrease the risk of neonatal mortality (PE=18%, 95%CI 4-30) and of low birth weight (PE=21%, 95%CI 14-27) in women in their first or second pregnancy.

Eisele TP, Larsen DA, Anglewicz PA, *et al. Lancet Infect Dis* 2012; http://dx.doi.org/10.1016/S1473-3099(12)70222-0.

Objectives of the meeting

To review / consider

1. Burden of vivax malaria in pregnant women and impact on birth outcome
2. Efficacy and safety of medicines to treat uncomplicated falciparum and vivax malaria in pregnancy
3. Pharmacokinetics of dihydroartemisinin, piperaquine, artesunate, artemether, lumefantrine, amodiaquine and mefloquine during pregnancy and implications for dose adjustments
4. Efficacy and safety of intermittent screening and treatment (IST) and intermittent preventive treatment (IPT) of MiP in Asia;
5. Effects of sulfadoxine-pyrimethamine (SP) and azithromycin protection against adverse birth outcomes related to sexually transmitted and reproductive tract infections (STI)
6. Key challenges / gaps regarding prevention and treatment MiP in HIV-infected women including: 1) the efficacy/effectiveness of co-trimoxazole prophylaxis ;2) efficacy/ effectiveness of IPTp; and 3) pharmacokinetics of antimalarials including interactions with anti-retroviral medicines (ARVs)

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Conclusions & recommendations for MPAC review

Q1 - What are the consequences of vivax malaria in pregnancy in terms of birth outcomes and morbidity for the pregnant women?

Q1bis - What are the consequences of falciparum and vivax co-infections in pregnancy in terms of birth outcomes and morbidity for the pregnant women?

Conclusions/recommendations

1. Overall incidence of *Plasmodium vivax* infection in pregnancy is low

- Clinical episodes associated with maternal anaemia, fetal loss, small for gestational age and preterm births, particularly in symptomatic pregnant women.

- Evidence reviewed does not support a change in the current recommendations on prevention, early diagnosis and treatment of clinical malaria followed by chloroquine prophylaxis to prevent parasitaemia following relapses.

2. Further research is needed on the effects of *P. falciparum* and *P. vivax* coinfection in pregnancy.

WHO ERG on malaria in pregnancy

Impact of *P. vivax* and *P. falciparum* malaria on maternal anemia and low birth weight.

	P. vivax						*P. falciparum*					
	Maternal anaemia *			Low birth weight			Maternal anaemia			Low birth weight		
	Adjusted OR †	(95% CI)	p-value	Adjusted OR	(95% CI)	p-value	Adjusted OR	(95% CI)	p-value	Adjusted OR	(95% CI)	p-value
At enrolment												
Non-infected	1		**0.009**	1		0.350	1		**0.001**	1		0.092
Asymptomatic malaria infection	0.96	(0.37–2.44)		0.92	(0.21–4.14)		4.01	(1.59–10.11)		2.03	(1.07–3.85)	
Clinical malaria	5.48	(1.83–16.41)		2.29	(0.74–7.04)		5.57	(1.22–25.34)		1.39	(0.16–12.03)	
At delivery												
Non-infected	1		0.754	1		0.298	1		0.122	1		**0.004**
Asymptomatic malaria infection	0.66	(0.22–1.96)		1.01	(0.22–4.63)		8.19	(1.08–62.38)		4.52	(1.63–12.49)	
Clinical malaria	1.05	(0.07–15.58)		9.39	(0.56–158.25)		1.29	(0.23–7.18)		4.29	(0.70-26-24)	
Non-infected	1		0.384	1		0.895	1		**<0.001**	1		**0.001**
Microscopic infection	0.62	(0.22–1.81)		0.90	(0.20–4.10)		4.07	(1.93–8.58)		4.28	(1.75–10.44)	
Non-infected	1		0.717	1		0.110	1		0.402	1		0.359
Sub-microscopic infection ‡	1.16	(0.52–2.59)		0.52	(0.23–1.16)		2.93	(0.24–36.23.16)		1.97	(0.46–8.46)	

* Maternal anaemia: Hb< 11 g/dL.

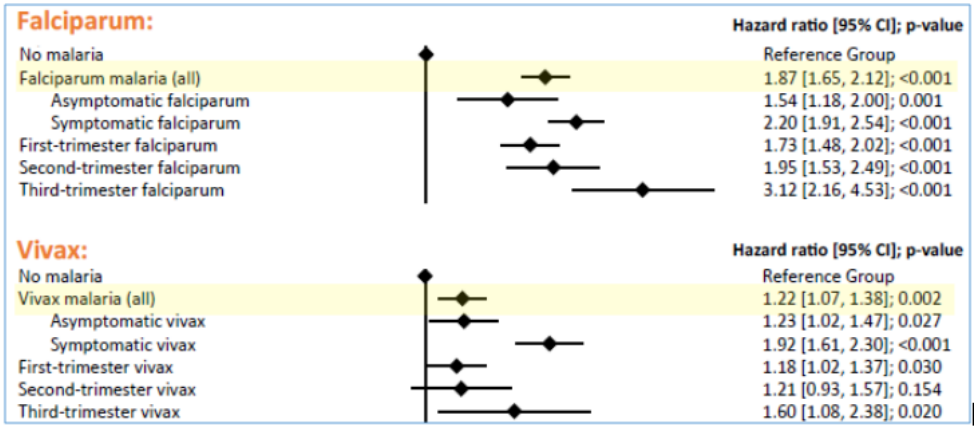
† Adjusted Odds Ratio (OR) for site and previous malaria episodes.

‡ Nested case-control study.

