Documentation related to Sessions 5 to 7 of the meeting Click on the links below to see the pre reads and presentations

Malaria Policy Advisory Committee (MPAC) Meeting,10–12 April 2019

Documentation related to Sessions 5 to 7

Thursday, 11 April 2019			
	Session 5	**Open**	
09:00 – 11:00	GMP policy-making and dissemination process updates: pathway, horizon scanning, preferred product characteristics and submission review	Dr Pedro Alonso	**For guidance**
11:00 – 11:30	*Coffee break*		
	Session 6	**Open**	**For approval**
11:30 – 12:45	Prioritization of new topics for policy recommendation development	Dr Pedro Alonso	
12:45 – 13:45	*Lunch*		
	Session 7	**Open**	**For guidance**
13:45 – 14:45	Update on the ERG on mass drug administration Background | Presentation	Dr Andrea Bosman	
14:45 – 15:45	Update on the ERG on malariogenic potential Background | Presentation	Dr Jan Kolaczinski Dr Kim Lindblade	

15:45 – 16:15	*Coffee break*		
	Session 8	**Open**	**For guidance**
16:15 – 17:00	Update on the Malaria Elimination Oversight Committee and STOP Malaria	Dr Frank Richards Dr Kim Lindblade	
17:00 – 17:30	Outcome of the technical consultation on external competence assessment of malaria microscopy	Dr Andrea Bosman	
17:30	*End of day*		

GMP Policy making and Dissemination process updates

Malaria Policy Advisory Committee

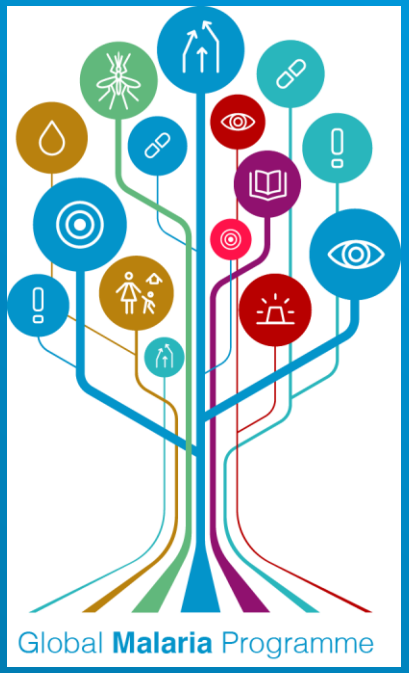
Geneva, Switzerland

Pedro L. Alonso

11 April 2019

Global **Malaria** Programme

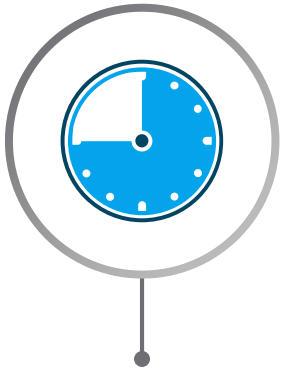
World Health Organization



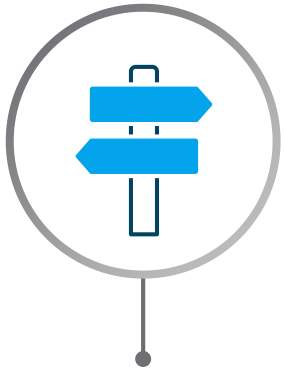
Presentation Outline

1. Brief reminder of rationale and objectives of the policy review
2. Key findings of the review and choice of focus areas
3. Key activities started in 2019
4. Detailed update on the GMP Policy Path
5. Key questions for discussion

Why did GMP review its policy making process?



Perceived lack of transparency and lengthy process



Inconsistencies in review standards

Sub-optimal use of GMP output at country level

How the review was done

Informed by interviewing 80+ stakeholders across value chain

Co-constructed with GMP staff & BCG to ensure accurate depiction

Built leveraging previous work on VCAG, I2I

Interview consensus: GMP policy making and dissemination process has dramatically improved since introduction of MPAC…

Organisation

> *MPAC fulfils its purpose in that it has the highest calibre of technical experts*
>
> **Procurer**

> *The role of VCAG has become clearer over the past 1.5 years*
>
> **Procurer**

Evidence & Expertise

> *Overall, evidence-based guidelines have been a huge step in the right direction for WHO*
>
> **PDP**

> *ERGs have quicker approach for understanding a very specific topic, gathering best experts, and go in depth on issues. They really expedite and quality check the process*
>
> **GMP**

Dissemination

> *WHO website has made good progress & GMP's newsletter is useful in disseminating new material*
>
> **Country Programme Manager**

> *It is a good thing GMP produces Guidelines since this gives a framework for use by countries and prevents them from being flooded with products they won't know what to do with*
>
> **Manufacturer**

Source: Interviews

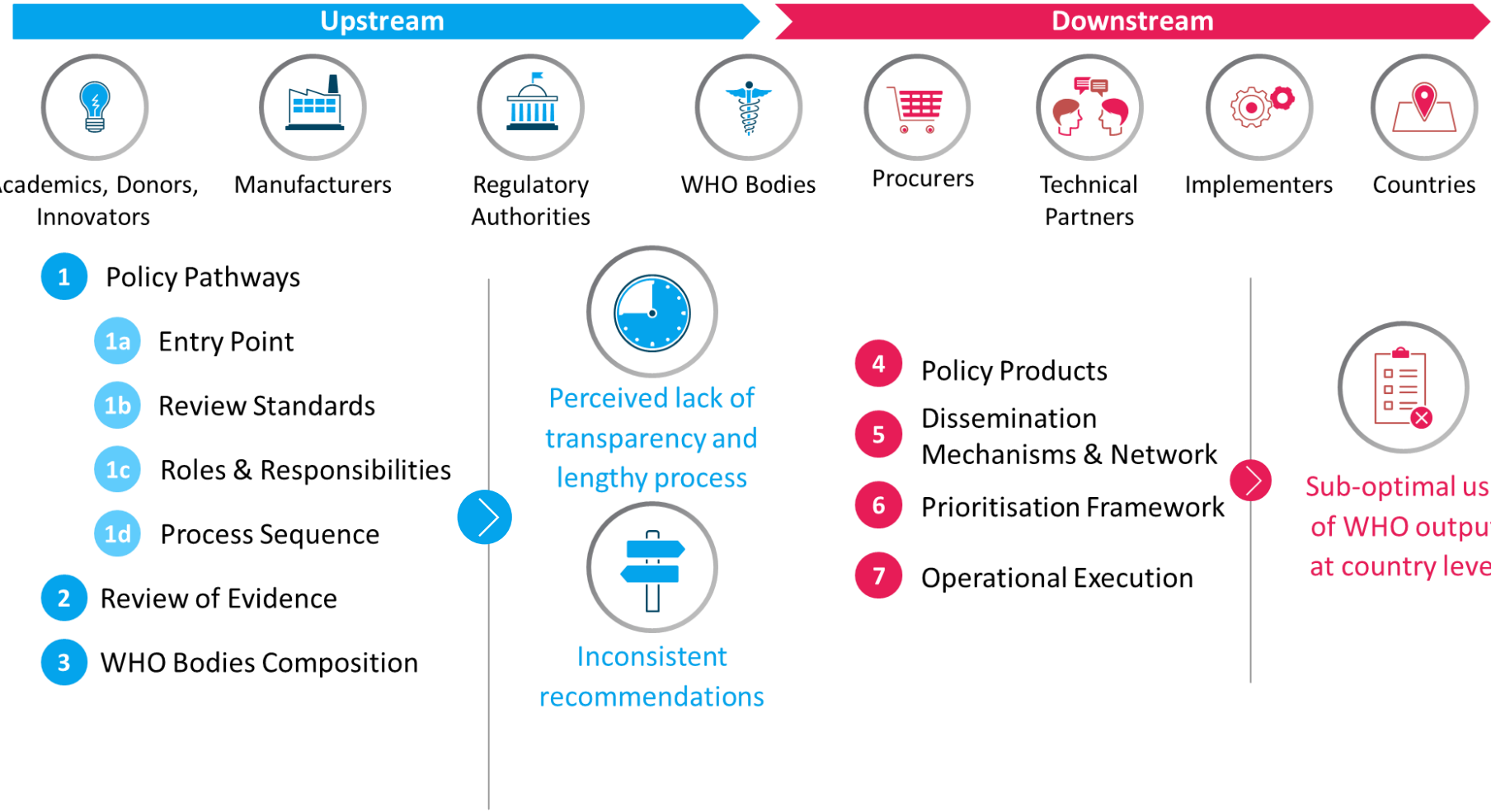
…and brings unique value to countries

> *All countries we work with look at WHO for the last word as per intervention selection*
>
> **Implementer**

> *WHO is an indispensable partner for low-income countries*
>
> **Technical Partner**

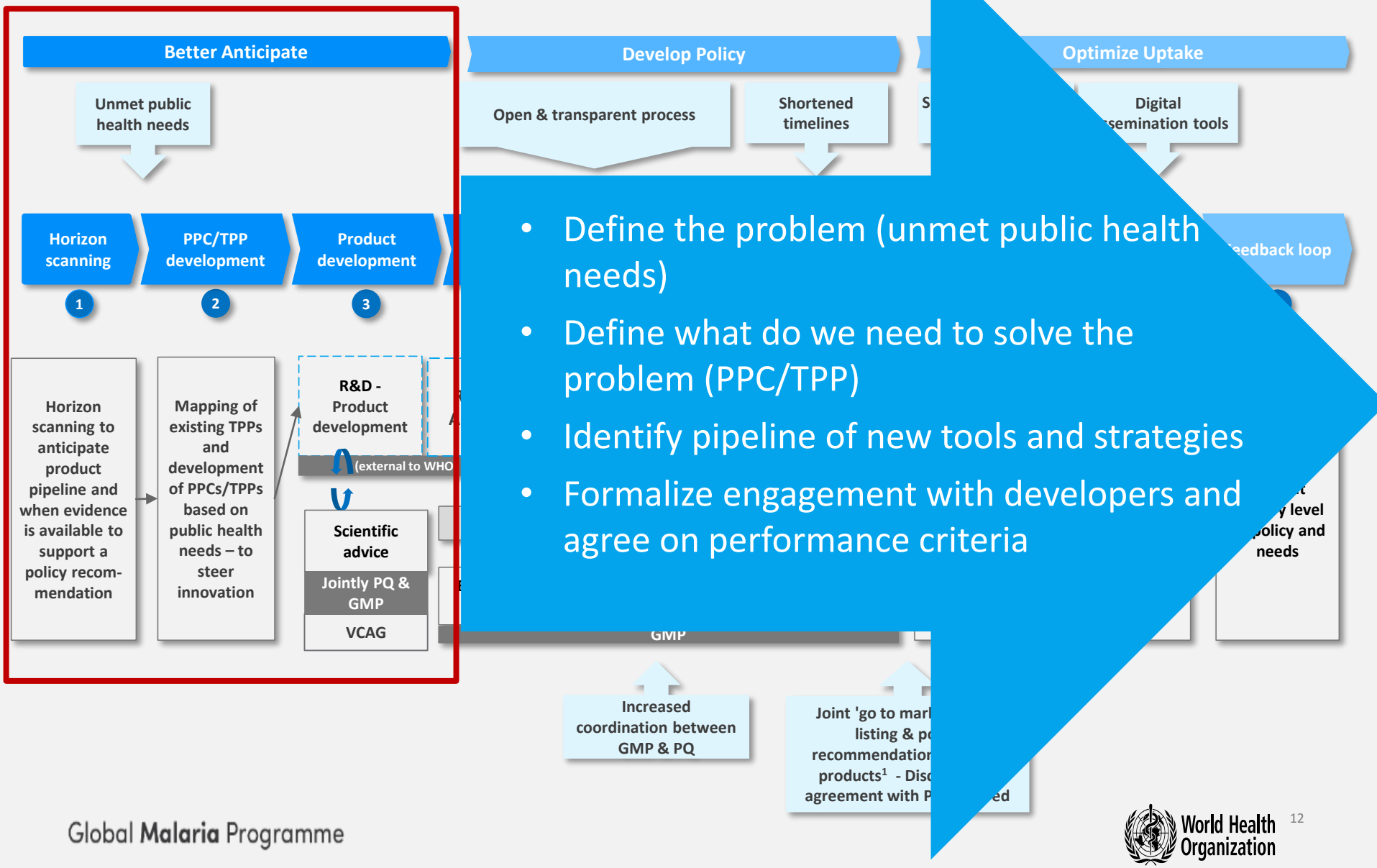
> *WHO plays an absolute key role in malaria endemic countries*
>
> **Manufacturer**

Analytical framework, 7 focus areas were identified



High level diagram of the GMP Policy Pathway – new products

(draft in discussion)



Unmet and (partially met) Public Health needs related to malaria

Purpose: to frame the prioritization of our work

How: inclusive process with a convening and online consultation

Result:

- Prioritized list of unmet and partially met public health needs related to malaria
- Builds on previous work of malERA and other analyses
- Provides a basis to map existing target product profiles
- Identifies gaps where preferred product characteristics could stimulate innovation

Action:

- Background analyses to inform consensus-building consultation
- Open portal to submit ideas (3 month pilot)

Horizon Scanning – for discussion and input

Purpose: to identify tools/strategies in development to inform the timing for potential policy recommendation development

How: Three key areas to monitor regularly

1. Product development pipelines (human trials?) – with support from product development partners
2. New evidence to update existing recommendations (tools/strategies)
3. Evidence to develop new recommendation – strategies

Preferred Product Characteristics / Target Product Profiles

Understanding product profiles as a continuum

Preferred Product Characteristic (PPC)

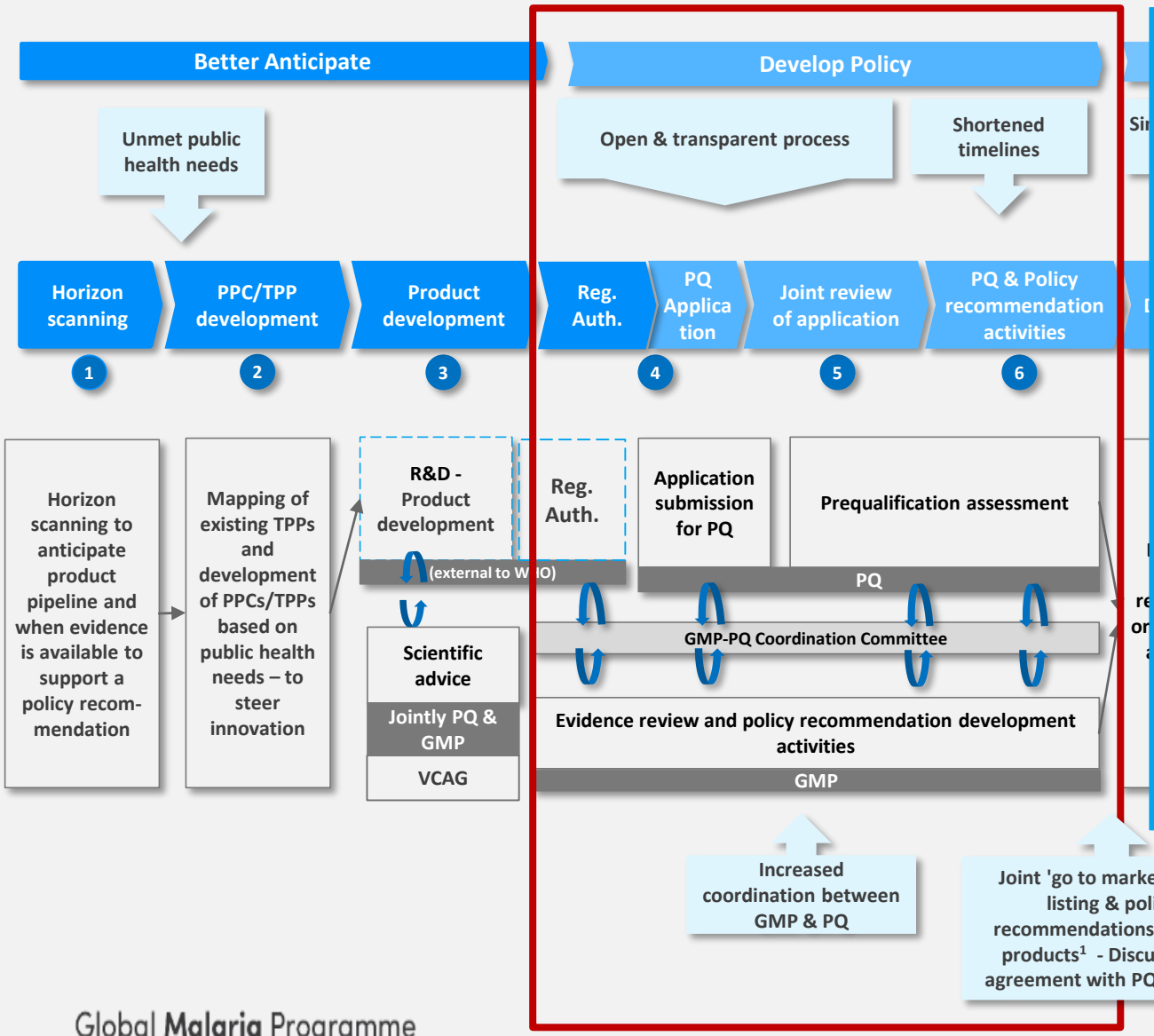
- GMP proposes to lead consensus development to address gaps
- product profile informs product developers, procurement agencies and funders on R&D and public health priorities
- intended to facilitate product development and evidence generation addressing the greatest and most urgent public health need – products and strategies

Target Product Profile (TPP)

- GMP proposes to collect and lead review of existing TPPs owned by partners
- Map against unmet/partially met public health needs for malaria to identify gaps
- Use TPPs to have a joint scientific dialogue with developers and PQ to inform performance criteria and evidence required for policy recommendation & PQ listing

High level diagram of the GMP Policy Pathway – new products

(draft in discussion)



- Reduce time from evidence to policy
- Linked policy recommendation & PQ listing
- Clarity on advisory body roles

Develop Policy What's new

Vision: Transparency Consistency Coordination Impact

Policy Pathway – Products and Strategies

- Following the standards of the Guideline Review Committee and Norms & Standards department
- Transparent prioritization of policy development via MPAC meetings
- Convene single GMP Guidelines Development Group to ensure consistency and coherence
- Develop guidance on intervention mixes and prioritisation
- Post review standards on GMP website and track process steps for transparency

Products only

- Explore using stringent regulatory authority submission as trigger to begin development of policy
- Contingent on data being made publically available
- Improved coordination between GMP and PQ to publish simultaneous policy recommendation and PQ listing for new tools

Advisory bodies – clarifying functions

Malaria Policy Advisory Committee (MPAC)

- No change – GMP's highest level advisory body

Development of Policy recommendations:

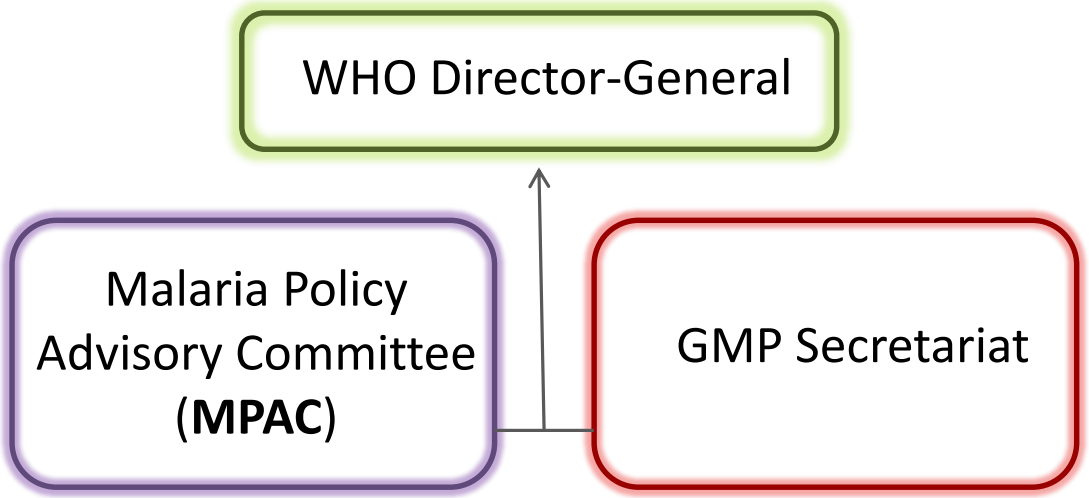
Guidelines Development Group (3 configurations)

- GDG alone
- GDG + technical experts
- ERG draft + GDG review

*Open call for experts – 30 April deadline for GDG w/ selection by June 2019; remains open for ERGs

Technical advice to GMP: Malaria Elimination Oversight Committee, Malaria Elimination Certification Panel, Vector Control Advisory Group, Strategic Advisory Group on malaria eradication, and other ad hoc technical consultations

GMP Advisory bodies structure



Policy

GMP Guidelines Development Group (GDG) + ad hoc ERGs

Advisory

Vector Control Advisory Group (VCAG) w/ NTD/PQ

Malaria Elimination Oversight Committee (MEOC)

Malaria Elimination Certification Panel (MECP)