Bardají A, Martínez-Espinosa FE, Arévalo-Herrera M, Padilla N, Kochar S, Ome-Kaius M, et al. (2017) Burden and impact of *Plasmodium vivax* in pregnancy: A multi-centre prospective observational study. PLoS Negl Trop Dis 11(6): e0005606. https://doi.org/10.1371/journal.pntd.0005606

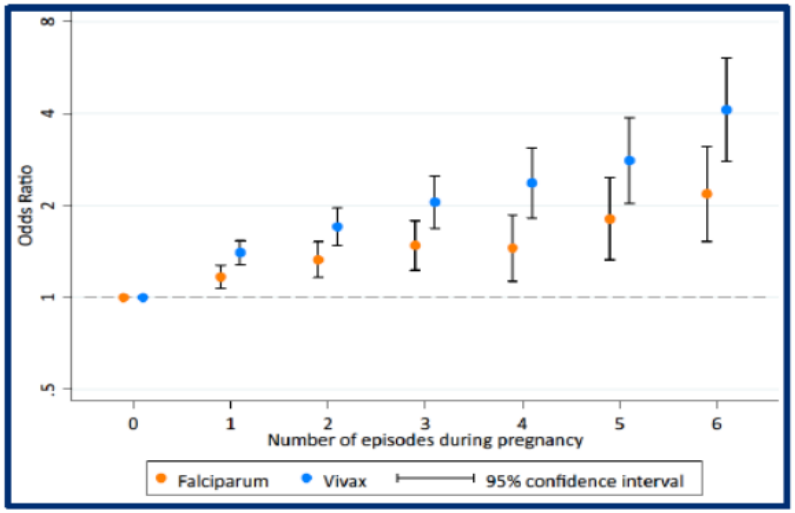
WHO ERG on malaria in pregnancy

malaria in pregnancy and fetal loss (miscarriage or stillbirth)



CI, confidence interval
Source: Moore et al., 2017 *(11)*

malaria episodes and small for gestational age



SGA, small for gestational age
Source: Moore et al., 2017 *(12)*

Conclusions & recommendations for MPAC review

Q2 – Is there evidence from clinical trials or PK/PD studies of specific PK changes in pregnancy of any of the following antimalarials: dihydroartemisinin, piperaquine, artesunate, artemether-lumefantrine, amodiaquine and mefloquine?

Is there evidence that these changes are affecting therapeutic efficacy or safety of antimalarial medicines for the treatment of uncomplicated falciparum malaria, so to require specific dose adjustments during pregnancy?

Conclusions/recommendations

3. PK effects of pregnancy vary substantially among the different studies and antimalarial medicines

- Findings inconsistent ; not entirely clear whether dosage adjustment is required during pregnancy.

- Importantly, the clinical relevance of PK changes needs to be established before any dosage modification in pregnant women is suggested.

WHO ERG on malaria in pregnancy

Antimalarial	Study patients	Country	Pregnancy effects
Artesunate	Pregnant women (n=24)	Thailand	Decreased exposure to DHA compared to historical controls.
	Pregnant and postpartum women (n=20/15)	Thailand	23% decreased exposure to DHA compared with postpartum women.
	Pregnant, postpartum and non-pregnant women (n=26/26/25)	DRC	42% decreased exposure to DHA compared with non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Burkina Faso	No difference in exposure to DHA compared non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Artemether	Pregnant and non-pregnant women (n=30/30)	Uganda	No difference in exposure to DHA compared non-pregnant women.
	Pregnant and non-pregnant women (n=33/22)	Tanzania	No difference in exposure to DHA compared non-pregnant women.
	Pregnant women (n=21)	Uganda	Decreased exposure to DHA compared to historical controls.
	Pregnant women (n=13)	Thailand	Decreased exposure to DHA compared to historical controls.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
DHA	Pregnant and non-pregnant women (n=32/33)	PNG	No difference in exposure to DHA compared to non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Thailand	38% decreased exposure to DHA compared to non-pregnant women.
	Pregnant and non-pregnant women (n=31/30)	Uganda	47% decreased exposure to DHA compared to non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		

DHA, dihydroartemisinin; DRC, Democratic Republic of the Congo; PK, pharmacokinetics; PNG, Papua New Guinea; Tanzania, United Republic of Tanzania

Source: Tarning et al., unpublished

Summary of PK properties of artemisinin derivatives in studies conducted among pregnant women

Studies showing an effect of pregnancy on antimalarial medicines PK properties are highlighted in red

Conclusions of the ERG for MPAC review

Q3 – Is intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin+piperaquine more effective in the prevention of the consequences of malaria in pregnancy compared to single screening and treatment?

Conclusions/recommendations

4. CRCT Indonesia (2 sites) compared

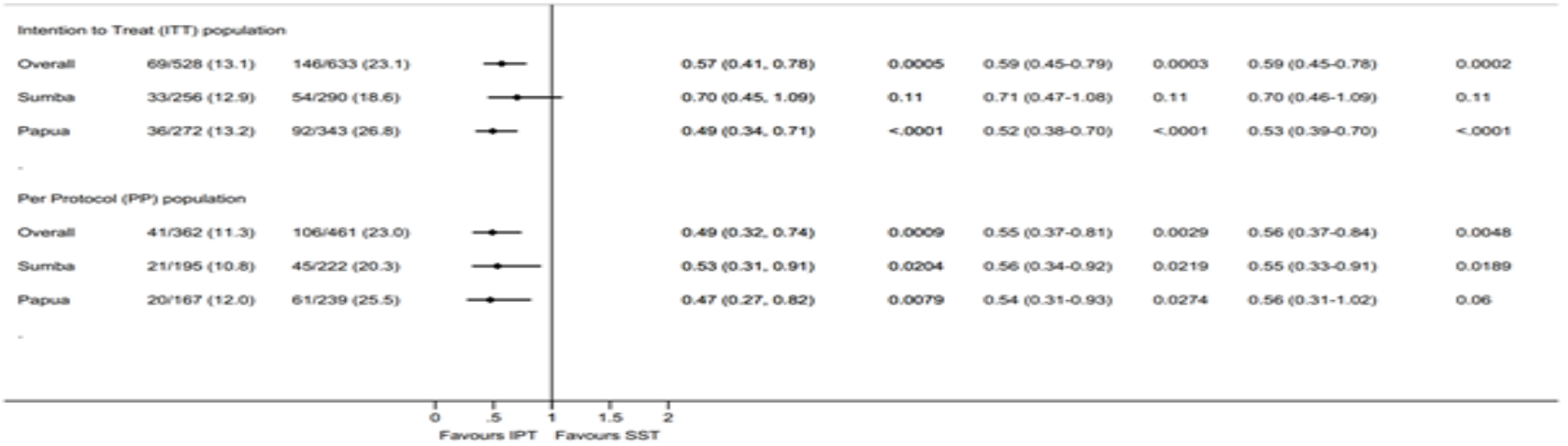
- monthly IPTp with dihydroartemisinin-piperaquine (DHA-PPQ)
- intermittent screening and treatment (IST) + DHA-PPQ single
- screening and treatment (SST) + DHA-PPQ conducted in two
- Preliminary results
  - IPTp halved risk of malaria c/w SST, but only in the higher transmission site in Papua Indonesia.
  - Study findings not consistent across sites and study outcomes
  - No consistent positive impact on birth outcomes.
  - IST did not detect more malaria infections than SST strategy.

-Based on the current level of evidence, IPTp-DHA-PPQ is not currently recommended for malaria prevention in pregnant women

WHO ERG on malaria in pregnancy

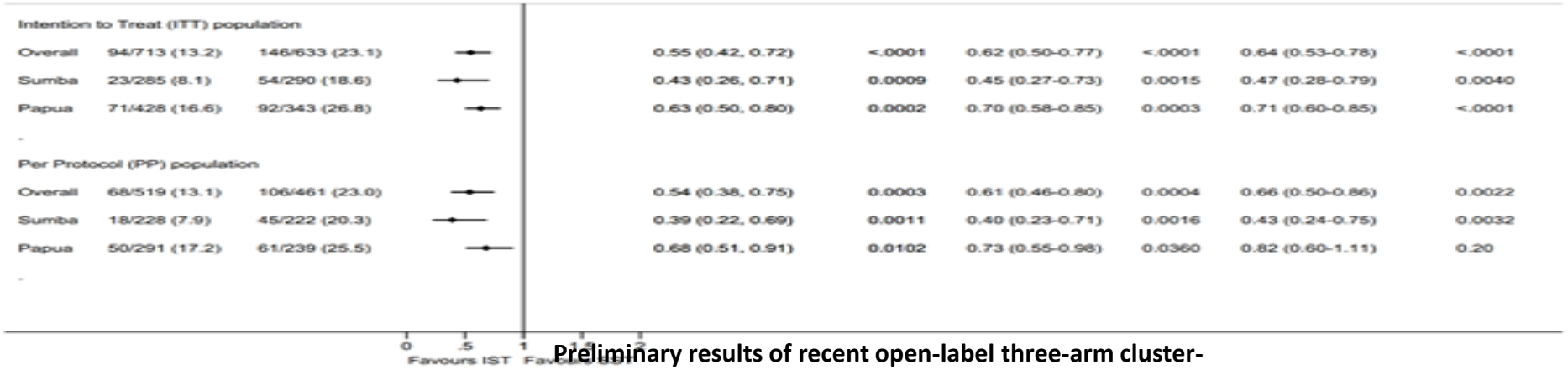
Malaria at delivery (primary endpoint) in the IPT and SST groups

IPT vs SST	IPT n/N (%)	SST n/N (%)	Crude RR (95% CI)	P-value	Adjusted RR (95% CI)	P-value	Adjusted RR (post-hoc) (95% CI)	P-value
Intention to Treat (ITT) population								
Overall	69/528 (13.1)	146/633 (23.1)	0.57 (0.41, 0.78)	0.0005	0.59 (0.45-0.79)	0.0003	0.59 (0.45-0.78)	0.0002
Sumba	33/256 (12.9)	54/290 (18.6)	0.70 (0.45, 1.09)	0.11	0.71 (0.47-1.08)	0.11	0.70 (0.46-1.09)	0.11
Papua	36/272 (13.2)	92/343 (26.8)	0.49 (0.34, 0.71)	<.0001	0.52 (0.38-0.70)	<.0001	0.53 (0.39-0.70)	<.0001
Per Protocol (PP) population								
Overall	41/362 (11.3)	106/461 (23.0)	0.49 (0.32, 0.74)	0.0009	0.55 (0.37-0.81)	0.0029	0.56 (0.37-0.84)	0.0048
Sumba	21/195 (10.8)	45/222 (20.3)	0.53 (0.31, 0.91)	0.0204	0.56 (0.34-0.92)	0.0219	0.55 (0.33-0.91)	0.0189
Papua	20/167 (12.0)	61/239 (25.5)	0.47 (0.27, 0.82)	0.0079	0.54 (0.31-0.93)	0.0274	0.56 (0.31-1.02)	0.06



Malaria at delivery (primary endpoint) in the IST and SST groups

Site	IST n/N (%)	SST n/N (%)	Crude RR (95% CI)	P-value	Adjusted RR (95% CI)	P-value	Adjusted RR (post-hoc) (95% CI)	P-value
Intention to Treat (ITT) population								
Overall	94/713 (13.2)	146/633 (23.1)	0.55 (0.42, 0.72)	<.0001	0.62 (0.50-0.77)	<.0001	0.64 (0.53-0.78)	<.0001
Sumba	23/285 (8.1)	54/290 (18.6)	0.43 (0.26, 0.71)	0.0009	0.45 (0.27-0.73)	0.0015	0.47 (0.28-0.79)	0.0040
Papua	71/428 (16.6)	92/343 (26.8)	0.63 (0.50, 0.80)	0.0002	0.70 (0.58-0.85)	0.0003	0.71 (0.60-0.85)	<.0001
Per Protocol (PP) population								
Overall	68/519 (13.1)	106/461 (23.0)	0.54 (0.38, 0.75)	0.0003	0.61 (0.46-0.80)	0.0004	0.66 (0.50-0.86)	0.0022
Sumba	18/228 (7.9)	45/222 (20.3)	0.39 (0.22, 0.69)	0.0011	0.40 (0.23-0.71)	0.0016	0.43 (0.24-0.75)	0.0032
Papua	50/291 (17.2)	61/239 (25.5)	0.68 (0.51, 0.91)	0.0102	0.73 (0.55-0.98)	0.0360	0.82 (0.60-1.11)	0.20



Preliminary results of recent open-label three-arm cluster-RCT in Indonesia comparing monthly IPT with DHA-PPQ, monthly IST with DHA-PPQ, and SST with DHA-PPQ (Ahmed et al., unpublished, STOPmalaria in pregnancy project)