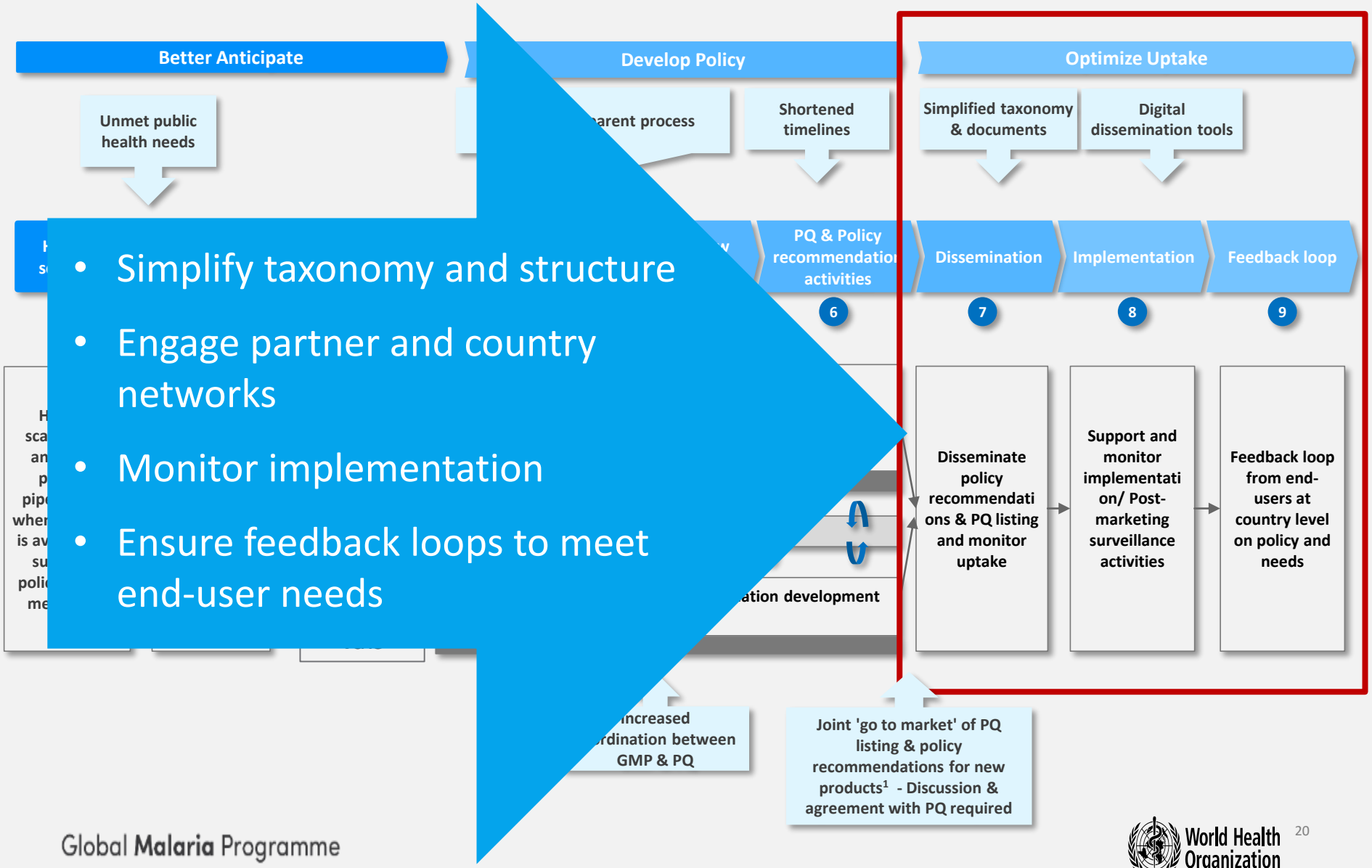
Strategic Advisory Group on malaria eradication

Malaria Vaccine Advisory Committee (MALVAC) w/ IVB

Other ad hoc technical consultations

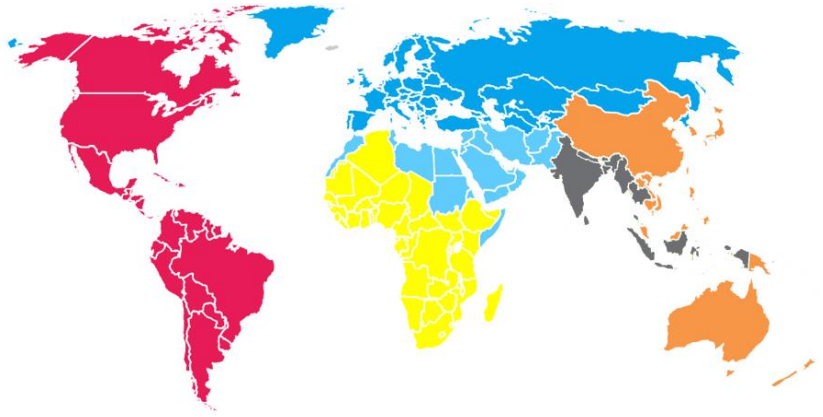
High level diagram of the GMP Policy Pathway – new products

(draft in discussion)



Optimize Uptake for Impact

Country survey conducted to understand barriers to uptake & suggestions for improvement - 96 responses



What we heard from National Programmes

- Difficult to locate relevant information on the GMP website
- Hard to understand how the different documents fit together
- Documents should be shorter/more concise and have consistency in naming
- Preference for digital documents via the website and mobile app; with needs remaining for printed materials
- Insufficient engagement from WHO on new policy at country level
- Feedback mechanisms from end-users are needed

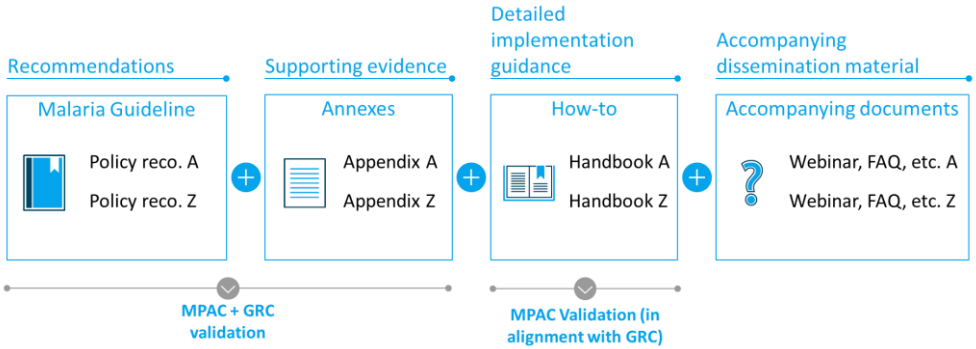
3 key levers identified:

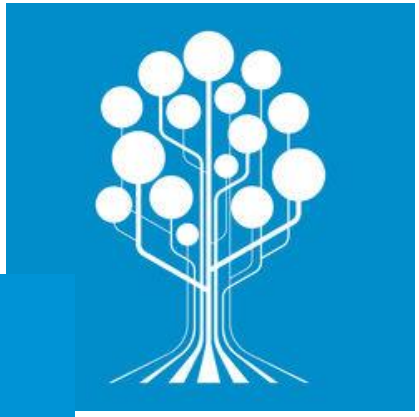
- Improve structure of documents
- Improve GMP website
- Develop new sharing opportunities

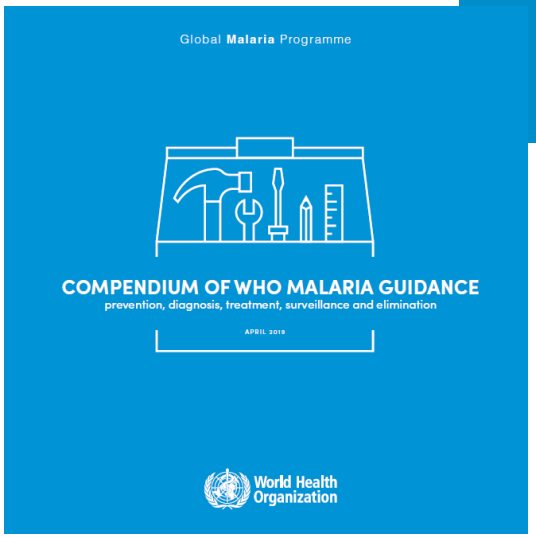
Optimize Uptake for Impact

How GMP is responding:

1. Improve the taxonomy and structure of GMP documents
2. Develop a compendium of all existing GMP policy guidance to show how the documents fit together – Quick win
3. Redesign the GMP website for accessing policy recommendations and operational guidance with input from end users – NMCP focus group
4. Expanding the World malaria report mobile app to include malaria guidance – December 2019
5. Engage WHO country and region staff in supporting dissemination & monitor uptake
6. Engage all malaria partners in dissemination







Multiple document types to consistent GMP taxonomy

Policy Product

- Malaria Guideline – consolidation of all existing malaria policy recommendations
- Policy Recommendation – one recommendation/or group on a specific topic (e.g., treatment of uncomplicated *P. falciparum* malaria)
- Appendix – annex document containing all supporting evidence, GRADE tables, analyses and references supporting the recommendation
- Operational manual – detailed document providing operational guidance on how to implement a policy
- Accompanying documents – webinars, Q&A, powerpoint slides to help raise awareness and dissemination a new policy recommendation
- Information note – document summarizing WHO's position on a specific topic

Improved Digital tools: new Policy Process website

Develop a Policy making process website

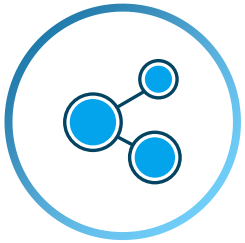
- To articulate policy process and review standards
- Communicate unmet and partially met public health needs
- Post and update horizon scanning reports for partner use including product pipelines
- Post PPCs and TPPs that are available to be shared
- List topics prioritized for recommendation development and track progress through pathway steps for increased transparency
- Provide a forum for online consultations
- Pilot launched this week with open consultations on unmet/partially met public health needs and nominations for policy recommendations (3 month pilot)
- gmpfeedback@who.int

Improved Digital tools: Policy recommendations and guidance

Redesign the Policy recommendation and guidance dissemination section to facilitate access

- Respond to end-user advice to improve uptake
- Intuitive topic-based navigation to help find relevant information easily
- Options presented to NMCP focus group for input in April
- Consistent with the structure of the Compendium
- Launch of redesigned site June

Energize Dissemination Network



Priority areas of work:

- Partner mapping & identification of upcoming meetings for dissemination opportunities
- Mobilize partner networks to support policy dissemination and uptake
- Orientation and engagement of WHO country staff
- Engagement with national programme managers
- Conduct a follow-up survey:
  - Pulse check to see if GMP response meeting needs
  - Track adoption, implementation and feedback on current WHO recommendations on malaria;
  - Identify technical assistance and training needs
  - Identify barriers to implementation or key challenges that may need updated policy recommendations
- gmpfeedback@who.int

Prioritization of new topics for policy recommendation development

Malaria Policy Advisory Committee

Geneva, Switzerland

Pedro L. Alonso

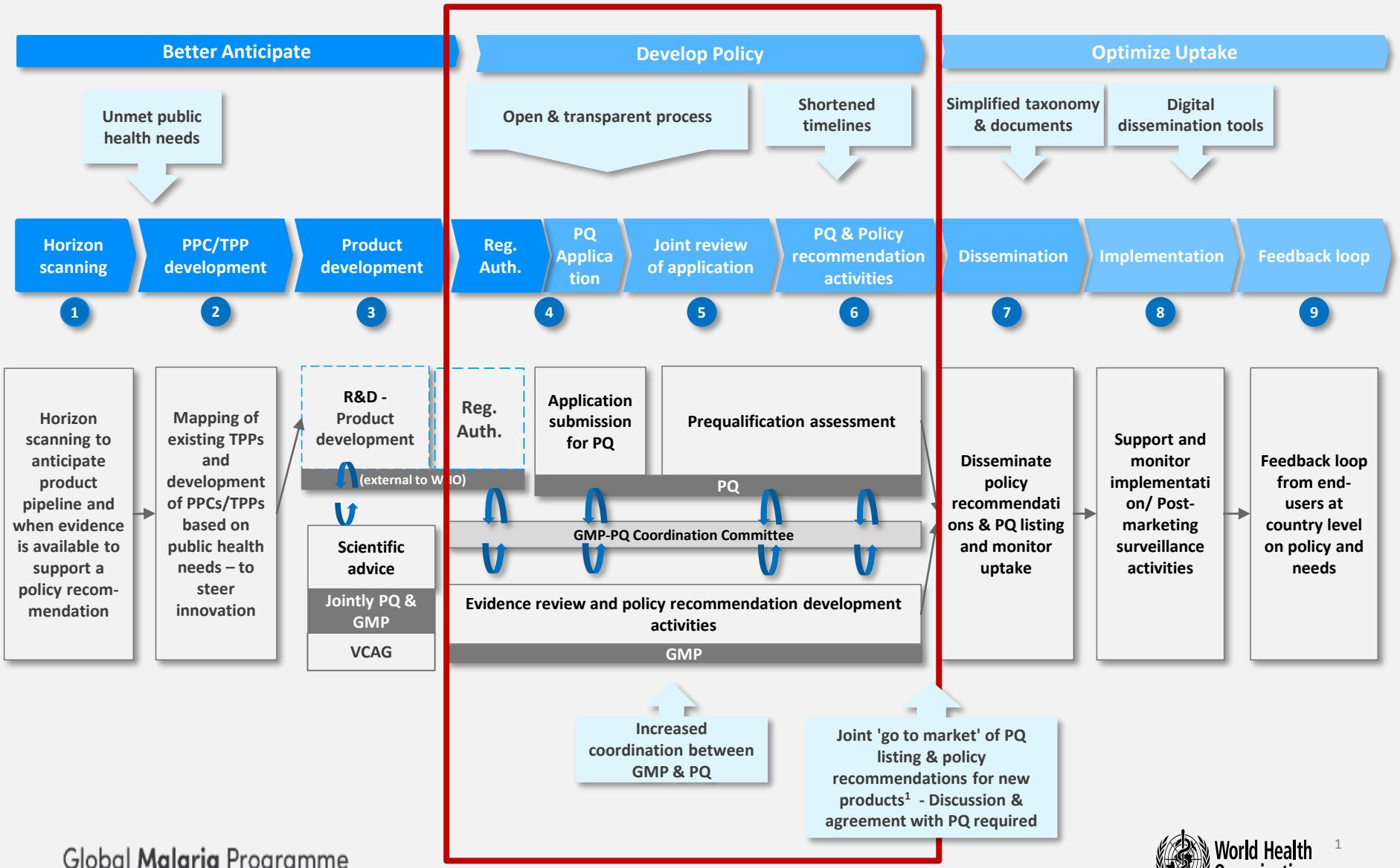
11 April 2019

Global **Malaria** Programme

World Health Organization

High level diagram of the GMP Policy Pathway – new products

(draft in discussion)



Global Malaria Programme

World Health Organization

Develop Policy
What's new

Vision:
Transparency
Consistency
Coordination
Impact

Policy Pathway – Products and Strategies

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Products only

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- Improved coordination between GMP and PQ to publish simultaneous policy recommendation and PQ listing for new tools

Prioritization of topics for policy development

Two areas for policy recommendation development:

- New tools/strategies for which adequate evidence is available
- Updating existing recommendations based on new evidence

Process:

- Horizon scanning to identify new evidence: product pipelines, published/unpublished literature, portal for nominations (pilot)
- Explore trigger for new drugs, diagnostics, vaccines: submission of stringent/regulatory dossier if evidence available
- GMP Secretariat conducts initial prioritization for discussion at MPAC
- Monitor process steps of development on new policy website

Proposed new topics for development of policy recommendation

1. Reactive strategies
2. Housing modifications for vector control
3. Vector control in emergency settings
4. Single-dose Tafenoquine for radical cure of *Plasmodium vivax* malaria (to be recommended with a point-of-care quantitative G6PD test)

* In no particular order

Reactive Strategies

1. What reactive strategies deployed after identifying an index malaria case will reduce or interrupt transmission in the area surrounding the index case?
2. Interventions:
   - Active detection and treatment of malaria cases in the household and/or neighbourhood/focus around a malaria case detected through passive case detection
   - Administration of a full treatment course of an antimalarial drug to all persons in the household and/or neighbourhood/focus around a malaria case detected through passive case detection
   - IRS or deployment of ITNs to the household and/or neighbourhood/focus around a malaria case detected through passive case detection
3. Comparator: Standard of care
4. Outcomes: Reductions in malaria incidence or prevalence or interruption of transmission

Housing modifications for vector control

1. To assess the effect of different house modifications on malaria disease burden
2. Interventions:
   - Modifications to primary construction design and specifications: choice of material used for walls, roofs or doors; house elevation; closed vs open eaves
   - Modifications or additions to existing houses including: screening of doors, eaves and/or windows; changes to size or number of windows or doors per household; filling in of cracks and crevices in walls or ceilings
   - Any structural house modification incorporating insecticide
3. Comparator: No modification to primary construction design and specifications; no modifications or additions to existing houses; no incorporation of insecticidal delivery system
4. Outcomes: Malaria case incidence, incidence of new malaria infections, malaria parasite prevalence

Vector control in emergency settings

1. To evaluate the impact of malaria vector control interventions deployed in humanitarian emergencies
2. Interventions:
   - Malaria vector control interventions for which 'general' WHO policy recommendations are in place, but for which there is no specification for use in humanitarian emergencies (ITNs, IRS, larvaciding)
   - Malaria vector control interventions for which one of the primary use-patterns is deployment in humanitarian emergencies and for which no WHO policy recommendation is currently in place (insecticide-treated tents, insecticide-treated plastic sheeting, insecticide-treated blankets)
3. Comparator: No other insecticidal malaria vector control intervention
4. Outcomes: Primary – case incidence, incidence of new malaria infection, parasite prevalence; Secondary – EIR, adult mosquito density, sporozoite rate; Epidemiological – anaemia prevalence; Adverse effects – poisoning, environmental, resistance, change in mosquito behaviour

Single-dose Tafenoquine for radical cure of *Plasmodium vivax* malaria (to be recommended w/ a point-of-care quantitative G6PD test)

1. Is single dose tafenoquine an alternative to 14 day primaquine for preventing relapses in patients aged 16 years and older with a G6PD activity of >70% who have received appropriate therapy for acute *P. vivax* infection?
2. Population: Patients aged 16 years and older with a G6PD activity of >70% treated for *P. vivax* malaria
3. Intervention: Single dose tafenoquine (300mg)
4. Comparator: Primaquine 0.25mg/kg daily for 14 days or placebo
5. Outcomes:
   - *P. vivax* relapse defined as reappearance of *P. vivax* parasitemia 6-12 months after the use of the medications (dependent on regional parasite relapse pattern).
   - Safety of tafenoquine

Existing recommendations to review available evidence - update

Current recommendations for prevention (vector control/chemoprevention)

- Potential revision of the IRS tables based on an expanded systematic review of the literature (protocol development for this is ongoing)
- Formulation of policy recommendation /GRADE table etc on the impact of pyrethroid resistance on ITN effectiveness. Systematic review on this has just been commissioned.
- Expanding GRADE tables to include explicit mention of the resources required to implement certain interventions
- Formulating a GRADE table and evidence to recommendation tables on PBO nets, based on recently published Cochrane review
- Chemoprevention for special risk groups – review new evidence on IPTp, IPTi and SMC
- Chemoprevention in travellers (in collaboration with International Travel and Health group and document)

Existing recommendations to review available evidence - update

Current recommendations for case management of malaria

- Treating uncomplicated *P. falciparum* malaria – potential addition of ACT; review of dose recommendation
- Treating uncomplicated *P. falciparum* malaria in special risk groups – complete review of ACTs in the first trimester of pregnancy; < 5 kg; HIV patients; travellers
- Preventing relapse in P. vivax or P. ovale malaria – review recommendation on treatment for people with G6PD deficiency (dosing)
- Update on Mass drug administration policy recommendations

Proposed topics for horizon scanning

To highlight as an important area and indicate research priorities:

- *An. stephensi* invasion into new geographical areas
- Testing and treatment at ports of entry

Malaria Policy Advisory Committee Meeting
10–12 April 2019, Geneva, Switzerland
Background document for Session 7

World Health Organization

Meeting report of the WHO Evidence Review Group on mass drug administration for malaria

11–13 September 2018, Geneva, Switzerland

Summary

Mass drug administration (MDA), the strategy of administering antimalarials to all age groups of a defined population (except those for whom the drugs are contraindicated) at the same time regardless of infection status, has recently received renewed interest for its potential to accelerate malaria elimination through rapid and sustained reduction of transmission.

In 2015, the World Health Organization (WHO) recommended that the use of time-limited MDA in combination with other malaria control measures could be considered in the following scenarios: in areas approaching interruption of *Plasmodium falciparum* transmission; in the Greater Mekong subregion (GMS) as a component of accelerated malaria elimination efforts; and in epidemics and complex emergencies to reduce morbidity and mortality. Since WHO's recommendation, new studies have been conducted in areas of low to moderate transmission in Africa and in the GMS, generating additional data on the role of MDA in rapidly reducing transmission. In light of the new data, WHO convened an evidence review meeting to revise and refine the current recommendations on MDA to accelerate malaria elimination, focusing on the evidence emerging from several studies in African countries and the GMS. Modelling studies and results of the update to the Cochrane Systematic Review were also presented and discussed at the meeting.

This meeting report provides a summary of the evidence presented, draft conclusions and a proposed update to the WHO recommendations. The report is submitted to the WHO Malaria Policy Advisory Committee (MPAC) for consideration.

Conclusions

Across all transmission settings:

- MDA may rapidly reduce, but does not interrupt, malaria transmission in the short term (1–3 months after the last round) across all transmission intensities when implemented along with vector control and case management.
- Short-term reductions in malaria transmission from MDA have only been sustained (4–36 months after the last round) in areas of very low to low transmission (RDT/microscopy parasite prevalence <10%) and in island settings with moderate transmission (up to 15% prevalence). Maintaining reductions in transmission after the last round of MDA requires additional

WHO/CDS/GMP/MPAC/2019.04

interventions, including vector control, case management, and intensified surveillance and response.

- Two factors strongly associated with the success of MDA in reducing malaria transmission in the short term are high coverage of the population with MDA (a large proportion of the population receiving at least one round of MDA), which may be achieved with more than one consecutive round per year, and focusing a second round on those missed in the first round.
- The decision to initiate an MDA campaign to accelerate elimination should be based on the balance between the risks of treating the whole eligible population, very few of whom (in a low transmission setting) may be at risk of malaria, and the potential benefits from cases averted. The decision to use MDA to rapidly reduce transmission should also consider whether MDA is cost-effective compared to other interventions.

In moderate to high transmission settings (parasite prevalence ≥10%):

- There is evidence from both a systematic review and the most recent research studies that MDA reduces the transmission of *P. falciparum* in moderate transmission settings (parasite prevalence 10–35%) in the first three months after the last round of MDA is completed, but the evidence is inconclusive from areas of high transmission (parasite prevalence ≥35%). Evidence suggests that the short-term impact of MDA programmes in moderate transmission settings has likely been enhanced by the presence of additional interventions, including vector control and case management.
- The evidence reviewed suggested that the reduction in malaria transmission from MDA could be sustained for up to three years in island settings in areas of moderate *P. falciparum* transmission up to a parasite prevalence of 15% when additional interventions are in place, including vector control, case management and intensified surveillance.

In very low to low transmission settings (parasite prevalence <10%):

- There is evidence from recent research studies that MDA reduces transmission of *P. falciparum* in the first three months after completion of the last round of MDA in low transmission settings (parasite prevalence 1–10%). However, there is no evidence that MDA, even in conjunction with vector control and good case management, can interrupt transmission. No evidence was available for review from very low transmission settings (parasite prevalence <1%).
- The impact of MDA on *P. falciparum* was sustained in many low transmission settings for more than 30 months when additional interventions were deployed, including vector control, community-based case management and intensified surveillance.

Impact on *P. vivax:*

- Two studies of MDA in the GMS using an artemisinin-based combination therapy (ACT) plus a single low dose of primaquine (PQ) reported differing results for *P. vivax*, with one study demonstrating only a short-term reduction in *P. vivax* transmission and the other study finding no effect.

- Historical and recent evidence shows a significant short-term reduction in *P. vivax* transmission, with lower incidence maintained until the following transmission season and up to six months in temperate areas, following the deployment of PQ mass prophylactic treatment for 14 days in combination with other malaria control interventions.

Impact on antimalarial resistance:

- Early results from modelling studies indicate that the risk of MDA in selecting for resistant strains rises with an increasing rate of importation of resistant strains into the MDA area. Conversely, the risk may decrease with increased access to antimalarial medicines that were not used for the MDA regimen in the immediate post-MDA period.

Proposed update to current recommendations on MDA

Based on the above conclusions, the ERG proposes that the existing recommendations on MDA be updated and replaced by the following draft recommendations, which are submitted for consideration to the WHO MPAC.

1. Use of MDA to accelerate progress towards elimination (i.e., significant reductions in malaria transmission sustained over time) of *P. falciparum* malaria can be considered in areas of very low to low transmission (parasite prevalence <10%) where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. Additionally, MDA can be considered in small islands (<500 000 population) with moderate transmission (*P. falciparum* parasite prevalence 10–15%) where there is limited risk of re-introduction of parasites, effective treatment, and effective implementation of vector control and surveillance.

2. In settings with moderate to high transmission, MDA may produce a short-term reduction in malaria burden, but so far there is no evidence that MDA, with or without additional interventions, will accelerate progress towards elimination. More evidence should be gathered to determine whether repeated rounds of MDA over multiple years in conjunction with other interventions in these settings could sustain reduced transmission and accelerate progress towards elimination.

3. Mass primaquine prophylactic treatment, requiring pre-seasonal MDA with daily administration of primaquine for two weeks, can be considered as a component of *P. vivax* elimination strategies in temperate regions, taking into consideration G6PD deficiency.

4. Given the threat of *P. falciparum* multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA should be considered as a component of accelerated malaria elimination efforts in the GMS where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. However, because of prevalent multidrug resistance in the region, the options are limited for effective antimalarials that can be used in MDA.

5. Use of time-limited MDA to rapidly reduce malaria morbidity and mortality may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions.[1]

6. Use of time-limited MDA to reduce malaria morbidity and mortality may be considered in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.[1]

7. Medicines used for MDA must be of proven efficacy in the implementation area and preferably have a long half-life. WHO recommends that a medicine different from that used for first-line treatment be used for MDA to reduce the risk of development of resistance. Programmes should include drug safety monitoring during MDA campaigns. Drug efficacy should be monitored after the campaign to identify potential emergence of resistance to the antimalarial medicines deployed for MDA.

8. WHO supports the need for more research on the optimum methods for implementing MDA programmes, promoting community engagement and compliance with treatment, and evaluating the effectiveness of MDA programmes. Modelling can help guide the optimum method for administering MDA in different epidemiological circumstances and help predict its likely impact.

Abbreviations

ACT	artemisinin-based combination therapy
AP	artemisinin-piperaquine
DP	dihydroartemisinin-piperaquine
ERG	Evidence Review Group
G6PD	glucose-6-phosphate dehydrogenase
GMP	Global Malaria Programme
GMS	Greater Mekong subregion
IRS	indoor residual spraying
LLIN	long-lasting insecticidal net
MDA	mass drug administration
MPAC	Malaria Policy Advisory Committee
MPPT	mass primaquine preventive treatment
NMCP	national malaria control programme
P.	*Plasmodium*
PCR	polymerase chain reaction
PQ	primaquine
RDT	rapid diagnostic test
WHO	World Health Organization

[1] No evidence was reviewed related to this recommendation and so it has not been updated.

1. Background

Mass drug administration (MDA) for malaria is defined by the World Health Organization (WHO) as the *administration of antimalarial treatment to all age groups of a defined population or every person living in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals (1,2).* It is one of the recommended interventions for preventive chemotherapy. Similar to chemoprophylaxis, intermittent preventive treatment of infants and pregnant women, and seasonal malaria chemoprevention, MDA deploys antimalarial medicines to prevent malaria infections and their consequences. MDA may be deployed for two distinct but complementary objectives: 1) to rapidly reduce transmission of malaria, which may accelerate progress towards elimination and control malaria epidemics, and 2) to rapidly reduce morbidity and mortality during epidemics and complex emergencies *(3)*.

Although MDA has been historically a key component of malaria control and elimination strategies, WHO has not promoted this intervention for some time; however, the role of MDA has recently received renewed interest for its potential to accelerate progress towards elimination through the rapid reduction of parasites in the human reservoir, which may then lead to a reduction in malaria transmission. After reviewing the evidence on the use of MDA in specific epidemiological settings in 2015 *(4)*, WHO recommended the use of MDA to interrupt *Plasmodium falciparum* transmission in areas approaching elimination; to reduce the risk of multidrug resistance spread in the Greater Mekong subregion (GMS) by contributing to *P. falciparum* elimination; during malaria epidemics as part of the initial response; and in exceptional complex emergencies to reduce morbidity and mortality *(5,6)*.

In the years following the publication of these recommendations, several large-scale trials and MDA campaigns were implemented across the transmission continuum, permitting the assessment of the potential role of MDA in interrupting or accelerating reductions in transmission in combination with other core interventions. In addition, a Cochrane Systematic Review on MDA for malaria, published in 2013 *(7)*, has been updated and additional modelling studies completed. As a result of the availability of new research and programmatic evidence, WHO convened an Evidence Review Group (ERG) to revise and refine the current recommendations, focusing on the role of MDA in decreasing transmission and accelerating progress towards elimination.

2. Objectives

The specific objectives of the ERG were to:

1. determine the effectiveness of MDA combined with other core interventions in reducing malaria incidence and prevalence of *P. falciparum* and *P. vivax* malaria in areas of low, moderate and high transmission, with particular attention to the effects of vector control, case management and intensified surveillance on the effectiveness of MDA, and the determinants of sustained post-MDA reduction in malaria transmission; and
2. review new evidence on the impact of MDA in areas of low to very low transmission in relation to current WHO recommendations on MDA for interrupting the transmission of *P. falciparum* malaria in areas approaching elimination and reducing the spread of multidrug resistance in the GMS.

3. Process

The WHO Secretariat of three units of the Global Malaria Programme (GMP) – 1) Prevention, Diagnostics and Treatment; 2) Elimination; and 3) Drug Efficacy and Response – jointly planned the meeting. Nine independent experts in malaria epidemiology, elimination and chemotherapy, and methodology specialists in the assessment of data from applied field research were convened, together with 18 participants representing national malaria control programmes (NMCPs) and collaborating technical research institutions, who were invited to present recent results from MDA field studies, MDA campaigns, systematic reviews and modelling studies. The pre-reads prepared by the presenters, together with relevant WHO reports, were shared with all the participants prior to the meeting (Annex 1). Six observers representing academia, philanthropic foundations and funding agencies, together with seven members of the WHO Secretariat, completed the list of participants (Annex 2).

The trials, reviews, programmatic data and studies were presented in plenary sessions during the first two days of the meeting. The sessions listed below were each followed by plenary discussions:

- Cochrane Systematic Review update of MDA for malaria
- MDA as accelerator of *P. falciparum* elimination in the African Region
- Modelling the contribution of MDA to malaria elimination and drug resistance
- MDA as accelerator of *P. falciparum* elimination in the GMS
- Other studies on impact of MDA on malaria transmission in the African Region
- Mass primaquine preventive treatment (MPPT) as an accelerator of *P. vivax* elimination.

The last day of the meeting was restricted to the independent experts and WHO Secretariat, focusing on the discussion of the meeting conclusions and development of the draft recommendations to be submitted to MPAC in March 2019. GMP provided a set of questions to the independent experts to facilitate the development of the draft recommendations. The questions and answers drafted by the ERG are attached in Annex 3.

The meeting report was compiled based on the meeting pre-reads, presentations and discussions that took place during the ERG meeting. The details of the field studies presented are summarized in Annex 4. All participants were invited to review the draft and provide further input to the final report.

4. Evidence review

Categories of transmission intensity

Based on the transmission levels presented in the WHO framework for malaria elimination, measured by microscopy or conventional rapid diagnostic tests (RDTs) *(8)*, the studies reviewed at the meeting are presented by country and transmission intensity, as shown in Table 1.

Table 1. Studies presented by category of transmission intensity

Level of transmission	Parasite prevalence	Country
High	≥35%	Uganda, Zambia
Moderate	10–35%	Comoros Islands (Anjouan and Grande Comore)
Low	1–10%	Mozambique, Zambia, Gambia, Myanmar, Viet Nam, Cambodia, Lao People's Democratic Republic
Very low	0–1%	None available

Cochrane Systematic Review update on MDA for malaria

A Cochrane Systematic Review published in 2013 reported on the impact of MDA on malaria based on 32 published studies *(7)*.

The review was updated in 2018 with revised inclusion criteria to select more rigorous study designs with control groups and balanced co-interventions across study arms. A draft of the updated review was presented at the meeting. The effect of MDA was assessed on the interruption of transmission in very low to low transmission settings (<10% prevalence) and on the reduction of malaria transmission in moderate to high transmission areas (≥10% prevalence). As a secondary objective, MDA-associated adverse events were evaluated. The primary outcomes were parasite prevalence, parasite incidence (i.e., incidence of infection from active surveillance), and confirmed malaria illness incidence (i.e., confirmed clinical infection from passive surveillance). Outcomes were stratified by pre-MDA (prior to the first round of MDA), during MDA (time period between the first and last rounds of MDA), and post-MDA (following the last round of MDA, categorized as <1, 1–3, 4–6, 7–12, 13–18, 19–24, 25–30, and 31–36 months) (*Shah, unpublished report*).

Out of 358 records identified from the search, 36 full-text articles were assessed for eligibility and nine studies met the inclusion criteria: five cluster-randomized trials were included in a quantitative synthesis (one additional trial was not analysed due to insufficient data) and three non-randomized (controlled before-and-after) studies were analysed separately. Two out of the 10 studies reviewed at the ERG meeting were also included in the Cochrane analysis.

Two cluster-randomized trials took place in Zambia and The Gambia in areas of moderate to high transmission. In Zambia, four rounds of MDA with dihydroartemisinin-piperaquine (DP) were conducted between 2015 and 2016, in combination with indoor residual spraying (IRS), long-lasting insecticidal nets (LLINs) and enhanced community case management. In The Gambia, one round of MDA with sulfadoxine-pyrimethamine plus artesunate was conducted in 1999 *(9,10)*. Based on the analysis of these data (*Shah, unpublished report*):

- MDA probably leads to little or no reduction in parasite prevalence at 1–3 months (n=1 study) and 4–6 months (n=1 study) post-MDA (*moderate certainty evidence*), and MDA may lead to little or no difference at 13–18 months (n=1 study) post-MDA compared to no MDA (*low certainty evidence*).
- MDA probably reduces parasite incidence at 1–3 months (n=1 study) post-MDA compared to no MDA (*moderate certainty evidence*), but, based on the available evidence, the effect at 4–6 months (n=1 study) post-MDA is unknown (*very low certainty evidence*).

- MDA may lead to no reduction in confirmed malaria illness incidence at 1–3 months (n=1 study) post-MDA compared to no MDA (*low certainty evidence*).

Three cluster-randomized trials were carried out in Myanmar, Zambia and Zanzibar, categorized as very low to low transmission settings (<10% prevalence) *(9,11,12)*. In Myanmar, three rounds of MDA with DP plus primaquine (PQ) were administered in combination with LLINs. In Zambia, four rounds of MDA with DP were administered with IRS, LLINs and enhanced community case management. In Zanzibar, two rounds of DP plus PQ were administered with IRS and LLINs. Based on analysis of these data (*Shah, unpublished report*):

- It is unknown whether MDA has an effect on the reduction of *P. falciparum* parasite prevalence at all post-MDA time points from <1 month through 31–36 months (*very low certainty evidence*).
- MDA probably reduces parasite incidence at 1–3 months post-MDA compared to no MDA (*moderate certainty evidence*).
- It is unknown whether MDA has an effect on the reduction of confirmed malaria illness incidence in the period between 1–3 months and 13–18 months post-MDA (*very low certainty evidence*).

P. vivax parasite prevalence was also reported in the study in Myanmar *(11)*. Based on evidence from this study, MDA may reduce *P. vivax* parasite prevalence at <1 month (*low certainty evidence*), but MDA may have little or no effect at 1–3 months post-MDA (*low certainty evidence*); it is unknown whether MDA has an effect at post-MDA time points from 4–6 months through 31–36 months (*very low certainty evidence*) (*Shah, unpublished report*).

Three non-randomized studies conducted before 1980 in moderate to high transmission areas in Burkina Faso, Kenya and Nigeria were also included in the Cochrane Systematic Review update *(13–15)*. In Burkina Faso, either seven ("low frequency") or 15 ("high frequency") MDA rounds of amodiaquine-primaquine or chloroquine-primaquine were administered in 1960–1961 with no co-interventions. In Kenya, two rounds of MDA with pyrimethamine were administered in 1953–1954 with no co-interventions. In Nigeria, either nine ("low frequency") or 23 ("high frequency") rounds of MDA with sulfadoxine-pyrimethamine were administered between 1970 and 1975. All studies reported the outcome of *P. falciparum* parasite prevalence. During the MDA rounds, parasite prevalence decreased in all studies (*Shah, unpublished report*). Two studies provided data at 1–3 months post-MDA (Burkina Faso and Kenya). Reductions were seen in the Kenyan study and in the low frequency arm but not the high frequency arm of the Burkina Faso study. Only one study (Kenya) reported outcomes at 4–6 and 7–12 months post-MDA and found sustained, but smaller, reductions in parasite prevalence over time (*Shah, unpublished report*).

Given the limited number of studies evaluated after the stratification by endemicity and time period in the Cochrane Systematic Review update, it was not possible to determine whether factors such as the drug's prophylactic duration, MDA coverage, concomitant interventions, or risk of re-introduction may modify the effect of MDA (*Shah, unpublished report*).

Key conclusions from the Cochrane Systematic Review update on MDA for malaria:

- In moderate to high transmission settings, there was evidence of short-term reduction (1–3 months post-MDA) in *P. falciparum* incidence, but no evidence of an effect on parasite prevalence or confirmed malaria illness incidence at any post-MDA time points.
- In very low to low transmission settings, there was evidence of a short-term reduction (1–3 months post-MDA) in *P. falciparum* incidence, but there was insufficient evidence to

determine whether there were any effects on parasite prevalence or confirmed malaria illness incidence at longer term post-MDA time points.

- Evidence from a single study suggests that MDA may reduce *P. vivax* parasite prevalence at <1 month, but MDA may have little or no effect at 1–3 months. There is insufficient evidence to determine the effect at other post-MDA time points.

New evidence on impact of MDA by level of malaria transmission and location

Evidence from nine studies (one ongoing and eight completed) deploying MDA in Africa and the GMS was presented to the ERG members.[2]

These studies have been stratified by transmission intensity in order to facilitate comparison of the results. The list of the studies reviewed is presented in Annex 4.

Moderate to high transmission settings (>10% prevalence)

The following studies located in settings with moderate to high transmission were presented:

Table 2. Studies located in moderate to high transmission settings

Level of transmission	Parasite prevalence (RDT)[3]	Country	Study design	Target population[4]	Drug, number of rounds	Vector control interventions
High	51% (<6 years old)	Zambia[5]	Randomized	45 442	DP, four rounds	LLINs, IRS
	35% (all ages)	Uganda	Non-randomized	16 777	DP, four rounds	LLINs, IRS
Moderate	13.5% (6 months to 16 years old)	Comoros Islands, Anjouan	Non-randomized, interrupted time series	321 635	AP+PQ or AP only, three rounds	LLINs
	10.6% (<5 years old)	Comoros Islands, Grande Comore	Non-randomized, interrupted time series	433 348	AP + PQ, two rounds	LLINs

Note: DP: dihydroartemisinin + piperaquine; AP: artemisinin + piperaquine; LLINs: long-lasting insecticidal nets; IRS: indoor residual spraying

High transmission (≥35% parasite prevalence)

Data were available for review from two studies:

- a community randomized controlled trial in Zambia during 2015 and 2016 to assess the impact of four rounds of MDA with a follow-up period of 18 months (until May 2016) *(9)*; and
- a two-year (2017–-2018) quasi-experimental study in Uganda of the impact of four rounds of IRS in combination with MDA (*Echodu, unpublished report*).

[2]An additional study in Cambodia evaluating three rounds of prophylaxis with DP was reviewed but determined not to meet the definition of an MDA because antimalarials were given only to volunteers and their families and not to the entire population of a geographic area.
[3] Parasite prevalence (RDT) at baseline
[4] Population targeted for treatment
[5] Results from this study were also included in the Cochrane Review.

Both studies combined MDA with LLINs and IRS. In Zambia, the standard of care package also included improved surveillance, community engagement and expansion of community case management with an increase in the number of community health workers (*Eisele, unpublished report*). In Uganda, case management with ACTs was widely accessible from all health clinics in the study area (*Echodu, unpublished report*).

In Zambia, four rounds of MDA had no immediate impact on parasite prevalence in children or on confirmed malaria incidence compared to the standard of care, although there was an immediate, short-term reduction in the cumulative incidence of *P. falciparum* infection measured by polymerase chain reaction (PCR) in the MDA group (*Eisele, unpublished report*). As the cohort ended three months following the last MDA round, it is unknown whether there was a sustained decrease in the infection incidence in Zambia. In Uganda, there was a large decrease in parasite prevalence in the two intervention arms (LLINs + IRS and LLINs + IRS + MDA) compared to the control arm (LLINs only); however, there was no statistically significant difference in the reduction between the LLINs + IRS + MDA arm and the LLINs + IRS arm (*Echodu, unpublished report*), suggesting that MDA had no effect. This study was limited, however, by having only one site per arm.

The strategy currently adopted by the National Malaria Elimination Programme of Zambia was also presented. Community-wide MDA is now implemented in eligible health facility catchment areas of the country, defined as those with a high coverage of LLINs and/or IRS, enhanced community case management, and a functional surveillance system capable of responding to index cases post-MDA, with between 50 and 500 cases per 1000 population. Following these criteria, two rounds of programmatic MDA were conducted in 2017, and two additional rounds were planned for 2018. Preliminary findings suggest a benefit of combining a full package of malaria interventions including MDA, but the analysis is still ongoing (*Busiku, unpublished report*).

Moderate transmission (10–35% parasite prevalence)

Data were available for review from two studies:

- an interrupted time series analysis of programmatic implementation of three rounds of MDA on Anjouan island in Comoros deployed in 2012 with a follow-up period of 18 months *(16)*; and
- an interrupted time series analysis of programmatic implementation of two rounds of MDA on Grande Comore (Ngazidja Island) in Comoros deployed in 2013 (*Bacar, unpublished report).*

MDA in combination with vector control has been used in three islands of the Comoros archipelago with a highly significant reduction in malaria transmission (*(16)* and *Bacar, unpublished report)*. Reports from two of the islands were available for review. In Anjouan Island, three rounds of MDA (approximately half of the population receiving AP and the other half receiving a single low dose of PQ in addition to the ACT) rapidly reduced malaria transmission, achieving approximately a 99% reduction in malaria incidence one year after the last round of MDA. Despite these gains, no additional difference in impact was seen in the areas receiving PQ. In Grande Comore, two monthly rounds of MDA with an ACT plus a single low dose of PQ were deployed to accelerate reductions in malaria transmission. In both cases, a rapid decline in *P. falciparum* malaria incidence was observed in the period immediately post-MDA. The effect was sustained in Anjouan for at least five years and in Grande Comore for three years. In both islands, there was intensified surveillance following the MDA campaigns, including proactive and reactive case detection.