Conclusions of the ERG for MPAC review

Q6 - What is the impact of intermittent treatment for malaria in pregnancy with ***sulfadoxine-pyrimethamine and azithromycin on adverse birth outcomes*** *?*
Q6bis - What is the ***additive impact of azithromycin when added to intermittent treatment with sulfadoxine-pyrimethamine*** *on adverse birth outcomes ?*
Q7 - What is the impact of intermittent treatment for malaria in pregnancy with ***sulfadoxine-pyrimethamine and azithromycin on sexually transmitted diseases*** *and reproductive tract infections?*

Conclusions/recommendations

5. IPTp SP does not cure sexually transmitted infections (STIs) and reproductive tract infections (RTIs). (NG, syphilis, TV, Chlamydia)

- -Impact of added azithromycin to IPTp SP on STIs or RTIs and adverse birth outcomes requires further research; evidence of improved outcomes limited. Noted risk of increases in antimicrobial resistance associated with azithromycin use.

6. Contradictory results on additional benefit of azithromycin to IPTp-SP for preventing adverse birth outcomes in Malawi. LBW and preterm birth rates were reduced in two studies but not in one of the largest studies. Further research is needed to assess impact of adding azithromycin to IPTp-SP on adverse birth outcomes.

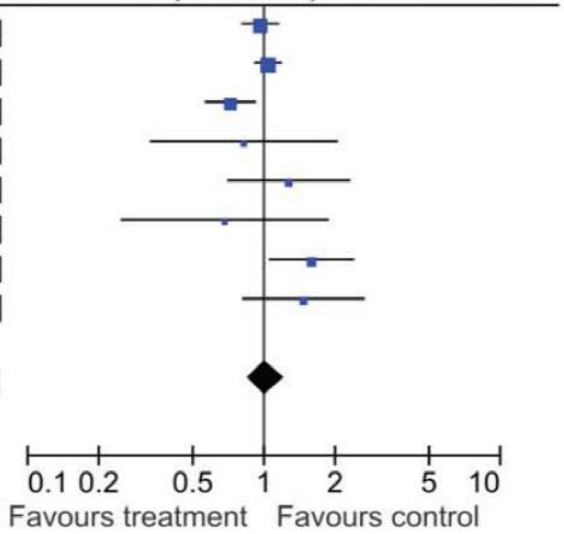
WHO ERG on malaria in pregnancy

Meta-analysis of trials of routine antibiotic prophylaxis in pregnancy that report preterm birth as outcome

	Antibiotics		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
APPLe 2009	184	1096	189	1087	23.2%	0.97 [0.80, 1.16]	
Goldenberg 2006	319	1240	303	1226	26.3%	1.04 [0.91, 1.19]	
Hauth 1995	110	426	68	190	19.3%	0.72 [0.56, 0.93]	
McGregor 1990	8	119	9	110	3.3%	0.82 [0.33, 2.05]	
Paul 1997	21	159	17	164	6.8%	1.27 [0.70, 2.32]	
Sen 2005	6	89	8	81	2.8%	0.68 [0.25, 1.88]	
Shennan 2006	33	53	18	46	11.4%	1.59 [1.05, 2.41]	
Vermeulen 1999	20	70	14	72	6.8%	1.47 [0.81, 2.67]	
Total (95% CI)		**3252**		**2976**	**100.0%**	**1.02 [0.85, 1.22]**	
Total events	701		626				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.75$, df = 7 (P = 0.04); $I^2 = 53\%$

Test for overall effect: Z = 0.20 (P = 0.84)



van den Broek NR, White SA, Goodall M, Ntonya C, Kayira E, Kafulafula G, et al. (2009) The APPLe Study: A Randomized, Community-Based, Placebo-Controlled Trial of Azithromycin for the Prevention of Preterm Birth, with Meta-Analysis. PLoS Med 6(12): e1000191. https://doi.org/10.1371/journal.pmed.1000191

Conclusions of the ERG for MPAC review

*Q8 – Among pregnant women with malaria and HIV co-infections, what is the **efficacy/effectiveness of co-trimoxazole prophylaxis** for prevention of malaria and its adverse consequences compared to the efficacy/ effectiveness of IPTp-SP.*

Conclusions/recommendations

7. HIV-infected pregnant women are particularly vulnerable to malaria. Co-trimoxazole (CTX) prophylaxis provides only partial protection against malaria during pregnancy. Research is needed to evaluate new strategies, including alternative medicines for IPTp to be safely administered concomitantly with CTX prophylaxis.

Main effects of HIV and malaria coinfection in pregnant women

Effect of HIV on malaria	• ↑ Risk of infection • ↑ Parasite density • ↓ Antibodies against placental-type parasites • Loss of parity-dependent malaria immunity
Effect of malaria on HIV	• ↑ HIV viral load • ↑ Production of IL-6, IFN-γ, TNF-α cytokines • Possible ↑ of MTCT of HIV (conflicting results, see Table 5)
Effect of dual infection	• ↑ Severity of illness • ↑ Maternal mortality • ↑ Adverse birth outcomes (LBW, FGR) • ↑ Neonatal mortality

FGR, fetal growth restriction; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; LBW, low birth weight; MTCT, mother-to-child transmission; TFN, tumour necrosis factor

Source: adapted from Hochman et al., 2009 (30)

Many thanks
for your kind attention

Global **Malaria** Programme

World Health Organization

List of participants

ERG Panel Members

- Karen BARNES
- Marta BOFFITO
- Michel COT
- Rose LEKE (Co-Chairperson)
- David MABEY
- Larry SLUTSKER (Co-Chairperson)
- Steve TAYLOR

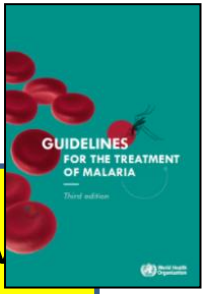
ERG Participants

- Rukhsana AHMED
- Azucena BARDAJI
- Daniel CHANDRAMOHAN
- Matthew CHICO
- Meghna DESAI
- Raquel GONZALEZ (Rapporteur)
- Jenny HILL
- Abel KAKURU
- Clara MENENDEZ

According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by experts organization, from any single malaria-related company exceeds 10,000 USD in a calendar year. Likewise, a shareholding in any one malaria-related company in excess of 1,000 USD would also constitute a "significant shareholding".

WHO recommendation for IPTp-SP

Intermittent preventive treatment of malaria in pregnancy



- In malaria-endemic areas in Africa, provide intermittent preventiv treatment with SP to all women in their first or second pregnancy (SP-IPTp) as part of antenatal care. Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.

Strong recommendation, high-quality evidence

In the systematic review, the reduction in risk for low birth weight was consistent for a wide range of levels of resistance to SP.

There are currently insufficient data to define the level of *P. falciparum* transmission at which IPTp-SP may cease to be cost-effective from a public health point of view.

Evidence-base of IPTp-SP recommendations

GRADE

In a systematic review of IPTp, seven trials involving direct comparison of two doses of SP with three or more doses monthly were evaluated. The trials were conducted in Burkina Faso, Kenya, Malawi, Mali and Zambia between 1996 and 2008.

In comparison with two doses of SP, three or more doses:

- Increased the mean birth weight by about 56 g (95% CI, 29–83; seven trials, 2190 participants, *high-quality evidence*);
- Reduced the number of low-birth-weight infants by about 20% (RR, 0.80; 95% CI, 0.69–0.94; seven trials, 2190 participants, *high-quality evidence*);
- Reduced placental parasitaemia by about 50% (RR, 0.51; 95% CI, 0.38–0.68; six trials, 1436 participants, *high-quality evidence*); and
- Reduced maternal parasitaemia by about 33% (RR, 0.68; 95% CI, 0.52–0.89; seven trials, 2096 participants, *high-quality evidence)*.

The trials conducted to date have not been large enough to detect or exclude effects on spontaneous miscarriage, stillbirth or neonatal mortality (*very low quality evidence*).

Other considerations

The guideline development group noted that the beneficial effects were obvious in women in their first and second pregnancies. There was less information on women in their third or later pregnancy, but the available information was consistent with benefit.

Kayentao K, *et al. JAMA* 2013; 309: 594–604.

Current WHO recommendations on ANC

WHO recommendations on antenatal care for a positive pregnancy experience (2016)

Antenatal care models with a minimum of eight contacts are recommended to reduce perinatal mortality and improve women's experience of care.

ANC Contact Schedule and Proposed Time of IPTp-SP Administration *(To be adapted to country context, also considering disease burden and health needs)*		MiP-related Interventions and Considerations during ANC Contacts
Contact 1: Up to 12 weeks		• Register pregnant women, provide ITNs, and counsel on their use. Screen for HIV. • Administer 30 to 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid. • **Counsel to return for a visit at 13 to 16 weeks (see contact 1a below) to receive the first dose of IPTp-SP (as directed by national guidelines).*** • Counsel on prompt diagnosis and effective treatment/malaria case management during pregnancy.
Additional contact (1a): *In moderate to high malaria transmission areas in Africa where IPTp-SP is policy,* ***a contact should be made early*** *in the* ***second trimester (13 to 16 weeks) to administer SP as early as possible.***	IPTp-SP dose 1	Remember: • Do not administer IPTp-SP before week 13 of pregnancy. • Administer the first IPTp-SP dose **as early as possible in the second trimester** to fully benefit from the protective capacity in this critical period of pregnancy.† • **Administer the second dose of IPTp-SP one month later.** • Administer the following doses of IPTp-SP starting from the scheduled contact at 20 weeks, **observing at least one-month intervals between SP doses.** • SP can be **safely** administered from the beginning of the second trimester until the time of delivery. • One full dose of IPTp-SP consists of 1,500 mg/75 mg SP (i.e., three tablets of 500 mg/25 mg SP). • Provide IPTp-SP by directly observed treatment. • Pregnant women on co-trimoxazole should not receive IPTp-SP due to an increased risk of adverse events when both drugs are given in parallel. • Continue to administer 30 to 60 mg of elemental iron and 400 mcg (0.4 mg) of folic acid. • Continue counseling as above.
Contact 2: 20 weeks	IPTp-SP dose 2	
Contact 3: 26 weeks	IPTp-SP dose 3	
Contact 4: 30 weeks	IPTp-SP dose 4	
Contact 5: 34 weeks	IPTp-SP dose 5	
Contact 6: 36 weeks	No SP administration if last dose was received at contact 5 in week 34	
Contact 7: 38 weeks	IPTp-SP dose 6 (if no dose was received at contact 6 in week 36)	
Contact 8: 40 weeks		

Implementing Malaria in Pregnancy Programs in the Context of World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience

April 2017 www.mcsprogram.org

This technical brief highlights recommendations for the prevention and treatment of malaria in pregnancy (MiP) in the context of the World Health Organization (WHO) *Recommendations on Antenatal Care for a Positive Pregnancy Experience*,[1] published in 2016. Readers should also refer to the key underlying documents, specifically the WHO *Guidelines for the Treatment of Malaria*, third edition,[2] and the WHO *Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP)*.[3]