Key factors in the success of the MDA campaign were community mobilization and participation to improve MDA uptake coverage, and the involvement of a large number of trained drug dispensers and

supervisors. In Anjouan Island, mobilization and training of the local team was done for three months to ensure correct deployment of the intervention, and a campaign to inform and engage the population was undertaken as well. On this island, the average coverage rates achieved varied from 85.7% to 92.9% *(16)*.

In Anjouan Island, the monitoring and treatment of travellers was also done in an attempt to control and monitor importation of parasites. At the airport and wharfs of the island, travellers were asked to complete information surveys and given antimalarial drugs for self-administration. Individual travellers were asked to visit a malaria diagnostic laboratory where they could have free microscopic testing for malaria infection *(16)*.

Very low to low transmission settings (<10% prevalence)

Based on the available evidence, the impact of MDA was evaluated for low transmission areas in Africa and the GMS. The following six studies were available for review:

Table 3. Studies located in low transmission settings

Level of transmission	Parasite prevalence (RDT)[6]	Country	Study design	Target population[7]	Drug, rounds	Vector control interventions
Low	7.5% (all ages)	Gambia	Non-randomized	4312 (year 2014) 4189 (year 2015)	DP, two rounds	LLINs, IRS
	9% (all ages)	Mozambique	Non-randomized	52 581 (year 2015) 61 868 (year 2016)	DP, four rounds	LLINs, IRS
	8% (<6 years old)	Zambia[8]	Randomized	37 694	DP, four rounds	LLINs, IRS
	6% (all ages)	Myanmar Viet Nam Cambodia Lao People's Democratic Republic	Randomized	4423	DP + PQ, three rounds	LLINs
	5.5% (all ages)	Myanmar (Eastern Kayin State)	Non-randomized	12 465	DP + PQ, three rounds	LLINs
	2.7% (≥18 years old)	Myanmar (Southern Kayin State)	Randomized	4618	DP + PQ, three rounds	LLINs

- a two-year pre-post, non-controlled study in The Gambia of the impact of a single MDA round per year for two years (2014 and 2015) *(17)*;
- a pre-post *quasi-experimental* study of a community mobilization campaign followed by one round of IRS and two rounds of MDA per year for two consecutive years (from November 2015

[6] Parasite prevalence (RDT) at baseline.
[7] Population targeted for treatment.
[8] These studies were also included in the Cochrane Review.

to February 2017) in Mozambique, followed by reactive focal drug administration on top of standard case management and bed-net distributions (*Galatas, unpublished report*);

- a community-randomized controlled trial in Zambia to assess the impact of two rounds of MDA two to five months apart during 2015 and 2016 *(9)*;
- a multisite, stratified, cluster-randomized trial in Myanmar, Viet Nam, Cambodia and Lao People's Democratic Republic between 2013 and 2017 to assess the effectiveness, safety, tolerability and acceptability of three rounds of MDA, with a follow-up period of 24 months in Myanmar and Viet Nam and 12 months in Cambodia and Lao People's Democratic Republic (*von Seidlein, unpublished report*);
- a targeted MDA study in transmission hotspots in four townships of Eastern Myanmar undertaken from 2014 to 2017, with follow-up still ongoing *(18–20)*; and
- a community-randomized controlled study of three rounds of MDA one month apart in 2015 in 'hotspot' villages near the Thai border in Southern Kayin State, Myanmar, with a follow-up period of 33 months (*McLean, unpublished report*).

In all these studies, MDA in combination with other interventions significantly reduced the malaria burden over the short term, but interruption of transmission was not achieved. In the study area in The Gambia, lower malaria prevalence was observed in the first three months post-MDA *(17)*. Similarly, in Mozambique (*Galatas, unpublished report*) and in Zambia (*Eisele, unpublished report)*, high vector control in combination with four rounds of MDA significantly reduced the malaria burden. In the GMS, a cluster-randomized trial in Myanmar, Cambodia, Viet Nam and Lao People's Democratic Republic that targeted a total of 16 villages observed that the *P. falciparum* prevalence had fallen considerably in the MDA villages three months after the last round of MDA (*von Seidlein, unpublished report*). In Eastern Myanmar, 50 hotspots received MDA in five campaigns, and the *P. falciparum* infection prevalence 12 months after MDA decreased by a median of 92% compared to pre-MDA levels *(18)*. The study conducted in Southern Myanmar, which also targeted hotspots of high transmission, observed a significantly lower *P. falciparum* infection prevalence in the intervention villages one month after the last round of MDA (*McLean, unpublished report).* Consistent with what has been described in other settings, a decrease in the malaria burden in the control arm was also observed during the study period, although to a much lesser degree than observed in the intervention arm (*McLean, unpublished report)*.

The long-term impact of MDA in reducing *P. falciparum* prevalence and incidence varied across sites. In The Gambia, the reduction in prevalence was sustained over two years in the areas of low transmission, but not in the areas of moderate transmission; a reduction in the risk of clinical malaria was seen throughout the transmission season *(17)*. During the second year of MDA rounds in Mozambique, the prevalence of malaria did not decline further (*Galatas, unpublished report*). In the GMS multisite trial, the *P. falciparum* prevalence one year after the last round of MDA was very low and even reached zero in four of the eight intervention villages, suggesting that in low transmission settings, MDA in combination with additional community-based strategies can help reduce, interrupt and sustain the reduction in *P. falciparum* transmission over a one-year period. The impact was seen to vary by country, being higher in villages with a baseline prevalence of *P. falciparum* over 5%. When comparing intervention and control arms, the prevalence of infection increased steadily over the nine months post-intervention, partly attributed to re-introduction from surrounding areas. However, this effect seems to have been mostly driven by sites located in a single county, given that it was not reflected at the village level for five out of eight of the intervention villages (*von Seidlein, unpublished report*). On the other hand, consistent with what has been seen in other settings, such as in Zambia or Myanmar (*Eisele, unpublished report; McLean, unpublished report*), a substantial reduction in malaria

transmission was also seen in the control villages that did not receive MDA. This reduction is attributable to the increased access to early diagnosis and treatment and the LLINs provided to all villages in the study (*von Seidlein, unpublished report*). In Southern Kayin State of Myanmar, the difference in *P. falciparum* prevalence between the intervention and control arms remained significant only up to three months after last round of MDA (as the prevalence in the control arm continued to decline over time with access to early diagnosis and treatment) (*McLean, unpublished report*), whereas in Eastern Kayin State, the reduction has been sustained for 20 months and follow-up is continuing *(18)*.

The available evidence shows that, in Mozambique, high vector control and reactive focal drug administration (*administering drugs to a subset of a population in a given area in response to detection of malaria cases at health facility levels (1)*) have been able to sustain the achieved low prevalence up to one year after the MDA (*Galatas, unpublished report*). In Zambia, malaria parasite prevalence in children remained low (87% reduction from baseline) up to 15 months after the last round of MDA with sustained high vector control coverage and improved access to diagnosis and treatment of malaria (*Eisele, unpublished report*), although there was no difference in malaria indicators between the intervention and control communities.

Community engagement campaigns were done in Mozambique prior to the first round of MDA, and reported LLIN usage increased significantly (*Galatas, unpublished report*). Further concomitant interventions implemented in the other studies that may have also contributed to the effectiveness of the package of interventions include intensified surveillance and community case management in Zambia and sensitization meetings in The Gambia prior to the trial. Intensive community engagement activities were also conducted in the GMS multisite trial prior to MDA in order to encourage uptake *(19, 20)*; of the people residing in the eight intervention villages during the three months of MDA, 86% completed at least one round and 57% completed the three rounds of MDA (*von Seidlein, unpublished report*). Along the same lines, community engagement activities that aimed to ensure understanding and acceptance of the strategy were also performed in the two studies located in Myanmar (*(18,23)* and *McLean, unpublished*). In Eastern Myanmar, community-based malaria posts provided increased access to early diagnosis and treatment to all villages, which was seen to help in decreasing the incidence of *P. falciparum* malaria in these hard-to-reach regions of the country *(18)*. Evidence of declines in malaria incidence with community-based malaria posts in the GMS has been reported elsewhere *(24,25)*.

Most low-density artemisinin- and piperaquine-resistant infections were cleared effectively with the available drugs. However, it was observed that higher density infections recrudesced more frequently, pointing to the need to closely monitor the efficacy of the ACTs deployed (*von Seidlein, unpublished report*). In Eastern Myanmar, the prevalence of wild-type genotype for K13 molecular markers of artemisinin resistance was monitored, and no evidence of worsening drug resistance was observed after drug deployment *(18)*.

In Southern Myanmar, *P. vivax* prevalence also decreased in the month following the last round of MDA, but the decrease was not sustained into the third month post-MDA (*McLean, unpublished*). By contrast, in Eastern Myanmar, little change in *P. vivax* incidence was observed during the study *(18)*.

Monthly intermittent preventive treatment to high-risk populations

A cluster-randomized trial conducted along the Cambodia–Thailand border in 2016 compared the effectiveness, safety and tolerability of monthly intermittent preventive treatment compared to focused screening and treatment of volunteers from military camps and their dependents (*Wojnarski,*

unpublished report). The intervention included monthly three-day course administration of DP plus low-dose weekly PQ for 12 weeks. Both groups had access to effective malaria diagnosis and treatment. Volunteers also received either insecticide-treated uniforms or water-treated uniforms based on cluster assignment. In the MDA arm, no benefit was observed from the insecticide-treated uniforms over drug therapy (*Wojnarski, unpublished report*). Significant reductions in *P. falciparum* incidence were seen up to six months post-intervention, while the impact on *P. vivax* incidence was modest, suggesting that reduction of *P. vivax* incidence in these settings will require different approaches (*Wojnarski, unpublished report*). This study was not included in the review, as the chemoprevention strategy deployed did not reach the entire population and, therefore, did not meet the definition of MDA.

Key conclusions about the impact of MDA in Africa and the GMS:

- In high transmission settings (parasite prevalence ≥35%), data were limited to two studies, neither of which showed a clear short-term effect of MDA on malaria burden.
- In moderate transmission settings (parasite prevalence 10–35%), MDA had a clear short-term effect in reducing malaria transmission when combined with vector control and case management, but the decline was not sustained in the long term.
- In island settings with moderate transmission up to 10–15% parasite prevalence, the short-term reductions in transmission resulting from MDA were sustained for up to three years when combined with vector control, case management, intensified surveillance and community engagement.
- In areas with low transmission (parasite prevalence 1–10%), MDA had a clear, short-term effect on malaria parasite prevalence and incidence when combined with vector control, case management and intensified surveillance. There was some evidence that these gains could be maintained over one or more years when combined with other interventions such as increased access to community-based diagnosis and treatment.
- No studies were reviewed from areas of very low transmission (parasite prevalence <1%).
- Despite the significant malaria reductions achieved with MDA in areas with low transmission intensity, no interruption of transmission (zero local cases) resulting from MDA has been documented.
- In areas with low transmission affected by multidrug resistance, the combination of increased access to early diagnosis, prompt treatment by community health workers and deployment of MDA has significantly decreased *P. falciparum* transmission, with many villages free from *falciparum* malaria for at least six months. Therefore, this package of interventions should be considered together with effective vector control in order to accelerate progress towards elimination in the region.
- No evidence of increased artemisinin or partner drug resistance has been documented related to MDA with ACTs, but further research and continuous monitoring of the effectiveness of ACTs are needed in areas considering MDA campaigns.
- MDA with ACTs has been shown to reduce transmission of *P. vivax* malaria in the short term, but there have been few studies addressing the impact of MDA on *P. vivax* in tropical areas.

Modelling the impact of MDA on malaria elimination and drug resistance

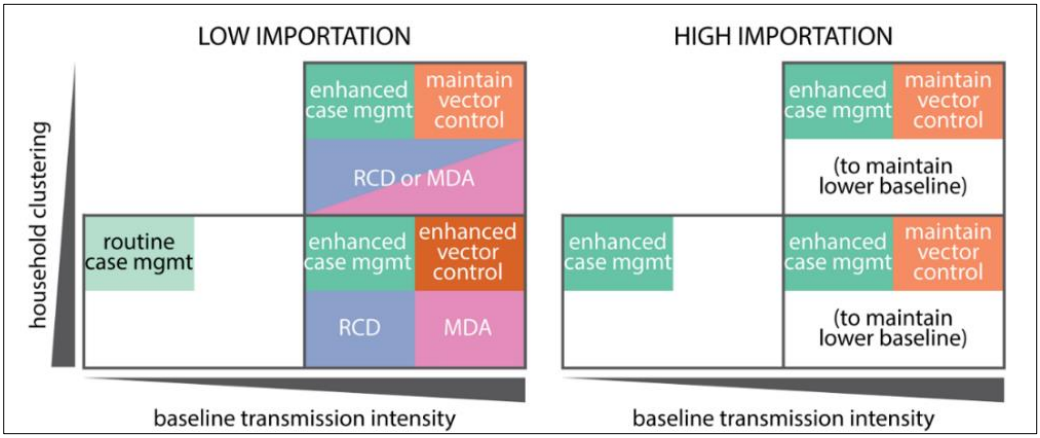
Testing combinations of strategies in the field is extremely challenging, particularly in terms of assessing the impact of multiple interventions in different epidemiological settings. In addition, the evaluation of the impact of different interventions in low transmission settings requires a large sample size, which is not always feasible. Given these limitations of field research, mathematical modelling can be a valuable approach to understanding the potential impact of different interventions across multiple epidemiological contexts.

Results from a consensus modelling effort indicate that the immediate reduction in transmission resulting from MDA in low transmission settings would be temporary and that, in the absence of high coverage with other interventions, such as vector control, transmission would return to pre-MDA levels. A key determinant of simulated effectiveness is the proportion of the population treated in a year, irrespective of whether people are treated through high coverage in a single round or new individuals are reached through implementation of several rounds. MDA is predicted to be more effective if continued over two years rather than one year, and if done at the time of year when transmission is lowest *(26)*.

Using household models of health facility catchment areas in the Lake Kariba region of the Southern Province of Zambia *(27)*, the role of a limited MDA programme for one to two years in combination with LLIN distribution, IRS, case management and reactive case detection was investigated. Additional hypothetical intervention scenarios were also tried, including counterfactuals. According to the model results, MDA can be an accelerator of malaria elimination if the following preconditions are met: excellent case management, effective vector control, low rates of parasite importation, good MDA coverage and appropriate timing of rounds (*Gerardin, unpublished report*). The same modelling exercise indicated that in low transmission areas with highly clustered households and low parasite importation rates, elimination can be achieved without the help of MDA if 100% of symptomatic cases are treated. However, MDA may play a substantial role in achieving elimination when case management is suboptimal, the MDA campaign is conducted early in an area's trajectory towards elimination, and thus a substantial infectious reservoir remains. In high transmission areas with dispersed households, elimination can be achieved when parasite importation rates are low or negligible, 100% of symptomatic cases are treated, and reactive case detection is very well implemented. In these situations, MDA has a small acceleration effect. In situations where case management and reactive case detection are not optimally implemented or where parasite importation rates are high, MDA can increase the likelihood of elimination being achieved, even though the overall probability of elimination remains low.

In conclusion, according to the model, the impact of MDA in accelerating the malaria elimination strategy depends on the baseline transmission intensity, household clustering, parasite importation rate, and quality and coverage of case management, reactive case detection and vector control (*Fig. 1*).

Fig. 1. Case scenarios and recommended elimination strategy



Source: Jaline Gerardin. Modelling intervention mixes in combination with MDA to accelerate malaria elimination. Institute for Disease Modelling. Unpublished report.

Also using data from Zambia, a conceptual, individual-based stochastic model of malaria transmission was developed to estimate the probability of resurgence after deployment of MDA and different co-interventions (*Smith, unpublished report*). The modelling showed that the two determinants of resurgence are the residual transmission (persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme *(1)*) and the routine case management coverage for remaining cases. In this context, the concomitant interventions needed for both transmission reduction and significant clearance of low-density infections are vector control and case management deployed at high coverage levels (>80%). High-level coverage of early detection and treatment following MDA may be sufficient to avert resurgence by removing the introduction of gametocytes from imported cases (*Smith, personal communication*). The model also indicated that MDA may lead to elimination by stochastic extinction in areas with a relatively low reproduction number (R_0) when applied at very high coverage in combination with vector control interventions in relatively small populations *(28)*. This was shown by Kaneko et al. in Aneityun Island, Vanuatu *(29)*.

Models have also been used to explore the effects of MDA implementation on the spread of drug resistance. Results of an individual-based stochastic model evaluating the impact on drug resistance of high coverage of MDA with DP in populations of 40 000 and 300 000 individuals were presented at the meeting (*Nguyen, unpublished report*). The model simulations indicated that MDA creates a genetic bottleneck that makes gene frequencies associated with drug resistance highly unpredictable. This bottleneck tends to promote genotypes that are resistant to DP. Modelling predicted that the importation of artemisinin-resistant *kelch13* genotypes is likely associated with MDA failure and that the mutants tend to fix in the period immediately following the bottleneck. In settings where there is low importation of *kelch13* mutants, the bottleneck effect is weak and MDA could succeed. According to the model, the best solution to avoid the development of resistance is to improve access to different antimalarials from those used for MDA in the period immediately following MDA in order to eliminate residual resistant parasites (*Nguyen, unpublished report*).

Key conclusions from modelling on the contribution of MDA to malaria elimination and drug resistance:

- Ideally, some preconditions should be met to ensure the usefulness of MDA: excellent case management, effective vector control, low importation, high coverage, and timing during a low transmission period. Nevertheless, in low transmission settings, MDA could compensate for pockets of suboptimal case management if timed correctly, whereas in areas of high transmission, MDA could compensate for poor reactive case detection.
- Overall population coverage of MDA is a key determinant of its impact and simulated effectiveness, whether high coverage is achieved in one or multiple rounds.
- Based on model results, the reduction in transmission from MDA is expected to be greater and longer lasting in lower transmission settings and within smaller populations.
- By deploying case management or other concomitant interventions post-MDA, the low levels of transmission achieved may be maintained.
- To reduce the risk of drug resistance, access to treatment with different antimalarials should be expanded immediately following the MDA – the most sensitive period for selection of resistance.

Mass primaquine preventive treatment (MPPT) as accelerator of P. vivax elimination

Lessons from the past

In the past, several countries aiming for *P. vivax* elimination deployed MPPT regardless of G6PD enzyme activity. The lessons learned from these large-scale MDA operations conducted in Azerbaijan, northern Afghanistan, Tajikistan and the Democratic People's Republic of Korea can help to inform and guide present and future implementation strategies. In these countries, over 8 million people received either a 14-day "standard" or a 17-day "interrupted" PQ treatment to control *P. vivax* malaria epidemics *(30)*.

The drugs were administered to the population by teams who carefully supervised the process and closely monitored for PQ-related severe adverse events *(31)*.

In Azerbaijan, the MPPT campaigns were first implemented from 1971 to 1975 in order to contain and control a *P. vivax* epidemic that occurred in 1970–1972. During the spring of 1971, approximately 90% of the targeted population received a full course of PQ treatment and coverage was maintained between 87% and 93% the following year *(30,32)*. A 60% reduction in malaria incidence was observed compared to the pre-MPPT period, and the reported frequency of adverse effects was very low, despite an overall 15.4% prevalence of G6PD deficiency with major variations from place to place. Following a malaria resurgence in 1979, another MPPT campaign was implemented between 1980 and 1986. By 1982, there had been a 60% reduction in malaria incidence, with no significant further decrease in malaria cases in subsequent years *(31)*.

Following the experience in Azerbaijan, MPPT was also deployed in North Afghanistan in 1972 and 1973. In this case, 14 villages were targeted with an overall coverage of around 90%. During the next malaria transmission season, the incidence of malaria was reduced three-fold in the treated population compared to the control villages, and the rate of adverse effects reported was less than 1%, despite variable prevalence of G6PD deficiency in the areas where MPPT was deployed *(33)*.

Following the re-establishment of local malaria transmission in Tajikistan in the 1980s, three MPPT campaigns were deployed in the country between 1983 and 2002. The first campaign was unable to achieve a very high coverage and so resulted in only a modest reduction in malaria transmission *(34)*. Following two additional MPPT campaigns in combination with other interventions, malaria was progressively reduced in the country, and the MPPT campaign in 2002 helped to reduce the malaria burden by around 40% *(35)*.

MPPT was implemented in five provinces of the Democratic People's Republic of Korea in five consecutive years from 2002 to 2006. These campaigns contributed to a significant reduction in *P. vivax* malaria in subsequent years *(36)*. More than 94% coverage was achieved in all the deployed MPPT campaigns, ranging from 94% in 2003 to 98% in 2006 *(31,36)*. G6PD deficiency prevalence in the Democratic People's Republic of Korea was estimated at 0.5–2.9%, and the frequency of side-effects was low with no cases of severe haemolysis reported. Even though the campaigns managed to achieve significant reductions in malaria morbidity and mortality, interruption of transmission was not achieved. Therefore, consistent with what has been observed in other scenarios, this example indicates that elimination is not feasible in the absence of complementary measures to accompany the drug-based campaigns *(31)*.

Based on these historical experiences, high coverage of MPPT in combination with vector control interventions has been, in general, highly effective in decreasing *P. vivax* transmission in temperate areas by preventing relapses. Moreover, tolerability of the drug has been good, with a low frequency of adverse events reported even with heterogeneous levels of G6PD deficiency *(31)*.

WHO recommendations on G6PD testing to support safe use of primaquine as anti-relapse treatment for *P. vivax* malaria

Since its introduction in 1952, PQ has remained highly effective for the treatment of *P. vivax* relapses. Nevertheless, the recommended dosage for safe use of the drug must be adapted to the G6PD status of the patient. However, this status is often unknown, as G6PD testing is not available in most malaria endemic settings *(37)*. Therefore, both the individual and public health threats posed by untreated *P. vivax* relapses and the risk of acute haemolytic anaemia need to be considered when discussing the risks and benefits of PQ anti-relapse therapy.