Background

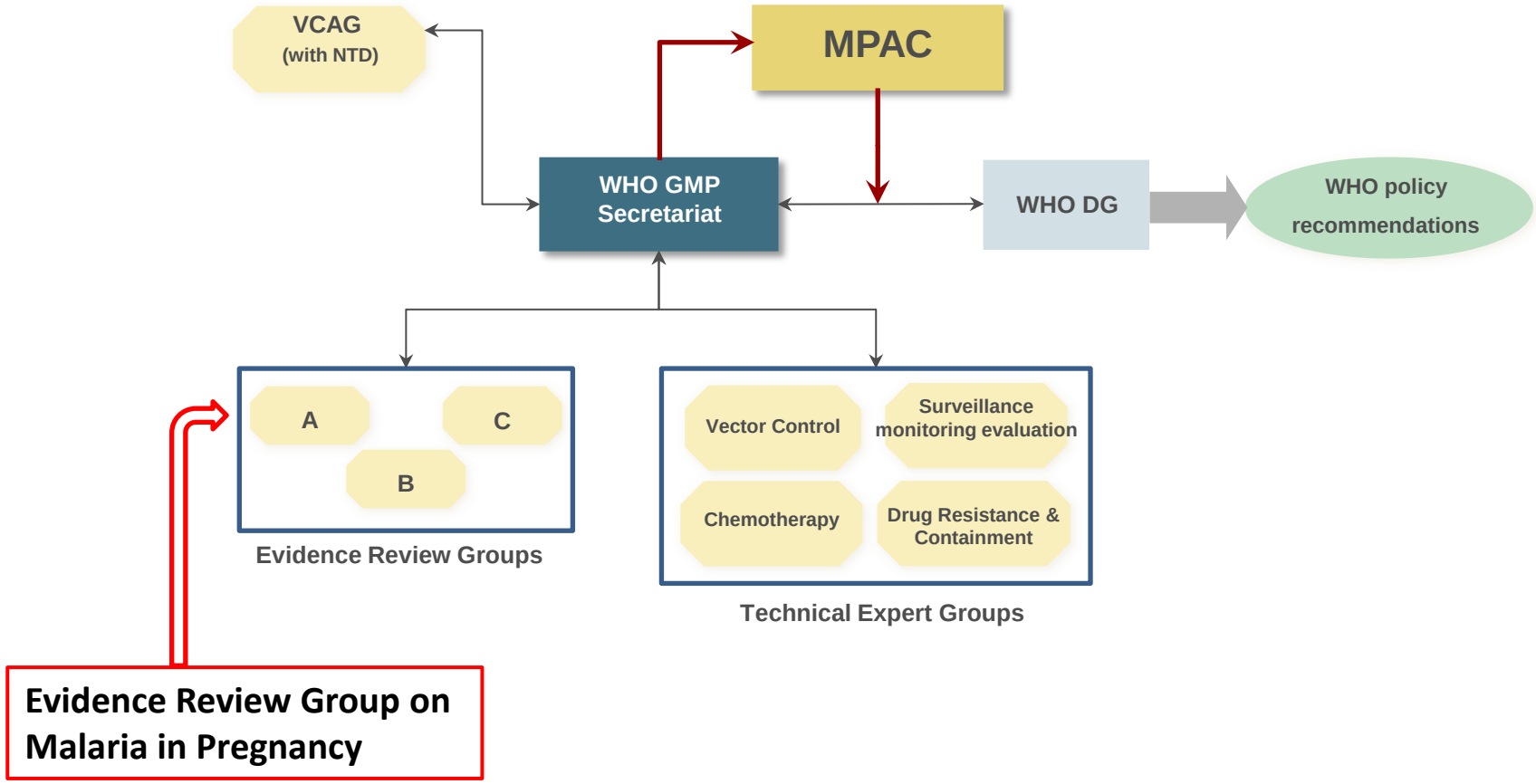
MiP is a major public health problem with substantial risks for mothers and their babies. Each year, MiP is responsible for 20% of stillbirths in sub-Saharan Africa, 11% of all newborn deaths in sub-Saharan Africa, and 10,000 maternal deaths globally.[4,5,6] WHO recommends a package of interventions for controlling malaria and its effects during pregnancy. In areas where malaria is a risk, WHO recommends delivery and use of insecticide-treated nets (ITNs) and effective management of cases by providing prompt quality diagnosis and effective treatment of malaria infections. In areas with moderate to high transmission of *Plasmodium falciparum*, WHO additionally recommends the administration of intermittent preventive treatment during pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) that is quality assured.[3] SP is the only drug currently recommended for administration in the context of IPTp, and it is important to note that SP continues to show benefit for both the mother and her baby, even in areas of

[1] World Health Organization. *WHO recommendations on antenatal care for a positive pregnancy experience*. 2016. Retrieved January 10, 2017, from http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experiences/en/.
[2] World Health Organization. *Guidelines for treatment of malaria*. Third edition. April 2015. Retrieved from http://www.who.int/malaria/publications/atoz/9789241549127/en/.
[3] World Health Organization. *WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP)*. 2013. Retrieved from http://www.who.int/malaria/publications/atoz/policy-brief-iptp-sp-2013.pdf?ua=1.
[4] Lawn J, Blencowe H, Waiswa P, et al. 2016. Stillbirths: rates, risk factors, and acceleration towards 2030. *The Lancet*. 387(10018), 587-603. doi: 10.1016/s0140-6736(15)00837-5.
[5] Desai M, ter Kuile FO, Nosten F, et al. 2007. Epidemiology and burden of malaria in pregnancy. *The Lancet Infectious Diseases*. 7(2), 93-104. doi: 10.1016/s1473-3099(07)70021-x.
[6] Guyatt HL and Snow RW. 2001. *The American Journal of Tropical Medicine and Hygiene*, 64(1-2 Suppl), 36-44. doi:10.4269/ajtmh.2001.64.36.
[7] World Health Organization. *A strategic framework for malaria prevention and control during pregnancy in the African region*. 2004.

Implementing MiP Programs in the Context of WHO Recommendations on ANC for a Positive Pregnancy Experience

World Health Organization

WHO policy-making process for malaria



Outline – MiP ERG

- WHO policy process
- Background
- Objectives
- Current WHO recommendations on MiP
- ERG members, participants, observers & secretariat
- Questions for the ERG
- Conclusions and draft recommendations

Questions for ERG Panel

Q1 - What are the consequences of vivax malaria in pregnancy in terms of birth outcomes and morbidity for the pregnant women?

Q1bis - What are the consequences of falciparum and vivax co-infections in pregnancy in terms of birth outcomes and morbidity for the pregnant women?

Q2 – Is there evidence from clinical trials or PK/PD studies of specific PK changes in pregnancy of any of the following antimalarials: dihydroartemisinin, piperaquine, artesunate, artemether-lumefantrine, amodiaquine and mefloquine? Is there evidence that these changes are affecting therapeutic efficacy or safety of antimalarial medicines for the treatment of uncomplicated falciparum malaria, so to require specific dose adjustments during pregnancy?