After a new point-of-care qualitative G6PD test was introduced to the market, WHO convened an ERG to assess the performance of the testing devices appropriate for use in resource-limited settings *(38)*. On this basis, WHO developed recommendations on G6PD testing to facilitate guidance and practical advice for NMCPs to ensure safe administration of PQ for preventing *P. vivax* relapses *(37)*. Currently, a 14-day course of PQ at 0.25–0.5 mg base/kg body weight is recommended daily in all transmission settings to treat *P. vivax* in children and adults known not to be G6PD deficient *(37)*. (Shorter regimens are not currently recommended due to low quality of evidence.) In people with known G6PD deficiency, WHO recommends a weekly dose of 0.75 mg base/kg body weight for eight weeks under close medical supervision. In cases where the G6PD status of the patient is unknown and testing is not available, the decision to prescribe the drug must be based on the assessment of the risks and benefits of adding PQ. Factors such as the relapse rate, the *P. vivax* incidence rate, the G6PD deficiency prevalence variants in the region, or the capacity of the health system to closely monitor potential adverse events should be considered in this context *(37)*.

Key conclusions about the role of MPPT in accelerating *P. vivax* elimination:

- In temperate areas, MPPT, especially in combination with vector control and other preventive measures, has resulted in rapid containment of *P. vivax* epidemics and may have contributed to the interruption of local transmission in low transmission settings.
- Health systems with properly functioning services capable of ensuring directly observed therapy and close monitoring of side-effects are needed for the success of MPPT campaigns.
- There are no data on the implementation of MPPT in tropical and subtropical areas.
- Further research is needed for large-scale chemoprevention of *P. vivax* with anti-hypnozoite drugs in the population that is not eligible for 8-aminoquinolines because of G6PD deficiency.

5. Highlighted knowledge gaps

The participants agreed that, after examining the available evidence, there are still many challenges and knowledge gaps regarding MDA that need to be addressed.

The evidence reviewed showed that islands were the only areas at the lower end of the moderate transmission spectrum (parasite prevalence 10–15%) that sustained the short-term impact of MDA. Additionally, the sustainability of transmission reductions was variable in low transmission settings. Further research is needed to assess how the effectiveness of MDA in accelerating elimination may be affected by parasite importation rates, especially in areas of low transmission intensity but high levels of population movement. In order to study this, new approaches to measuring parasite importation and population movements may be needed, including molecular epidemiological methods.

Additional research is also needed to understand the impact of low-density asymptomatic infections on malaria transmission depending on population-level immunity.

The current review showed that MDA campaigns deployed more recently have produced a longer lasting impact on transmission compared to MDA campaigns conducted in the past, most likely due to the concomitant interventions deployed with the MDA. Therefore, more attention needs to be paid to the other interventions deployed before and after the MDA. More research is needed to understand which interventions combined with MDA can achieve the highest impact and which activities are needed to sustain the effect over a longer period of time in each scenario.

It still needs to be clearly determined the number of MDA rounds and number of years for which these should be implemented in order to achieve levels of transmission low enough to enable implementation of reactive strategies, as well as the level of transmission at which MDA campaigns should stop and be replaced with investigation and clearing of individual cases, management of foci and follow-up.

Additional areas requiring further research include the optimal timing of MDA rounds and the level of coverage that could be defined as “high”, and how best to measure coverage. Another question that still needs to be addressed is how best to maximize adherence to drug regimens.

With the available evidence, it is difficult to separate the synergistic effects on malaria transmission resulting from different interventions deployed at the same time as the MDA, for example, access to treatment, improved vector control and intensified surveillance. Modelling could help to shed light on the relative impact of different interventions, identify the best mix of interventions in different epidemiological scenarios and inform the decision-making process.

Concerns about the safety of ACTs in the early stages of pregnancy were also raised. Even though most field trials have excluded pregnant women in the first trimester, the large-scale deployment of MDA will unintentionally expose women in the early stage of pregnancy to these medicines. The need for more safety data was highlighted. This will require intensified pharmacovigilance and follow-up of pregnant women in the post-MDA period in order to monitor the effect of inadvertent exposure to ACTs in the first trimester.

Given the results of the studies applying MDA to selected high-prevalence villages, more research is needed to define the minimum population size for MDA implementation, considering local transmission dynamics. These studies will inform the best deployment strategies for focal MDA, including the need for synergistic interventions to sustain impact and accelerate elimination.

One of the major research gaps identified was the lack of evidence regarding the impact of MDA on *P. vivax* in tropical areas, which could be addressed through pilot studies, field trials and modelling. The need for more research to expand the safe use of PQ, and also potentially tafenoquine, as part of chemoprevention strategies taking into consideration G6PD deficiency testing was also emphasized. Additionally, research efforts should address whether MDA deployed over multiple years in non-island settings of moderate to high transmission could help to reduce transmission over the long term.

Given that the sustainability of an intervention depends on its comparative cost and effectiveness, more research is needed on the cost-effectiveness of MDA in combination with other interventions. Research should also include analyses of social acceptability and programmatic suitability, as well as the economic costs of updating NMCPs' policies and mobilizing health workers to facilitate deployment of the intervention. Research on community engagement methods would also be needed, as well as studies to ascertain the extent to which MDA also promotes higher treatment-seeking rates and training of community health workers who can provide other health services such as case management.

6. Conclusions and recommendations

General considerations

MDA can play an important role in malaria control and elimination. Regardless of whether the final aim of the strategy is the reduction of morbidity and mortality or reduction of transmission, there are some fundamentals that should always be applied *(5)*:

- High levels of coverage of the eligible population should be achieved to ensure maximum impact.
- MDA should be deployed as a component of a package, in combination with other strategies such as vector control, case management and intensified surveillance.
- Effective pharmacovigilance procedures should be implemented to ensure that the antimalarial medications deployed are safe.
- The community should be engaged at the local, district and national levels to improve acceptance and adherence.
- Post-MDA activities, in particular intensified surveillance and improved access to case management, should be in place to help sustain the gains achieved.

Proposed recommendations

Based on the review of the new evidence generated since 2015, the ERG proposed to update the current WHO recommendations as follows.[9]

Recommendation 1:
Use of MDA to accelerate progress towards elimination (i.e., significant reductions in malaria transmission sustained over time) of *P. falciparum* malaria can be considered in areas of very low to low transmission (parasite prevalence <10%) where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. Additionally, MDA can be considered in small islands (<500 000 population) with moderate transmission (*P. falciparum* parasite prevalence 10–15%) where there is limited risk of re-introduction of parasites, effective treatment, and effective implementation of vector control and surveillance.

There is no evidence that MDA, even in conjunction with other interventions, can interrupt transmission, yet MDA has been shown to rapidly decrease *P. falciparum* prevalence and incidence when deployed in combination with good access to malaria case management, vector control and intensified surveillance. In low transmission areas, several studies have demonstrated sustained reductions after completion of the MDA campaigns. Several factors contributed to sustaining the decreased transmission levels after the MDA campaign, including improved access to malaria case management, optimized vector control, and intensified surveillance and response. Similar factors contributed to sustaining decreased transmission levels in island settings, but it is likely that reduced parasite importation contributed importantly to maintaining the impact of MDA over several years in those settings.

Recommendation 2:
In areas with moderate to high transmission, MDA may produce a short-term reduction in malaria burden, but so far there is no evidence that MDA, with or without additional interventions, will accelerate progress towards elimination. More evidence should be gathered to determine whether repeated rounds of MDA over multiple years in conjunction with other interventions in these settings could sustain reduced transmission and accelerate progress towards elimination.

There is clear evidence that MDA, in combination with enhanced case management, effective vector control and intensified surveillance, reduces *P. falciparum* malaria health outcomes in the first three months post-MDA in moderate transmission settings, but the results from high transmission areas are inconclusive. However, reports from areas of moderate transmission have shown that no areas have managed to sustain those reductions post-MDA, except for island settings. There was interest in the potential impact of multi-year programmes, combining MDA with other post-interventions to sustain post-MDA reductions in moderate, non-island transmission settings.

Recommendation 3:
Mass primaquine prophylactic treatment, requiring pre-seasonal MDA with daily administration of primaquine for two weeks can be considered as a component of *P. vivax* elimination strategies in temperate regions taking into consideration G6PD deficiency. More evidence should be gathered on the use of MDA with anti-hypnozoite medicines to reduce *P. vivax* transmission in tropical and subtropical areas.

[9] Modified from the previous recommendation. New recommendation.

Based on the evidence presented, a significant impact on *P. vivax* transmission has been observed following deployment of mass PQ prophylactic treatment in combination with vector control interventions in temperate regions. Nevertheless, the need for directly observed therapy and close monitoring of acute haemolytic anaemia in people with G6PD deficiency should always be taken into consideration. Two studies noted only a short-term impact of MDA on *P. vivax* in the GMS. There is a pressing need to investigate the potential role of MDA as a component of elimination programmes in tropical and subtropical settings where *P. vivax* relapses are common.

Recommendation 4:
Given the threat of *P. falciparum* multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA should be considered as a component of accelerated malaria elimination efforts in the GMS where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. However, because of prevalent multidrug resistance in the region, the options are limited for effective antimalarials that can be used in MDA.

Given the declared urgent need to eliminate malaria in the GMS due to the high levels of antimalarial drug resistance, MDA should be considered as a component of malaria elimination strategies, always with close monitoring of drug safety and resistance. Currently, in some parts of the GMS, a limited number of antimalarial medications remain effective and can be used in MDA campaigns.

Recommendation 5:
Use of time-limited MDA to rapidly reduce malaria morbidity and mortality may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions.

Not reviewed as part of this ERG

Recommendation 6:
Use of time-limited MDA to reduce malaria morbidity and mortality may be considered in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.

Not reviewed as part of this ERG

Recommendation 7:
Medicines used for MDA must be of proven efficacy in the implementation area and preferably have a long half-life. WHO recommends that a medicine different from that used for first-line treatment be used for MDA. Programmes should include drug safety monitoring during MDA campaigns. Drug efficacy should be monitored after the campaign to identify potential emergence of resistance to the antimalarial medicines deployed for MDA.

The ERG members raised their concerns about the safety of MDA, particularly in the first trimester of pregnancy, and the potential emergence of drug resistance, recognizing the need to continue monitoring drug safety and efficacy in MDA deployment areas.

Recommendation 8:
WHO supports the need for more research on the optimum methods for implementing MDA programmes, promoting community engagement and compliance with treatment, and evaluating the effectiveness of MDA programmes. Modelling can help guide the optimum method for administering MDA in different epidemiological circumstances and predict its likely impact.

The need for further guidance on research requirements and study designs (i.e., standardization of outcomes and diagnostics used) to generate evidence in a way that would inform policy-making at global and country levels was also highlighted.

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Annexes

8. Annex 1. List of pre-reads

1.	*Mass drug administration for malaria*		Shah, unpublished report
2.	*Large-scale artemisinin-piperaquine mass drug administration with or without primaquine dramatically reduces malaria in a highly endemic region of Africa*	*(16)*	
3.	*Combined impact of mass drug administration and long-lasting insecticidal nets on malaria in Ngazidja (Grand Comore), Union of the Comoros*		Bacar, unpublished report
4.	*a) Impact of 4 rounds of mass drug administration with dihydroartemisinin-piperaquine implemented in Southern Province Zambia* *b) Summary of long-term follow-up of malaria outcomes 15-months after conclusion of a mass drug administration trial in Southern Province Zambia*		Eisele, unpublished report
5.	*MDA expansion in the context of acceleration of malaria elimination in Zambia*		Busiku, unpublished report
6.	*The Magude Project: impact of a malaria elimination demonstration project in Southern Mozambique*		Galatas, unpublished report
7.	*a) Effectiveness of reactive case detection for malaria elimination in three archetypical transmission settings: a modelling study* *b) Does MDA accelerate elimination timelines in southern Zambia?*	*(39)*	Gerardin, unpublished report
8.	*a) Role of mass drug administration in elimination of Plasmodium falciparum malaria: a consensus modelling study* *b) Resurgence of malaria infection after mass treatment: a simulation study*	*(26)*	Smith, unpublished report
9.	*Modelling the impact of malaria mass drug administration on the development of drug resistance*		Nguyen, unpublished report
10.	*The impact of targeted malaria elimination with drug administrations on falciparum malaria in South-East Asia: a cluster randomized trial*		von Seidlein, unpublished report
11.	*Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on Plasmodium falciparum malaria in Eastern Myanmar: an observational study of a regional elimination programme*	*(18)*	

12.	*Mass drug administration trial in Myanmar – Summary*		McLean, unpublished report
13.	*Defining effective, appropriate, implementable strategies for malaria elimination in military forces in Cambodia: a cluster-randomized controlled clinical trial comparing focused mass drug administration with focused screening and treatment*		Wojnarski, unpublished report
14.	*a) Synergy and timing: a concurrent mass medical campaign predicted to augment indoor residual spraying for malaria*		Elliott, unpublished report
	b) Impact of population based indoor residual spraying in combination with mass drug administration on key malaria indicators in a high transmission setting in North Eastern Uganda		Echodu, unpublished report
15.	*Mass drug administration with dihydroartemisinin-piperaquine and malaria transmission dynamics in The Gambia – a prospective cohort study*	*(17)*	
16.	*Mass primaquine treatment to eliminate vivax malaria: lessons from the past*	*(31)*	
17.	*Testing for G6PD deficiency for safe use of primaquine in radical cure of P. vivax and P. ovale malaria: policy brief*	*(37)*	
18.	*Mass drug administration for malaria: research landscape*		MESA, unpublished report

Annex 2. List of participants

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Annex 3. Proposed questions for the ERG on MDA

Overall statement**: There are multiple use-case scenarios for MDA. This review focuses on the impact of MDA on decreasing transmission and accelerating progress towards elimination. This meeting did not address issues of cost or cost-effectiveness, which may be important considerations for some use-case scenarios.**

In relation to the first objective of the meeting:
To determine the effectiveness of MDA combined with other core interventions in reducing *falciparum* or *vivax* malaria incidence and prevalence in areas of moderate to high transmission, with particular attention to the effects of vector control, case management and intensified surveillance on the effectiveness of MDA, and the length of time over which reduction in malaria transmission is sustained post-MDA.

a. In areas of moderate transmission to high transmission[1], does MDA with antimalarial medicines reduce malaria incidence and/or prevalence in the first three months post-intervention compared to no MDA intervention?

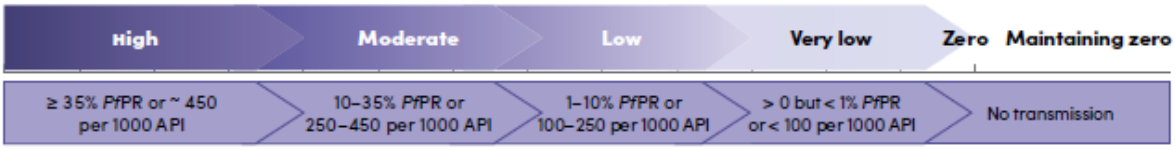
   i. Is there compelling evidence that MDA reduces incidence or prevalence of *P. falciparum* and/or *P. vivax* in the first three months following the last round (e.g., based on comparison to an appropriate contemporaneous control group without MDA, or an interrupted time series analysis with sufficient time points before and after MDA rounds)?

   - **There is no clear evidence that MDA reduces incidence and prevalence of *P. falciparum* in the first three months after MDA in moderate to high transmission settings (*Eisele, unpublished report; Echodu, unpublished report)*.**

   - **No evidence has been presented on the impact of MDA on *P. vivax* in moderate to high transmission settings. Given that incidence and prevalence are generally lower for *P. vivax* than for *P. falciparum,* the number of areas of moderate to high *P. vivax* transmission is limited.**

   ii. What factors were associated with failure or success of MDA in reducing incidence or prevalence of malaria, including coverage achieved during MDA rounds, type of antimalarial medicines used (i.e., short vs. long-acting, two- vs. three-day dosage), addition of primaquine as gametocytocide or anti-relapse therapy, additional interventions implemented during the same period (including case management, vector control, reactive case detection and focal response) and estimated level of parasite importation?

[1] Indicative categories of transmission intensity (from Framework for malaria elimination. Geneva; World Health Organization; 2017)



- **The following factors are associated with the success of MDA in reducing incidence and prevalence:**
    - **The MDA coverage:**
        - **High overall population coverage (>80%) is needed. If the proportion of the population that is not eligible is very high (~15–20%), or if there are substantial subpopulations repeatedly missed by MDA rounds, the impact of MDA will be compromised.**
        - **According to consensus modelling results, the proportion of the population treated in a year is a key determinant of simulated effectiveness, irrespective of whether people are treated through high coverage of a single round or new individuals are reached by implementation of several rounds *(Brady et al., 2017 (26))*.**
    - **The number of rounds:**
        - **There is empirical evidence that multiple rounds per year achieve higher impact than yearly single-round MDA if the additional rounds mean that more people are reached for treatment *(Eisele, unpublished report; Mwesigwa et al., 2018 (17); Brady et al., 2017 (26))*.**
- **There is limited evidence comparing different antimalarial medicines used in MDA and no clear evidence of the advantage of adding a single low dose of primaquine.**
- **There is no clear empirical evidence that the timing of MDA rounds with respect to malaria transmission seasons affects impact, although modelling suggests a greater impact if MDA is done in the dry season or at the end of the rainy season compared to at the beginning of the rainy season (*Brady et al., 2017 (26)*).**

iii. Is the reduction in incidence or prevalence attributed to MDA sufficiently large that the programme could begin intensified surveillance[2] and focal response for malaria elimination? That is, can MDA in this circumstance be considered as an accelerator for malaria elimination?

- **In settings with transmission at the higher end of moderate (>15% parasite prevalence), there is no clear evidence that one to two years of MDA acts as an accelerator towards malaria elimination (i.e., reducing transmission to the level where intensive surveillance and focal response can prevent onward transmission from remaining cases), alone or in combination with other interventions.**
- **In settings with transmission at the lower end of moderate (<15% prevalence), there is some evidence that high coverage of MDA in combination with vector control and case management can reduce transmission to low levels manageable with intensive surveillance and focal response (*Deng et al., 2018 (16); Affane, unpublished report).***
- **In areas of moderate to high transmission, there is a need for more research to determine whether repeated years of MDA could reduce transmission sufficiently to have a sustained impact. This concept is analogous to repeated annual rounds of IRS.**

[2] While the point at which intensified surveillance for elimination can begin depends on caseload and health system capacity, most countries should be able to begin reactive case detection and investigations when cases are few (for example, no more than three malaria cases per week per investigation team). From Malaria surveillance, monitoring and evaluation: a reference manual. Geneva: World Health Organization; 2018 (https://www.who.int/malaria/publications/atoz/9789241565578/en/).

The incremental cost-effectiveness of a multi-year MDA strategy in the context of a package of interventions (i.e., vector control, case management, etc.) should be compared to that of other interventions.

b. In areas of moderate to high transmission where MDA successfully reduced incidence or prevalence in the first three months, was there an increase, decrease or no change in incidence over the following nine months?

   i. Is there compelling evidence that the impact of MDA on reducing the incidence or prevalence of *falciparum* and/or *vivax* malaria can be maintained for up to one year following the last round (e.g., based on comparison to an appropriate contemporaneous control group without MDA, or an interrupted time series analysis with sufficient time points before and after MDA rounds)?

   - **While there is clear evidence that MDA reduces the incidence of *P. falciparum* in the first three months after MDA in areas of moderate to high transmission, there is no compelling evidence of a sustained impact and transmission generally returns to baseline levels rapidly.**

   - **However, in island settings (Comoros) with transmission at the lower end of moderate intensity (i.e., up to 15% prevalence), high coverage of MDA in combination with vector control and case management, and subsequently followed by intensified surveillance, was associated with a large and sustained decrease in malaria prevalence and incidence *(Deng et al., 2018 (16); Affane, unpublished report)*.**

   ii. What factors were associated with failure or success of maintaining reductions in incidence or prevalence of malaria for one year following the last round of MDA, with respect to additional interventions implemented during that period, including vector control intervention, intensified surveillance and focal response, and estimated level of parasite importation?

   - **The factors associated with success in achieving and maintaining a one-year reduction in malaria incidence or prevalence were:**

     - **baseline parasite prevalence in children of up to 15%;**
     - **implementation of intensified surveillance and malaria case management at the community level;**
     - **effective and enhanced vector control with LLINs and/or IRS.**

   Although the level of importation was not well characterized in most studies, limited movement of people in island communities may also have contributed to the sustained low levels of malaria transmission post-MDA in those settings.

c. In areas of moderate to high transmission where MDA successfully reduced incidence or prevalence in at least the first three months, was there evidence that MDA provided selective pressure for emergence of drug resistance, particularly for *P. falciparum*? Does antimalarial MDA increase or decrease the risk of resistance, compared to deployment of the medicine as first-line treatment, considering the reduction in transmission and incidence of clinical cases that follows the MDA intervention?

   - **No new evidence was presented for or against selective pressure for emergence of drug resistance.**

- **Early results from modelling studies indicate that the risk that MDA selects for an increased frequency of resistant strains varies according to the importation of these strains into the MDA area, as well as access to antimalarial medicines that were not used for the MDA regimen in the immediate post-MDA period (*Nguyen, unpublished report)*.**

In relation to the second objective of the meeting:
To review new evidence on the impact of MDA in areas of low to very low transmission in relation to current WHO recommendations on MDA for interrupting *falciparum* malaria transmission in areas approaching elimination.

d. In areas of low to very low transmission has malaria transmission been interrupted following MDA with antimalarial medicines, compared to no MDA intervention?

   i. Is there compelling evidence that MDA interrupts *falciparum* and/or *vivax* malaria transmission in areas with low to very low transmission (e.g., based on comparison to an appropriate contemporaneous control group without MDA, or an interrupted time series analysis with sufficient time points before and after MDA rounds)?

   - **In areas of low transmission, there was no evidence that MDA, even in conjunction with vector control and good case management, can interrupt transmission. However, MDA contributed to decreasing *P. falciparum* transmission to very low levels when deployed in combination with good access to malaria case management, vector control and intensified surveillance, thus accelerating progress towards elimination. This effect was seen particularly in island settings.**

   - **No evidence was presented on the impact of MDA in areas of very low (prevalence <1%) transmission.**

   - **A significant impact on *P. vivax* transmission (lower transmission potential maintained up to six months) has been observed in temperate areas following deployment of primaquine mass prophylactic treatment in combination with other malaria control interventions *(Kondrashin et al., 2014 (31))*.**

e. In areas of low to very low transmission, where *falciparum* and/or *vivax* malaria transmission has been interrupted for up to one year following MDA with ACTs (+/- primaquine), which epidemiological factors and malaria interventions have contributed to maintaining the area malaria-free during this time period?

   - **While there was no evidence of interruption of transmission following MDA in low transmission areas, factors contributing to the maintenance of very low transmission levels achieved with MDA are:**

     - **island settings;**

     - **improved access to malaria case management by increasing the number of community health workers *(Landier et al., 2018 (18); Eisele, unpublished report; McLean, unpublished report)* and thereby decreasing the distance to a malaria treatment provider *(Eisele, unpublished report)*;**

     - **optimized vector control along with the MDA;**

     - **intensified surveillance and response.**

- **According to modelling, in transmission settings with >5% prevalence, infection importation rates represent a very small proportion of the total infections and, therefore, seem to have little effect on the impact of MDA. Nevertheless, with lower prevalence rates, imported cases represent a critical factor that increases transmission (*Brady et al., 2017 (26)*).**

f. For areas of low to very low transmission where interruption of *falciparum* and/or *vivax* malaria transmission has been maintained up to one year post-MDA, what was the coverage of MDA, LLINs and/or IRS, access to treatment and intensified surveillance implemented in the same areas?

- **While there was no evidence of interruption of transmission following MDA in low transmission areas, high coverage levels of MDA, LLINs and/or IRS, together with good access to treatment and intensified surveillance, were implemented in the areas where transmission was maintained at very low levels following MDA.**

g. In areas of very low transmission, is there a level of malaria incidence or prevalence below which antimalarial mass drug administration is no longer considered an appropriate intervention in terms of cost-effectiveness or risk of drug-induced adverse events?

- **No reports on the use of MDA in very low transmission settings were available for review.**

- **In very low transmission settings, the decision to initiate MDA in combination with other interventions should be based on the balance between the risks and benefits of treating the whole eligible population, very few of whom will be at risk of malaria, compared to the cases averted, and the cost-effectiveness of reducing malaria with ongoing interventions.**

Annex 4. Summary of the studies presented

Table 4. Summary of the studies presented

Level of transmission	Country	Parasitaemia pre-MDA (RDT)	Drug used	Number of rounds	Coverage1	Effect seen	Reference
High	Uganda	35% (*Pf*)	DP	4	77%	Decline, seven months sustained (follow-up ongoing)	*Echodu, unpublished*
	Zambia	50.6% (*Pf*)	DP	4	71%[2]	No impact of four rounds of MDA on parasite prevalence in children in the short term	*Eisele, unpublished*
Moderate	Comoros (Anjouan Island)	13.5% (*Pf*)	AP AP + PQ[3]	3	90% (AP) 89% (AP + PQ)	Decline, sustained	*(16)*
	Comoros (Grande Comore)	10.6% (*Pf*)	AP + PQ	2	82% (round 1)[4]	Decline, three years sustained	*Bacar, unpublished*
Low	Mozambique	9.1% (*Pf*)	DP	4	65%	Decline, sustained with concomitant interventions	*Galatas, unpublished*
	Zambia	7.7% (*Pf*)	DP	4	71%	No significant difference between MDA arms and control arms at later time points	*Eisele, unpublished*
	Gambia	<5% (*Pf*)	DP	2	70%	Decline, sustained through the transmission season	*(17)*
	• Myanmar • Viet Nam • Cambodia • Lao PDR	4.1% (*Pf*)	DP + PQ	3	57% completed 3 rounds 14% completed 2 rounds 14% completed 1 round	Decline, with incidence increasing over time, but without returning to baseline levels	*von Seidlein, unpublished*
	Myanmar	5.5% (*Pf*)	DP + PQ	3	60% completed 3 rounds 16% completed 2 rounds 13% completed 1 round	Decline, 20 months sustained (follow-up ongoing)	(18–20)
	Myanmar	2.7% (*Pf/Pv*)	DP + PQ	3	63% completed 3 rounds 16% completed 2 rounds 12% completed 1 round	Decline, three months significantly sustained	*McLean, unpublished*
	Cambodia	10% (*Pf*)	DP + PQ	3	90%	Decline, six months sustained	*Wojnarski, unpublished*

Note: DP: dihydroartemisinin + piperaquine; AP: artemisinin + piperaquine; PQ: primaquine

[1] Average coverage or coverage reporting for consecutive rounds
[2] Overall coverage for high and low transmission households
[3] AP was administered to half of the communities, and the other half received AP + PQ.
[4] Coverage during the second round was not measured.

Evidence Review Group on Mass Drug Administration for Malaria

Dr A. Bosman

Malaria Policy Advisory Committee (MPAC) Meeting

10 – 12 April 2019, Salle A, World Health Organization, Geneva, Switzerland

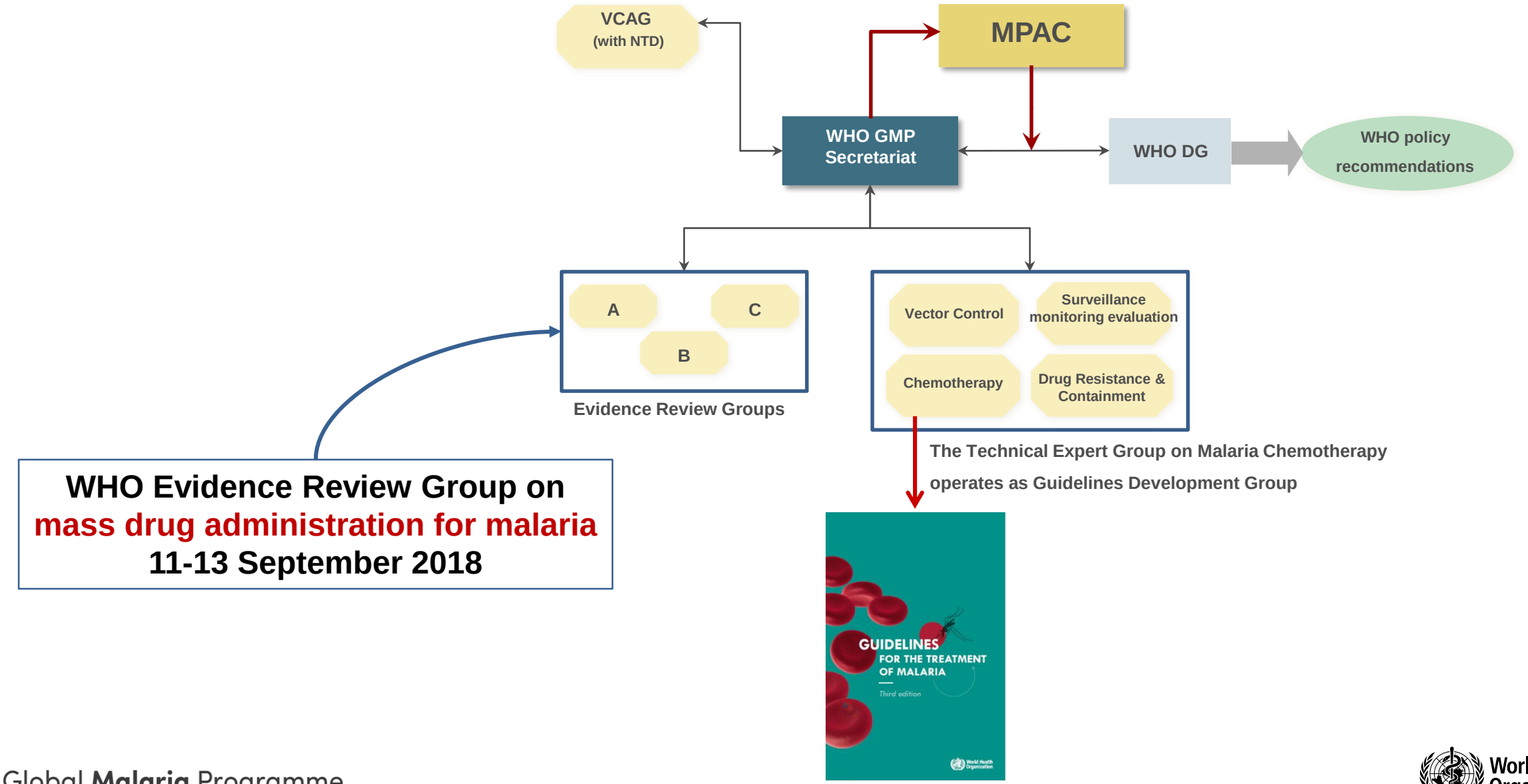
Global **Malaria** Programme

World Health Organization

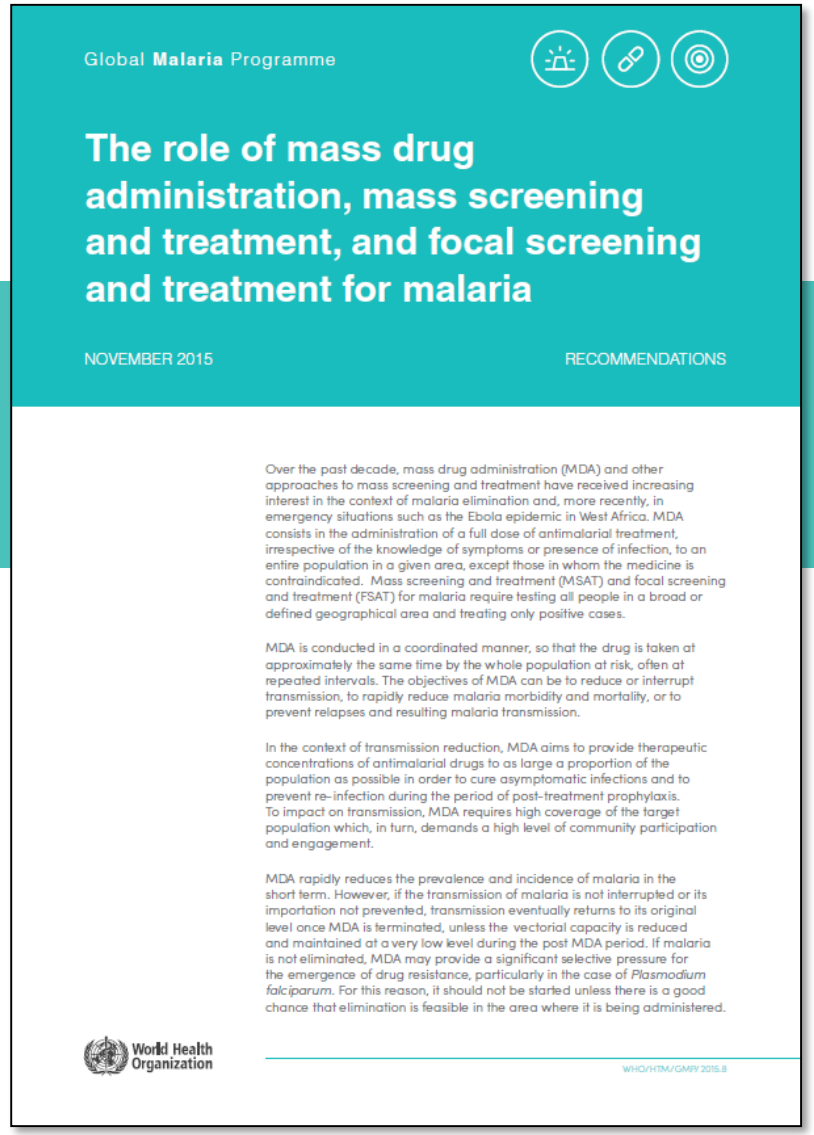
Outline of the presentation

- Rationale for evidence review on ERG
- Objectives of the ERG
- Evidence reviewed and main findings
- Proposed new recommendations on MDA
- Highlighted knowledge gaps
- Discussion

Current WHO policy making process for malaria



WHO Evidence Review Group on
mass drug administration for malaria
11-13 September 2018



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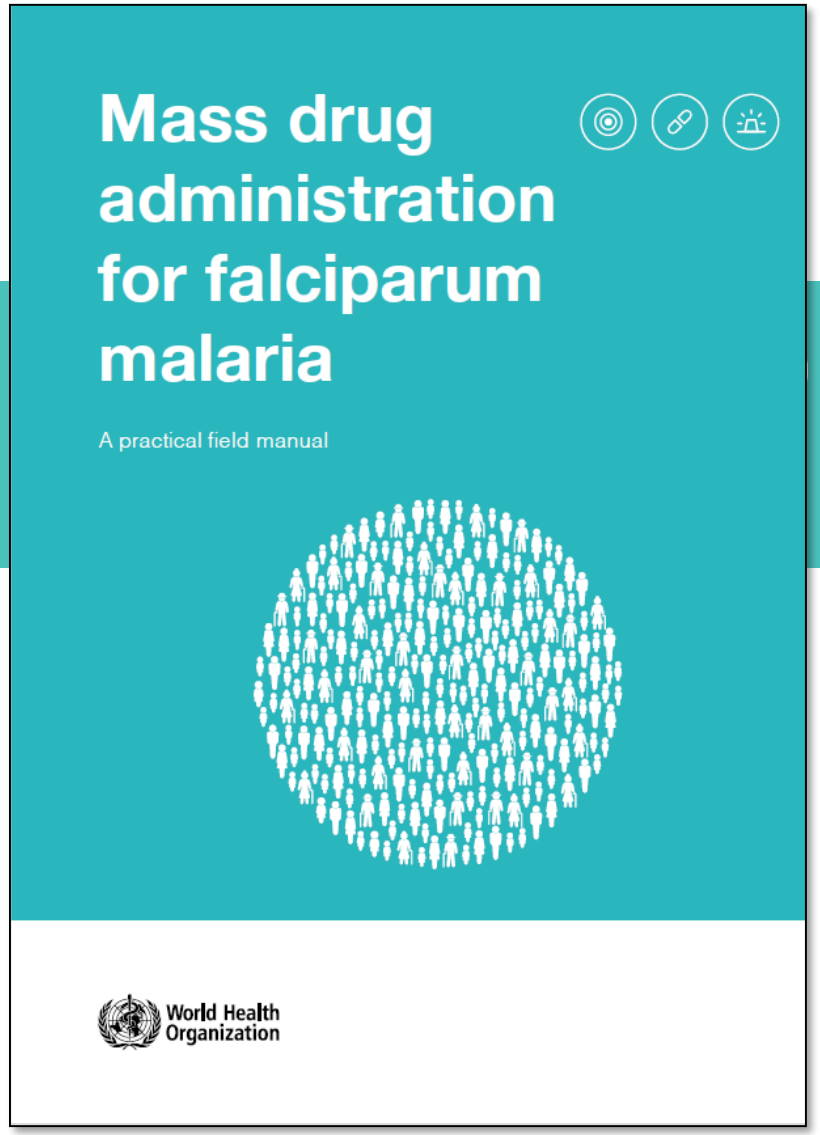
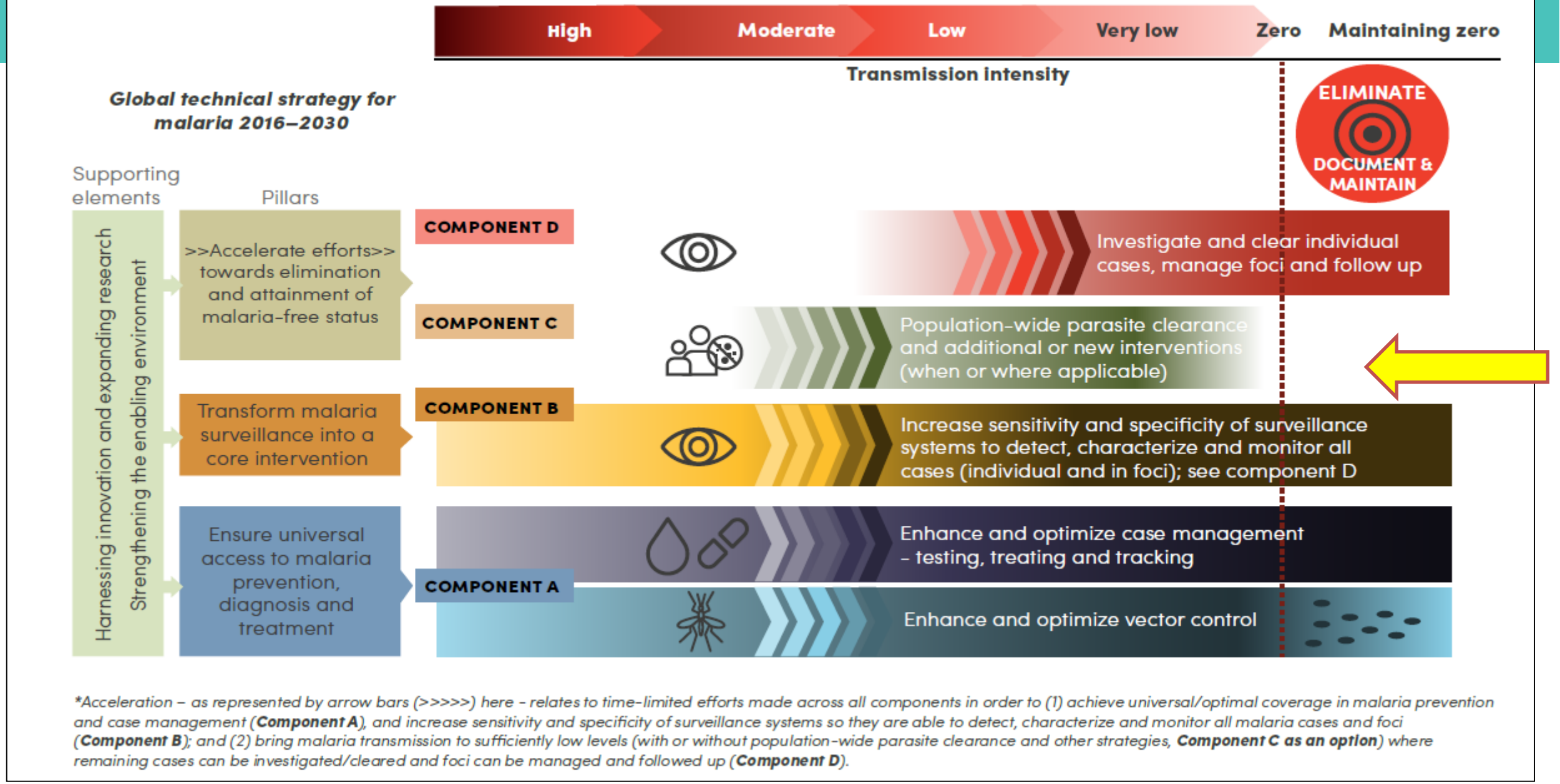


http://apps.who.int/iris/bitstream/10665/259367/1/9789241513104-eng.pdf?ua=1



Acceleration – as represented by arrow bars (>>>>>) here - relates to time-limited efforts made across all components in order to (1) achieve universal/optimal coverage in malaria prevention and case management (Component A**), and increase sensitivity and specificity of surveillance systems so they are able to detect, characterize and monitor all malaria cases and foci (**Component B**); and (2) bring malaria transmission to sufficiently low levels (with or without population-wide parasite clearance and other strategies, **Component C as an option**) where remaining cases can be investigated/cleared and foci can be managed and followed up (**Component D**).*

A framework for malaria elimination, WHO Geneva, 2017

Rationale for ERG on MDA for malaria

- Since the last WHO evidence review on MDA in April 2015, several large-scale trials have been implemented to evaluate the role of MDA combined with other core interventions in accelerating progress towards malaria elimination in areas of moderate transmission. In particular, MDA with artemisinin+piperaquine has been implemented in the Comoros Islands in combination with LLINs, with DHA+piperaquine together with IRS (pirimiphos-methyl) in the Magude Province of Mozambique and with DHA+piperaquine in combination with LLINs in the Southern Province of Zambia. In Mozambique and Zambia, interventions were implemented over two years and results made available to WHO for review.
- The Cochrane systematic review [4] on MDA for malaria based on 32 studies and published in 2013, was updated with additional 9 studies included and analysis, still unpublished was shared with WHO for the ERG meeting. In addition, modelling work on the impact of MDA on malaria elimination and drug resistance was presented at the meeting.

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

Objectives of the ERG

1. To determine the effectiveness of MDA combined with other core interventions in reducing malaria incidence and prevalence of *P. falciparum* and *P. vivax* in areas of low, moderate and high transmission, with particular attention to the effects of vector control, case management and intensified surveillance on the effectiveness of MDA, and the determinants of sustained post-MDA reduction in malaria transmission.

2. To review new evidence on the impact of MDA in areas of low to very low transmission in relation to current WHO recommendations on MDA for interrupting the transmission of falciparum malaria in areas approaching elimination and reducing the spread of multi-drug resistance in the Greater Mekong subregion.