Q3 – Is intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin+piperaquine more effective in the prevention of the consequences of malaria in pregnancy compared to single screening and treatment?

Q4 – Is intermittent screening and treatment with artesunate+sulfadoxine/pyrimethamine more effective in the prevention of the consequences of malaria in pregnancy compared to passive case detection?

Questions for ERG Panel (continued)

Q5 - Is intermittent screening and treatment with dihydroartemisinin+piperaquine or with artesunate+sulfadoxine/pyrimethamine feasible and cost-effective in the context of the studies implemented in India and Indonesia?

Q6 - What is the impact of intermittent treatment for malaria in pregnancy with sulfadoxine-pyrimethamine and azithromycin on adverse birth outcomes ?

Q6bis - What is the additive impact of azithromycin when added to intermittent treatment with sulfadoxine-pyrimethamine on adverse birth outcomes ?

Q7 - What is the impact of intermittent treatment for malaria in pregnancy with sulfadoxine-pyrimethamine and azithromycin on sexually transmitted diseases and reproductive tract infections?

Q8 – Among pregnant women with malaria and HIV co-infections, what is the efficacy/effectiveness of co-trimoxazole prophylaxis for prevention of malaria and its adverse consequences compared to the efficacy/ effectiveness of IPTp-SP.

Q9 – Is there evidence from clinical trials or PK/PD studies of specific changes in HIV+ pregnant women affecting the therapeutic efficacy or safety of medicines for the treatment of uncomplicated falciparum malaria, so to require specific dose adjustments during pregnancy?

Preparations and pre-reads

- Collaborations with Professor Feiko ter Kuile and Dr Jenny Hill, Liverpool School of Tropical Medicine, as well as with Dr Clara Menendez and Dr Raquel Gonzales, Barcelona Institute for Global Health and Dr Stephan Duparc, Medicines for Malaria Venture in the planning of the ERG meeting, selection of studies and experts to prepare the literature reviews.
- Pre-reads of the meeting:

Session I - Burden of *P. vivax* malaria in pregnancy (13 published papers)

Section II - Treatment of falciparum and vivax malaria in pregnancy (1 publication and 4 manuscripts)

Section III – Prevention of falciparum and vivax malaria in pregnancy (2 publications and 7 manuscripts)

Section IV – SP and AZ against sexually transmitted diseases and reproductive tract infections (10 publications)

Section V – HIV and malaria in pregnancy (4 publications and 3 manuscripts)

Malaria Policy Advisory Committee Meeting

17–19 October 2017, Geneva, Switzerland
Background document for Session 8

Update on the Malaria Elimination Oversight Committee and the Malaria Elimination Certification Panel

October 2017, Geneva, Switzerland

Background

In March 2017, MPAC endorsed the creation of two new committees to support malaria elimination goals: the Malaria Elimination Oversight Committee (MEOC) and the Malaria Elimination Certification Panel (MECP). The responsibilities of the MEOC are to:

- Evaluate national and regional progress towards malaria elimination according to established milestones and timelines;
- Determine the need for corrective actions to address programmatic or operational bottlenecks, and evaluate plans developed to address such issues;
- Identify any risks to malaria elimination that need to be addressed by WHO, regional initiatives or national programmes;
- Provide WHO/Global Malaria Programme (GMP) with observations and/or draft recommendations with respect to policies or guidance related to malaria elimination for MPAC's consideration;
- Question the status quo and confront difficult issues.

The MEOC is charged with helping countries reach malaria-free status, whereas the MECP is responsible for reviewing evidence and recommending when a country has met the criteria for elimination and therefore should be certified by the Director-General.

The specific duties of the MECP are to:

- Review submitted country documentation and national elimination reports;
- Conduct country assessments and field missions to verify findings in the national elimination report;
- Develop a final evaluation report and submit it to MPAC through WHO/GMP with a recommendation either to certify malaria elimination or to postpone certification, based on the analyses described above.

WHO/HTM/GMP/MPAC/2017/11

Malaria Elimination Oversight Committee

Nominations for MEOC members were solicited from WHO Regional Offices and GMP coordinators and team leaders. The selection of two MPAC members needs to be discussed. After review of nominations, the selection committee identified 10 highly qualified candidates for the MEOC, to be complemented by two MPAC malaria experts. The MEOC membership roster will be completed with the selection of representatives from two malaria-eliminating countries who will serve for 1 year as adjunct members. The MEOC membership is undergoing final review and approval by the Assistant Director General (ADG), after which the terms of reference and membership list will be posted to the WHO website. The first meeting of the MEOC is planned to coincide with the Global Forum of malaria-eliminating countries in June 2018.

Malaria Elimination Certification Panel

An open call for membership applications was placed through announcements on the WHO website and through the GMP listserv; more than 70 applications were received.[1]

After reviewing applications, the selection committee chose 12 highly qualified applicants to form the MECP. The panel roster has been approved by the ADG and the terms of reference and membership list will be posted shortly to the WHO website. A database will be maintained containing information on the applicants not chosen for the first panel. In order to supplement the core MECP members, some applicants may be asked to participate in country certification missions, depending on their specific expertise, experience and language abilities. The first meeting of the MECP is scheduled for 13–14 December 2017. The objective of the first meeting will be to review standard operating procedures related to the development of national elimination reports, the procedures for verifying the national elimination report through country missions, and the procedure for recommending to WHO that a country is ready to be certified as free of malaria.

Contact

For more information, please contact:

Kim Lindblade, Malaria Elimination Team Lead, WHO HQ, Global Malaria Programme, lindbladek@who.int

[1] http://www.who.int/malaria/news/2017/call-for-applications-elimination-certification-panel/en/

Malaria Elimination Oversight Committee and Malaria Elimination Certification Panel

Dr Kim Lindblade, Elimination Team Lead

18 October 2017

Global **Malaria** Programme

World Health Organization

Malaria Elimination Oversight Committee

- Independent body to advise WHO on malaria elimination
  - Similar to committees for polio, Guinea worm and onchocerciasis
  - External validation of progress
  - Established based on recommendation of Malaria Policy Advisory Committee
- Functions:
  - Monitor and report on progress in specific countries according to established milestones and timelines
  - Provide technical advice to address programmatic or operational bottlenecks
  - Identify risks to elimination that need to be addressed
  - Share observations and recommendations with WHO on policies or guidance related to malaria elimination
  - Question the status quo and confront difficult issues
- 12 members with malaria or disease elimination experience
  - 8 from nominations by WHO regional offices and GMP Coordinators
  - 2 from MPAC
  - 2 adjunct members representing malaria-eliminating countries
- Meetings held 1-2 times per year, with one meeting to coincide with Global Forum of Malaria-Eliminating Countries
- Committee to stand up by Q4 2017

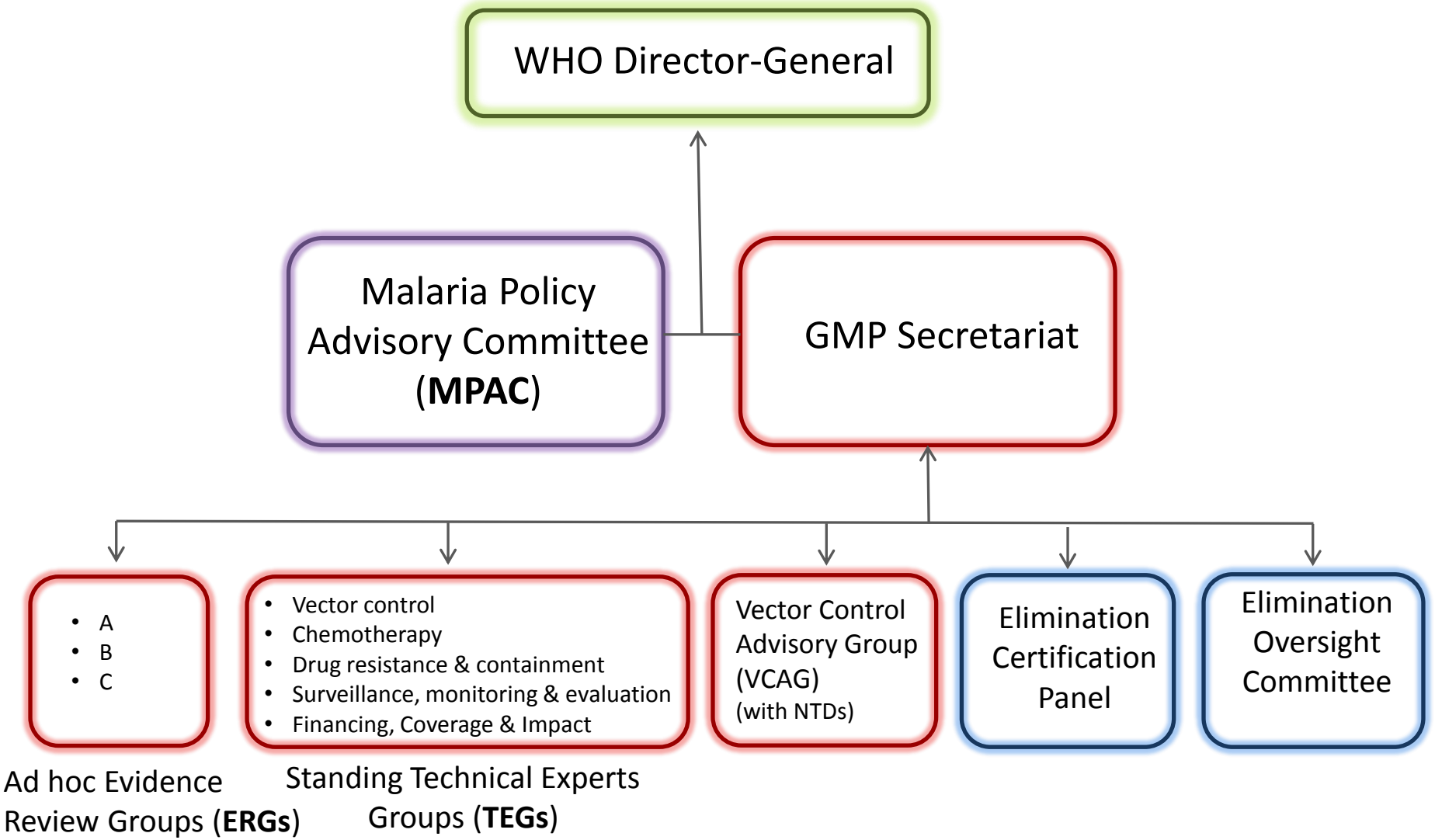
Malaria Elimination Certification Panel

- Recommends to WHO whether countries should be certified as malaria-free
- Functions:
  - Advise WHO on the certification procedures
  - Review submitted country documentation and national elimination reports
  - Conduct country assessments and field missions to verify findings in the national elimination report
  - Develop a final evaluation report and submit it to the MPAC through WHO/GMP with a recommendation to certify malaria elimination or to postpone
- 12 members selected with malaria expertise to form the panel, and 45 applicants to serve as pool for ad hoc members of missions
- Most meetings will likely be virtual
- SOPs for preparation of national reports and procedures for the MECP are being prepared for review at first meeting, 13-14 December
- Procedures for MPAC review of recommendations to forward to the DG to be discussed

Order of events in certification and MPAC role

- Countries submit official request for certification to WHO
- Pre-certification assessment missions by WHO staff to determine timeline and assure country is prepared
- Malaria Elimination Certification Panel
  - Review national elimination reports (all members)
  - Field assessment, draft evaluation reports (subset of MECP + adhoc members)
  - Review and finalize evaluation reports (all members)
  - Submission final evaluation reports to WHO/GMP (preferably at least one month before MPAC meeting)
- MPAC
  - Receive national elimination report and MECP evaluation report from WHO
  - Review and comment on reports
    - Subset of MPAC?
    - Proposed time frame for raising questions or concerns is 1 month after receipt of reports
  - Formulate final recommendation to WHO DG on certification at MPAC meeting
- In case there is an urgent need for an MPAC recommendation between MPAC meetings, an expedited review procedure is proposed
  - Recommendation will be formulated through discussion by email and/or teleconference

WHO malaria policy-making process



Thank you