Preparations and process for the WHO ERG

- WHO Secretariat of Prevention, Diagnostics and Treatment (PDT) and Elimination (ELI) Units jointly planned the meeting.
- The Chairperson was Professor B. Greenwood and the Rapporteur was Ms M. Tusell. Nine independent experts in malaria epidemiology, elimination and chemotherapy, and methodology specialists in the assessment of data from applied field research were convened, together with 18 participants representing national malaria control programmes (NMCPs) and collaborating technical research institutions, who were invited to present recent results from MDA field studies, MDA campaigns, systematic reviews and modelling studies. Six observers representing academia, philanthropic foundations and funding agencies, together with seven members of the WHO Secretariat, completed the list of participants
- A total of 18 pre-reads prepared by the presenters, including 7 scientific publications, were shared with all the participants prior to the meeting.

Summary of studies reviewed by ERG

Level of transmission	Country	Parasitaemia pre-MDA (RDT)	Drug used	Number of rounds	Coverage[1]	Effect seen	Reference
High	Uganda	35% (*Pf*)	DP	4	77%	Decline, seven months sustained (follow-up ongoing)	*Echodu, unpublished*
	Zambia	50.6% (*Pf*)	DP	4	71%[2]	No impact of four rounds of MDA on parasite prevalence in children in the short term	*Eisele, unpublished*
Moderate	Comoros (Anjouan Island)	13.5% (*Pf*)	AP AP + PQ[3]	3	90% (AP) 89% (AP + PQ)	Decline, sustained	*(16)*
	Comoros (Grande Comore)	10.6% (*Pf*)	AP + PQ	2	82% (round 1)[4]	Decline, three years sustained	*Bacar, unpublished*
Low	Mozambique	9.1% (*Pf*)	DP	4	65%	Decline, sustained with concomitant interventions	*Galatas, unpublished*
	Zambia	7.7% (*Pf*)	DP	4	71%	No significant difference between MDA arms and control arms at later time points	*Eisele, unpublished*
	Gambia	<5% (*Pf*)	DP	2	70%	Decline, sustained through the transmission season	*(17)*
	• Myanmar • Viet Nam • Cambodia • Lao PDR	4.1% (*Pf*)	DP + PQ	3	57% completed 3 rounds 14% completed 2 rounds 14% completed 1 round	Decline, with incidence increasing over time, but without returning to baseline levels	*von Seidlein, unpublished*
	Myanmar	5.5% (*Pf*)	DP + PQ	3	60% completed 3 rounds 16% completed 2 rounds 13% completed 1 round	Decline, 20 months sustained (follow-up ongoing)	(18–20)
	Myanmar	2.7% (*Pf/Pv*)	DP + PQ	3	63% completed 3 rounds 16% completed 2 rounds 12% completed 1 round	Decline, three months significantly sustained	*McLean, unpublished*
	Cambodia	10% (*Pf*)	DP + PQ	3	90%	Decline, six months sustained	*Wojnarski, unpublished*

Note: DP: dihydroartemisinin + piperaquine; AP: artemisinin + piperaquine; PQ: primaquine

Conclusions of ERG on MDA for malaria - 1

Across all transmission settings:

- MDA may rapidly reduce, but not interrupt, malaria transmission in the short term (1–3 months after the last round) when implemented with vector control and case management.
- Two factors strongly associated with the success of MDA in reducing malaria transmission in the short term are high coverage of the population with MDA (a large proportion of the population receiving at least one round of MDA), which may be achieved with more than one consecutive round per year, and focusing a second round on those missed in the first round.
- The decision to initiate an MDA campaign to accelerate elimination should be based on the balance between risks of treating the whole eligible population, very few of whom (in a low transmission setting) may be at risk of malaria, and potential benefits from cases averted. The decision to use MDA to rapidly reduce transmission should also consider whether MDA is cost-effective compared to other interventions.

Studies in moderate to high transmission settings

Level of transmission	Parasite prevalence (RDT)[3]	Country	Study design	Target population[4]	Drug, number of rounds	Vector control interventions
High	51% (<6 years old)	Zambia[5]	Randomized	45 442	DP, four rounds	LLINs, IRS
	35% (all ages)	Uganda	Non-randomized	16 777	DP, four rounds	LLINs, IRS
Moderate	13.5% (6 months to 16 years old)	Comoros Islands, Anjouan	Non-randomized, interrupted time series	321 635	AP+PQ or AP only, three rounds	LLINs
	10.6% (<5 years old)	Comoros Islands, Grande Comore	Non-randomized, interrupted time series	433 348	AP + PQ, two rounds	LLINs

Note: DP: dihydroartemisinin + piperaquine; AP: artemisinin + piperaquine; LLINs: long-lasting insecticidal nets; IRS: indoor residual spraying

Conclusions of ERG on MDA for malaria - 2

In moderate to high transmission settings (parasite prevalence ≥10%):

- There is evidence from both a systematic review and the most recent research studies that MDA reduces the transmission of *P. falciparum* in moderate transmission settings (parasite prevalence 10–35%) in the first three months after the last round of MDA is completed, but the evidence of short term impact is inconclusive from areas of high transmission (parasite prevalence ≥ 35%). Evidence suggests that the short-term impact of MDA programmes in moderate transmission settings has likely been enhanced by the presence of additional interventions, including vector control and case management.
- The evidence reviewed suggested that the reduction in malaria transmission from MDA could be sustained for up to three years in island settings in areas with moderate P. falciparum transmission up to a parasite prevalence of 15% when additional interventions are in place, including vector control, case management and intensified surveillance.

Studies in low to very low transmission settings

Level of transmission	Parasite prevalence (RDT)[6]	Country	Study design	Target population[7]	Drug, rounds	Vector control interventions
Low	7.5% (all ages)	Gambia	Non-randomized	4312 (year 2014) 4189 (year 2015)	DP, two rounds	LLINs, IRS
	9% (all ages)	Mozambique	Non-randomized	52 581 (year 2015) 61 868 (year 2016)	DP, four rounds	LLINs, IRS
	8% (<6 years old)	Zambia[8]	Randomized	37 694	DP, four rounds	LLINs, IRS
	6% (all ages)	Myanmar Viet Nam Cambodia Lao People's Democratic Republic	Randomized	4423	DP + PQ, three rounds	LLINs
	5.5% (all ages)	Myanmar (Eastern Kayin State)	Non-randomized	12 465	DP + PQ, three rounds	LLINs
	2.7% (≥18 years old)	Myanmar (Southern Kayin State)	Randomized	4618	DP + PQ, three rounds	LLINs

No study available from very low transmission areas (parasite prevalence <1%).

Conclusions of ERG on MDA for malaria - 3

In very low to low transmission settings (parasite prevalence <10%):

- There is evidence from recent research studies that MDA reduces transmission of *P. falciparum* in the first three months after completion of the last round of MDA in low transmission settings (parasite prevalence 1–10%). However, there is no evidence that MDA, even in conjunction with vector control and good case management, can interrupt transmission. No evidence was available for review from very low transmission settings (parasite prevalence <1%).
- The impact of MDA on *P. falciparum* was sustained in many low transmission settings for more than 30 months when there were additional interventions were deployed, including vector control, community-based case management and intensified surveillance.

Conclusions of ERG on MDA for malaria - 4

Impact on *P. vivax:*

- Two studies of MDA in the GMS using ACT plus a single, low dose of primaquine reported differing results for P. vivax, with one study demonstrating only a short-term reduction in *vivax* transmission and the other study no effect.
- Historical and recent evidence shows a significant short-term reduction in *P. vivax* transmission, with lower incidence maintained until the following transmission season and up to six months in temperate areas, following the deployment of PQ mass prophylactic treatment for 14-days, in combination with other malaria control interventions.

Impact on antimalarial resistance:

- Early results from modelling studies indicate that the risk of MDA in selecting for resistant strains rises with an increasing rate of importation of resistant strains into the MDA area. Conversely, the risk may decrease with increased access to antimalarial medicines that were not used for the MDA regimen in the immediate post-MDA period.

Proposed new WHO recommendations on MDA (I)

Current recommendation: 1

Use of MDA for the elimination of *P. falciparum* malaria can be considered in areas approaching interruption of transmission where there is good access to treatment, effective implementation of vector control and surveillance, and a minimal risk of re-introduction of infection.

Modified text | New text

Proposed new recommendation: 1

Use of MDA to accelerate progress towards elimination (i.e., significant reductions in malaria transmission sustained over time) of *P. falciparum* malaria can be considered in areas of very low to low transmission (parasite prevalence <10%) where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. Additionally, MDA can be considered in small islands (<500 000 population) with moderate transmission (*P. falciparum* parasite prevalence 10–15%) where there is limited risk of re-introduction of parasites, effective treatment, and effective implementation of vector control and surveillance.

Proposed new WHO recommendations on MDA (II)

Current recommendation: 2

Given the threat of multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA may be considered as a component of accelerated malaria elimination efforts in areas of the GMS with good access to treatment, vector control and surveillance.

Proposed new recommendation: 2

Given the threat of P. falciparum multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA should be considered as a component of accelerated malaria elimination efforts in the GMS where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. However, because of prevalent multidrug resistance in the region, the options are limited for effective antimalarials that can be used in MDA.

Modified text | New text

Proposed new WHO recommendations on MDA (III & IV)

Current recommendation: 3 & 4

Use of time-limited MDA to rapidly reduce malaria morbidity and mortality may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions.

Use of time-limited MDA to reduce malaria morbidity and mortality may be considered in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.

No proposed changes

No evidence was reviewed related to these two recommendations

RECOMMANDATIONS NOT UPDATED

Proposed new WHO recommendations on MDA (V)

Current recommendation: 5

In the absence of sufficient evidence, WHO does not recommend the use of MDA in situations other than for areas approaching elimination, epidemics, and complex emergencies, as specified above (see recommendations 1-4) .

Proposed new recommendation: 5

In areas with moderate to high transmission, MDA may produce a short-term reduction in malaria burden, but so far there is no evidence that MDA, with or without additional interventions, will accelerate progress towards elimination. More evidence should be gathered to determine whether repeated rounds of MDA over multiple years in conjunction with other interventions in these settings could sustain reduced transmission and accelerate progress towards elimination.

Modified text | New text

Proposed new WHO recommendations on MDA

Current recommendation: 6

Mass primaquine prophylactic treatment, requiring pre-seasonal MDA with daily administration of primaquine for two weeks without G6PD testing, is not recommended for the interruption of vivax transmission.

Proposed new recommendation: 6

Mass primaquine prophylactic treatment, requiring pre-seasonal MDA with daily administration of primaquine for two weeks can be considered as a component of P. vivax elimination strategies in temperate regions taking into consideration G6PD deficiency. More evidence should be gathered on the use of MDA with anti-hypnozoite medicines to reduce P. vivax transmission in tropical and subtropical areas.

Modified text | New text

Proposed new WHO recommendations on MDA (VII)

Current recommendation: 7

Medicines used for MDA must be of proven efficacy in the implementation area and preferably have a long half-life. WHO recommends that a medicine different from that used for first line treatment be used for MDA. Programs should include monitoring of efficacy, safety and the potential emergence of resistance to the antimalarial medicines deployed for MDA.

Proposed new recommendation: 7

Medicines used for MDA must be of proven efficacy in the implementation area and preferably have a long half-life. WHO recommends that a medicine different from that used for first-line treatment be used for MDA. Programmes should include drug safety monitoring during MDA campaigns. Drug efficacy should be monitored after the campaign to identify potential emergence of resistance to the antimalarial medicines deployed for MDA.

Modified text | New text

Highlighted knowledge gaps on MDA for malaria

- More research is needed to assess how effectiveness of MDA is affected by:
  - Parasite importation rates, in areas with high levels of population movements
  - Low-density asymptomatic infections
  - Number and timing of MDA rounds and number of years of implementation
- Need to clarify
  - Long-term impact of multi-year implementaion in moderate-high transmission areas
  - Impact and cost-effectiveness of combined interventions – modelling studies may help
  - Economic costs, social acceptability and programmatic suitability
  - Level of transmission at which MDA should stop and be replaced by active case finding and management of foci
  - How best to measure coverage, and promote adherence to treatment
  - Minimum population size for MDA implementation
  - Impact of MDA on *P. vivax* in tropical areas

Discussion

Malaria Policy Advisory Committee Meeting
10–12 April 2019, Geneva, Switzerland
Background document for Session 7

Meeting report of the WHO Evidence Review Group on the assessment of malariogenic potential to inform elimination strategies and plans to prevent re-establishment of malaria

2–4 October 2018, Geneva, Switzerland

Summary

Malariogenic potential is the risk of transmission in a given area; it arises from a combination of receptivity (inherent potential of the vector–human ecosystem to transmit malaria), vulnerability (traditionally used within malaria to refer to the risk of importation of parasites) and infectivity (vector–parasite compatibility). Malariogenic potential is a critical factor in determining strategies to achieve elimination and prevent re-establishment of transmission. The World Health Organization (WHO) recommends that countries approaching elimination or working to prevent re-establishment of malaria stratify their geographical units by malariogenic potential, to help in targeting appropriate interventions; WHO also recommends that this assessment should determine whether vector control can be withdrawn after transmission is interrupted in an area. There is a lack of guidance on methods to measure the components of malariogenic potential and on thresholds relevant for programmatic decisions. Therefore, WHO convened an evidence review group (ERG) to review methods reported in the literature to measure receptivity and vulnerability, and to review evidence for incompatibility between vectors and parasite strains from other regions.

The report of the meeting – with a summary of the evidence presented, draft conclusions and proposed updates to definitions of terms in the WHO glossary – is submitted to the WHO Malaria Policy Advisory Committee (MPAC) for consideration.

Conclusions

- The ERG considered malariogenic potential to be an important concept, and noted the urgent need for a clear definition of the term and of its components, to be informative, consistent and useful.
- Several terms related to malariogenic potential and its components require definitions in *WHO malaria terminology (1)* to be updated to align with current use and understanding. In particular, the ERG suggested that "importation risk" was preferable to the term "vulnerability", because the former is a clear expression of what is being measured and the latter is often used to express "susceptibility" or "risk of harm".
- Several methods exist to assess receptivity but they have not been cross-validated or compared.
- The extent of reduced compatibility of local mosquitoes to parasite strains imported from distant areas should be further investigated, to help inform response strategies to imported cases.

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- Importation risk can be measured in several different ways but these methods have not been cross-validated or compared in a systematic way.
- Development of thresholds for malariogenic potential to inform strategies to prevent re-establishment of transmission will require additional investigation and modelling.

Proposed recommendations

1. Add or update the following terms in the WHO malaria terminology document *(1)*:
    - **[ADD] Malariogenic potential**: Likelihood of local transmission that is the product of receptivity, risk of importation of malaria parasites and infectivity of imported parasites. *Note: The concept of malariogenic potential is most relevant for elimination and prevention of re-establishment when indigenous transmission is mostly or entirely eliminated.*
    - **[UPDATE] Receptivity**: Degree to which an ecosystem in a given area at a given time allows for the transmission of *Plasmodium* spp. from a human through a vector mosquito to another human. *Note: This concept reflects vectorial capacity, susceptibility of the human population to malaria infection, and the strength of the health system, including malaria interventions. Receptivity can be influenced by ecological and climatic factors.*
    - **[MODIFY] Vulnerability**: Likelihood of malaria infection based on living conditions or behavioural risk factors, or likelihood of increased risk of severe morbidity and mortality from malaria infection.
    - **[MODIFY] Importation risk**: Risk or potential influx of parasites via infected individuals or infected *Anopheles* spp. mosquitoes. *Note: "Infected individuals" includes residents infected while visiting endemic areas as well as infected immigrants.*
    - **[ADD] Infectivity**: Ability of a given *Plasmodium* strain to establish an infection in an *Anopheles* mosquito species and undergo development until the mosquito has sporozoites in its salivary glands.
2. Update the WHO *Malaria surveillance, monitoring & evaluation: a reference manual (2)*to:
    a. more clearly articulate the importance for entomological surveillance to identify principal versus secondary vectors, given ongoing and likely temporal and spatial changes in vector distribution and abundance; and
    b. provide more detailed guidance on site selection, and on the frequency and timing of entomological surveillance, to inform assessment of receptivity.
3. Revise other current WHO guidance documents in line with points (1) and (2), to ensure consistency.
4. Give priority to further development of methods for assessing malariogenic potential (receptivity, importation risk and infectivity) to ensure that these are applicable and informative for programmatic use. This includes:
    a. comparison of methods for the three potential measures of receptivity for selected countries, to ascertain comparability within countries, between countries or between neighbouring regions, to inform their use in receptivity assessments;
    b. comparison of entomological parameters, as well as each of their associations with parasitological indicators, to identify key components that should be included in assessment of receptivity;
    c. examination of outbreak data from certified countries, to determine the origin of the imported parasite strains and the number of resultant infections;

d. comparison of existing data on infections identified through border or workplace screening with those identified through passive case detection at clinics, to ascertain whether information from passive case detection provides an accurate picture of importation risk; and

e. examination of examples where countries can generalize data on imported cases for populations in specific regions to other areas with similar population movement or influxes.

5. Identify relevant and feasible methods for measurement of the components of malariogenic potential, interpret these measurements and develop thresholds to guide programmatic decision-making regarding maintenance of vector control and intensified surveillance.

6. Further evaluate the issue of infectivity with respect to the mosquito and parasite factors that may reduce vector competence for different strains of *Plasmodium*, to determine whether there are programmatic implications for these findings. This may require additional review of evidence in future.

Contents

1. Background

Understanding the underlying potential for malaria transmission in a given geographical area provides the foundation for the design of cost-effective intervention programmes to decrease malaria burden, eliminate transmission and prevent re-establishment of malaria. This transmission hazard has been referred to as *malariogenic potential*, with various definitions presented over time. For example, during a World Health Organization (WHO) working group meeting on the topic held in 1978, malariogenic potential was defined as the product of receptivity, vulnerability and infectivity *(3)*, and although no definition of malariogenic potential was provided in the recent *WHO malaria terminology (1)*, several of the individual components as stated above were defined to some extent.

The WHO *Framework for malaria elimination (4)* recommends that transmission intensity, receptivity and vulnerability underpin subnational stratification, to inform the selection of interventions for eliminating malaria transmission. Measurement of receptivity and vulnerability is also critical to prevent the re-establishment of transmission following elimination. The *Guidelines for malaria vector control (5)* indicate that in areas where transmission has been interrupted, the scale-back of vector control should be based on a detailed analysis that includes assessment of receptivity and vulnerability, active disease surveillance, and capacity for case management and vector-control response. However, guidance on how to define, measure and classify receptivity and vulnerability has been scant, leaving countries with no clear recommendations on methods or thresholds.

Vector competence to transmit imported parasites is a component of malariogenic potential that is not frequently considered – yet there is evidence that parasite–vector specificity exists *(6, 7)*. Parasites imported from neighbouring countries are as likely to infect local *Anopheles* spp. mosquitoes as the strains of parasites circulating within the country. However, the increased potential for local compared with distant parasite strains to avoid mosquito immune systems, reproduce sexually and infect a new human host (i.e. vector competence) should be explored.

There has been an increasing demand for WHO guidance on the assessment of malariogenic potential, especially from countries that are working to prevent re-establishment of transmission either at the subnational or national level. Additional evidence and new techniques and approaches are now available to inform the development of such guidance, along with greater accumulated experience in elimination and post-elimination settings. WHO therefore convened an evidence review group (ERG) to meet from 2 to 4 October 2018 in Geneva, Switzerland, to clarify the definition of malariogenic potential and advise on the definition, measurement and classification of its constituent components. It is anticipated that better guidance on assessing malariogenic potential will aid the development or refinement of national strategies to eliminate and prevent re-establishment of malaria, and further enable achievement of the goals and targets outlined in the *Global technical strategy for malaria 2016–2030 (8)*.

2. Objectives of the ERG

The main objective of the ERG meeting was to review and recommend appropriate methodologies for assessing malariogenic potential to inform elimination strategies and plans to prevent re-establishment. The specific objectives were as follows:

1. To review current definitions of receptivity, vulnerability and malariogenic potential contained in the WHO glossary and, if required, to recommend improvements to ensure that the definitions are valid and appropriate.
2. To review available methodologies for assessing receptivity, and recommend appropriate and valid methodological approaches, including data requirements, for national malaria control programmes (NMCPs) to use to measure receptivity in their respective countries.

3. To advise WHO on options for classifying receptivity according to programmatically relevant categories aimed at guiding interventions to prevent re-establishment of transmission.

4. To review the validity and practicality of available methods for assessing vulnerability, and to recommend appropriate and valid methodological approaches, including data requirements, for NMCPs to use to assess vulnerability in their respective countries.

5. To review data on the regional receptivity ("infectivity") of endemic *Anopheles* spp. mosquitoes to exotic strains of human malaria.

6. To advise WHO on approaches to combining measures of receptivity, vulnerability and infectivity, to guide NMCPs in designing strategies to prevent re-establishment of transmission.

3. Specific outputs of the ERG

The anticipated outputs from the ERG meeting were:

- revised definitions, where needed, for updating of the WHO malaria terminology document;
- recommendations on options for classifying receptivity according to programmatically relevant categories;
- recommendations on methods and data requirements for assessment of vulnerability;
- recommendations on how measures of receptivity, vulnerability and infectivity may be combined to inform strategies to prevent re-establishment of transmission; and
- a priority list of next steps to improve guidance on assessment of malariogenic potential and the use of such assessments.

4. Proceedings of the ERG meeting

An ERG meeting was convened by the WHO Global Malaria Programme (GMP) on 2–4 October 2018. The meeting included seven ERG members, three NMCP managers, five additional subject matter experts (as presenters), one observer from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), and the WHO Secretariat. Professor Azra Ghani was appointed as chair of the meeting. The agenda is provided as Annex 1, and the list of meeting participants and their affiliations is provided as Annex 2.

The meeting included open sessions on proposed methods for assessing receptivity, vulnerability and infectivity, as well as an examination of stratification and intervention mixes. A plenary discussion was held on the final day to develop draft conclusions, which were then finalized along with recommendations in the closed session. ERG members, NMCP managers, presenters, observers and the WHO Secretariat attended the open sessions, whereas the closed sessions included ERG members and the WHO Secretariat only.

Opening and orientation to the topic (open session)

The meeting was opened and attendees were welcomed by Dr Pedro Alonso, Director of GMP. Dr Alonso reiterated the importance of the ERG in providing a basis for clearer guidance for the development of strategies for malaria elimination as well as prevention of re-establishment. A focus on high-burden countries is essential; for example, through the new WHO "high burden to high impact" initiative that focuses on the 11 countries (10 on the African continent, plus India) that account for about 70% of the global malaria burden. However, the number of countries approaching elimination continues to increase – the *World malaria report 2018 (9)* indicates that there are now 46 countries

with fewer than 10 000 cases. Therefore, better guidance for these countries is deemed essential to enable achievement of the goals, milestones and targets outlined in the *Global technical strategy for malaria 2016–2030 (8)*, which include "*prevent re-establishment of malaria in all countries that are malaria-free*". Dr Alonso thanked the ERG members, NMCP managers and presenters for their contributions to the work of WHO in support of Member States.

Declarations of interest provided by ERG members had previously been assessed by Dr Jan Kolaczinski and Dr Kim Lindblade. Based on that review, it was decided that one of the declarations constituted a conflict of interest in this context, and that one of the experts considered could participate in the meeting but be subject to partial exclusion (i.e. be recused from the final session on Day 3, in which recommendations were finalized). All of the other experts considered were able to participate fully in the meeting, subject to the public disclosure of their interests. The statement of declarations *of interests* was read aloud to the meeting; the declarations are provided as Annex 3.

Dr Kolaczinski then explained the background, objectives and expected outputs of the meeting (as set out above). Dr Kolaczinski stated that understanding malaria transmission risk in a given geographical area provides the foundation for the design of cost-effective intervention programmes to decrease malaria burden, eliminate transmission and prevent re-establishment of malaria. The increasing demand for WHO guidance on the assessment of receptivity and vulnerability was noted, especially from countries working to prevent re-establishment of transmission. However, there is little guidance in this area; hence, there have sometimes been substantial investments in data collection (especially entomological surveillance) without a clear link to programmatic decision-making. Vector susceptibility to imported parasites contributes to malariogenic potential, but is a factor that is often not taken into consideration. Some opportunities for the development of improved guidance were identified, including the availability of more sophisticated methods and data sources, such as model-based geostatistical frameworks, cell phone information and other remotely sensed data for population mobility. In addition, useful information to inform guidance development is increasingly becoming available, through practical experience with transitioning programmes from control activities to more targeted designs aimed at eliminating malaria or preventing its re-establishment.

The current WHO guidance related to malariogenic potential was presented. The WHO *Framework for malaria elimination (4)* recommends subnational stratification to inform the selection of interventions; measurement of receptivity and vulnerability to prevent re-establishment of transmission after elimination; and maintenance of vector-control coverage after elimination in areas with high malariogenic potential. In addition, the WHO document *Malaria surveillance, monitoring & evaluation: a reference manual (2)* identifies characterization of receptivity to guide stratification and selection of interventions as one of the main objectives of entomological surveillance. In this guidance, entomological parameters considered in risk characterization include the competency of the vector species present, and bionomic traits such as biting (e.g. time, place and host preference), dispersal and resting behaviour.

Examples of approaches used to quantify receptivity, vulnerability and infectivity were presented. An example of heterogeneity in transmission risk (based on median annual parasite incidence) was presented in brief for Sri Lanka *(10)*, along with the current WHO terminology and understanding of components of malariogenic potential; that is, receptivity, vulnerability and infectivity *(1)*. For each of these components, examples were drawn from the literature to reiterate the variety of approaches that have been taken for definition and measurement.

The ERG members were encouraged to consider the most practical and informative approach (or approaches) for determining malariogenic potential, considering the variation of settings and capacities across countries.

4.1 Proposed methods for assessing receptivity

4.1.1 Review of receptivity assessments

Dr Joshua Yukich presented a background paper on the definitions and practice and case studies related to receptivity, based on work completed for a literature review commissioned by WHO,[1] the purpose of which was to review the available evidence on receptivity and its assessment by NMCPs and their research partners, and to develop a draft methodology for the assessment of receptivity. This required the following approach: develop and conduct a review of peer-reviewed and grey literature; engage with countries on experiences and methods of receptivity assessment; describe methods being used and their advantages and disadvantages; provide a draft methodology and rationale for that methodology; and develop a draft paper for review at the ERG meeting and finalize it based on feedback. The literature review included 85 documents, of which 45 (53%) had qualitative definitions and 21 (25%) had quantitative definitions. Country case studies focused on Eswatini, Georgia, Malaysia and Sri Lanka.

The review found that "receptivity" to malaria is a construct developed during the era of the Global Malaria Eradication Programme (GMEP). Receptivity has been defined in varied ways in the decades since, but no consistent, quantitative definition has emerged. In the WHO malaria terminology document, the definition of receptivity – "*receptivity of an ecosystem to transmission of malaria*" – was indicated as being poorly formulated because it constitutes a circular reference and is ambiguous. The definition also includes the note that "*a receptive ecosystem should have e.g. the presence of competent vectors, a suitable climate and a susceptible population*" *(1)*, which is not necessarily aligned with current general understanding or specific definitions used elsewhere *(*e.g. *11)*.

Despite the lack of consistency in defining this construct, the idea of receptivity has remained important in planning around malaria elimination, especially in the prevention of re-establishment period following malaria elimination. Dr Yukich presented an examination of the use of this construct through published (and unpublished) literature since the 1950s, and also used case studies to document the current use of the construct in country planning.

A definition of "receptivity" was proposed, which could be implemented in elimination and prevention of re-establishment programmes globally, along with suggested thresholds that could be used for stratification, measurement and estimation methods. These were discussed at length, with the definition later refined by the ERG, as presented below.

Based on the review of the evidence, Dr Yukich considered that the minimum approach to measuring receptivity could include one of the following:

- reproductive numbers – case counts, or case-based surveillance data classified as local or imported (relapsing);
- vectorial capacity – human landing catch or mosquito density, human blood index, extrinsic incubation period, parous rate and, possibly, vector competence; and
- historical parasite prevalence of *Plasmodium falciparum* in children aged 2–10 years ($Pf\text{PR}_{2-10}$) or malaria baseline prevalence – pre-intervention parasite prevalence data, and post-intervention parasite prevalence data with additional information on intervention coverage and other confounding factors.

Other issues raised by Dr Yukich for the ERG to consider when formulating conclusions and recommendations included the fact that *P. vivax* and *P. ovale* (i.e. relapsing malaria species) may necessitate separate estimates of receptivity. Measuring receptivity for these parasites will require differentiation into primary and relapsing cases, as well as consideration of Duffy negativity or other factors affecting human susceptibility to infection. The geographical scope of assessment was also

[1] The review is accessible from WHO upon request (kolaczinskij@who.int).

raised because receptivity may vary dramatically over small scales, as well as parasite species and strain compatibility in relation to the competence of local vectors to transmit infections.

The ERG concluded that the current WHO definition of the term "receptivity" is poorly worded. The use of the term in the literature and practice is inconsistent, and assessment methods used are varied and poorly characterized. Measurement of the construct is likely to be difficult, but the most suitable metrics for its assessment are reproductive numbers, vectorial capacity and historical *Pf*$PR_{2–10}$. Assessment via reproductive numbers provides the most intuitive stratification systems and methods of assessment that use only human surveillance data. All elimination programmes are already expected to collect the right surveillance data and to classify cases in the manner that would allow these data to be used for receptivity assessment (i.e. differentiation into local and imported cases). Other assessment methods are potentially useful, but many of the systems in practical use have never been tested for accuracy against any gold standard system.

4.1.2 Bayesian geospatial approaches to receptivity assessment

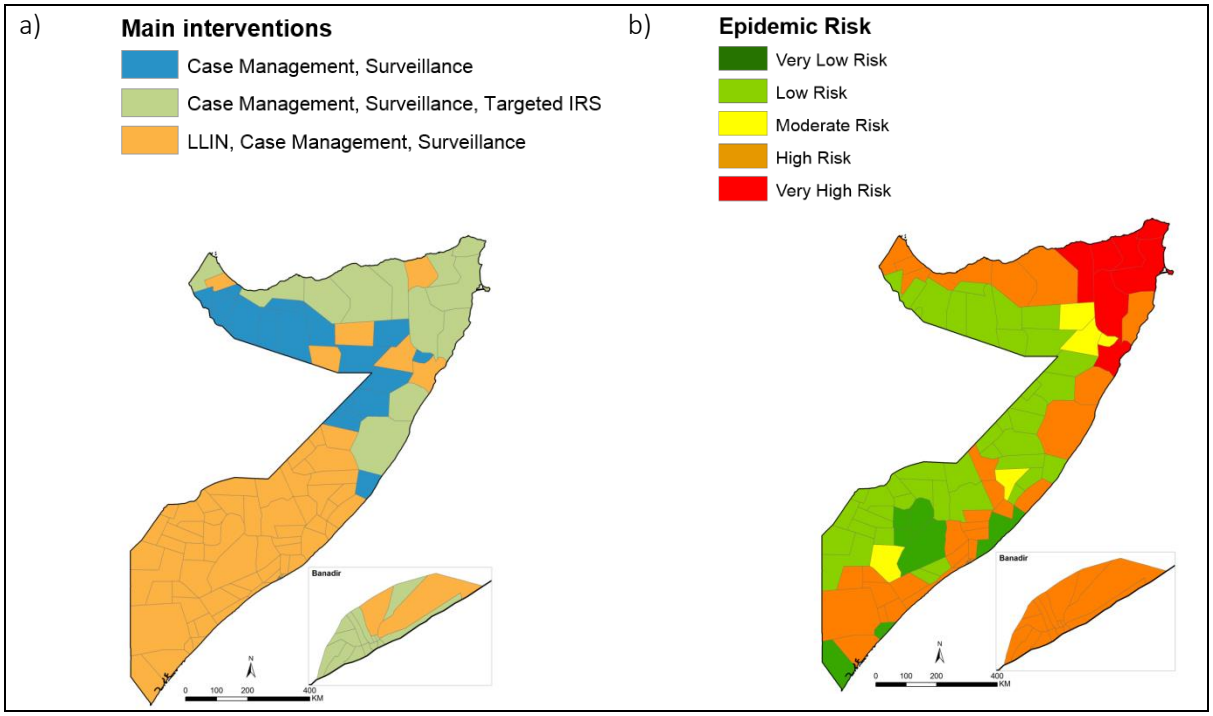
Dr Abdisalan Noor presented (remotely) on experiences in the use of model-based geostatistical analysis of historical *Pf*$PR_{2–10}$ to estimate receptivity. His presentation drew on published examples from three countries – Somalia, Namibia and Kenya – as outlined below.

Example from Somalia

For Somalia, the purpose of the study was to explore the use of *Pf*$PR_{2–10}$ as proxy for receptivity to guide intervention targeting *(12)*. A total of 1558 *Pf*$PR_{2–10}$ data points from the period 2007–2011 were used for Bayesian spatial–temporal models. Selected environmental covariates (urbanization, rainfall, temperature and distance to potential mosquito larva breeding sites) were included. Maps of *Pf*$PR_{2–10}$ were produced at 1 × 1 km spatial resolution for each year from 2007 to 2010. Maximum prediction for each at a pixel level was used as a measure of receptivity. Maps of population totals at similar resolution were combined with the *Pf*$PR_{2–10}$ maps to produce population-adjusted *Pf*$PR_{2–10}$ (PA*Pf*$PR_{2–10}$) by district. The "receptive" *Pf*$PR_{2–10}$ map was then used to define packages of interventions in each district as a basis for Somalia's grant application to the Global Fund (Fig. 1a). Case management and surveillance were recommended everywhere, with targeted indoor residual spraying (IRS) proposed in areas with PA*Pf*$PR_{2–10}$ of less than 1% and epidemic prone (green), but not those areas where PA*Pf*$PR_{2–10}$ was less than 1% but not epidemic prone (blue). Long-lasting insecticidal nets (LLINs) were recommended only in areas with PA*Pf*$PR_{2–10}$ of more than 1% (orange).

Epidemic prone areas were then mapped using information on receptive *Pf*$PR_{2–10}$; rainfall seasonality and frequency of anomalies, and their relationship with weekly malaria cases from sentinel sites; ecological zones; and village maps. A 3-month period of above normal rainfall preceded most epidemics, and the median amount of rainfall for these 3 months was about 40% above average rainfall. Villages were ranked into quintiles based on the number of such 3-month blocks from 2005 to 2015, the estimated *Pf*$PR_{2–10}$ from the continuous prevalence maps, and the ecological zone (central south, north-east and north-west). A composite index of epidemic risk was then developed from these estimates.

Fig. 1. Example from Somalia of the use of PAPfPR2–10 to determine a) main intervention mixes and b) epidemic risk



IRS: indoor residual spraying; LLIN: long-lasting insecticidal net; PA*Pf*PR$_{2–10}$: population-adjusted *Plasmodium falciparum* prevalence in children aged 2–10 years (Excerpt from presentation by A. Noor).

Example from Namibia

For Namibia, estimates of the spatial distribution of receptive areas and current risk using *Pf*PR$_{2–10}$ data were generated to inform recommendations on targeting of vector control, and to provide information for future analyses of receptivity and vulnerability to inform elimination *(13)*. Data comprised 3260 *Pf*PR$_{2–10}$ points from 1967 to 1992 and 120 *Pf*PR$_{2–10}$ points from 2009, with selected environmental covariates (urbanization, temperature, enhanced vegetation indices and precipitation) considered. Estimates indicated that areas of the highest historical transmission were concentrated in the Okavango and Caprivi areas. Those areas with more than 5% historical prevalence were recommended for vector-control targeting. There were no data available for the epidemic years of 1993, 1996, 2000, 2001 and 2004. It was noted that it would be worth comparing estimates with data from the recent epidemics of 2013–2015. However, this study indicated that historical maximal risks are not truly a measure of intrinsic transmission due to coincident intense control, although accuracy was higher than for estimates based on data from 2009.

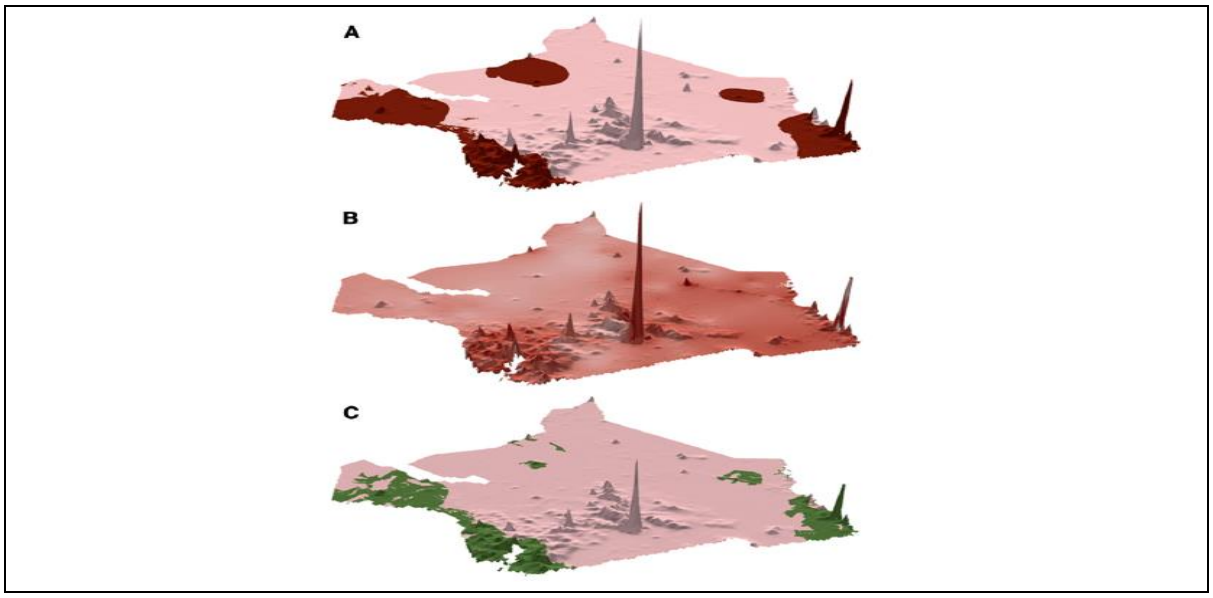
Example from Kenya

The example presented for Kenya was originally generated based on a request from the NMCP to develop an approach for better targeting of mass campaigns for insecticide-treated mosquito net (ITN) distributions where funding is limited, meaning that distributions across the whole country are not possible *(14)*. Work was undertaken to update model-based geostatistical maps of *Pf*PR generated based on malaria indicator survey data from 2007 and other historical data *(15)*. Three maps were developed (

Fig. **2**). Under a targeted approach, the population at risk in 2010 was estimated to be 15.2 million compared with a total population of 40.5 million. The total number of LLINs needed to achieve universal coverage in the targeted area, accounting for estimated valid LLINs in the population, was 5.5 million, compared with 16.4 million across the whole country. Estimated savings in cost of commodities alone was about US$ 55 million for the campaign that followed. This targeting approach

is still used by the Kenya NMCP. There was no evidence of increase in malaria transmission in districts where LLIN coverage was not maintained.

Fig. 2. A) A 3D population map showing areas where $PfPR_{2–10}$ was <1% (pink) and >1% (dark red); B) map showing percentage ITN use: the darker the colour the higher the predicted ITN coverage; C) population that need LLINs in areas to be targeted based on a criteria of >1% $PfPR_{2–10}$ and >1 person per km2 (green) and those additional individuals who will need LLINs if the whole country were targeted (pink)



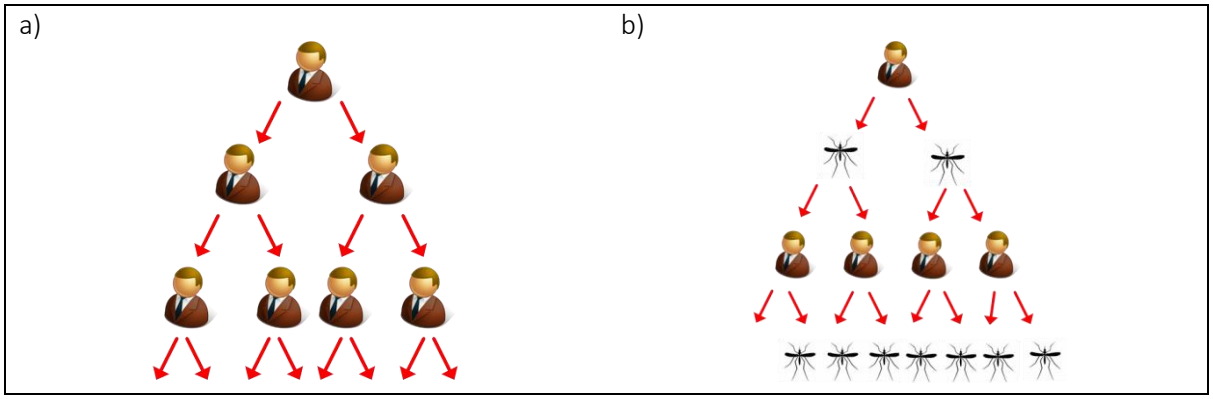
ITN: insecticide-treated mosquito net; LLIN: long-lasting insecticidal net; PA*Pf*$PR_{2–10}$: population-adjusted *Plasmodium falciparum* prevalence in children aged 2–10 years (Excerpt from presentation by A. Noor).

Dr Noor concluded that use of model-based geostatistical estimates of *Pf*$PR_{2–10}$ as surrogate measures of receptivity will depend on the context and purpose. The process of selecting maximum *Pf*$PR_{2–10}$ prediction was not probabilistic but was instead a direct extraction of the highest mean pixel prediction; therefore, it was not possible to quantify uncertainty. The examples also showed that interventions and other secular effects and the low temporal signal in data can have a major impact on *Pf*$PR_{2–10}$ predictions. However, it is almost impossible to find *Pf*PR data from a period of "true" absence of control. Using *Pf*PR data together with good entomological measurements is likely to be more informative.

4.1.3 Estimation of R0 for receptivity assessment

Professor Azra Ghani presented on estimating the basic reproductive number (R_0) as a measure of malaria receptivity. The concept of R_0 was explained as a measure of how many additional people one person infects over the course of their infection, which is one of the most important quantities governing an epidemic; that is, R_0 applies to the start of an epidemic when no individuals are immune, and for an epidemic to "take off" R_0 needs to be more than 1. For vector-borne diseases, one person gets infected and that person infects mosquitoes, which then infect more people, who then go on to infect more mosquitoes. Nevertheless, the definition of R_0 remains the number of new people infected by each person (Fig. 3).

Fig. 3. Conceptual representation of the basic reproductive rate (R0) for a) infectious diseases of humans and b) vector-borne diseases of humans



Excerpt from presentation by A. Ghani.

R_0 is closely related to vectorial capacity and is defined as "*the number of secondary cases that a single infection (index case) would generate in a completely susceptible population*" *(1)*. The definition of vectorial capacity – that is, "*the number of new infections that the population of a given vector would induce per case per day at a given place and time, assuming that the human population is fully susceptible to malaria*" *(1)* – is similar but does not take into account the transmission bottlenecks (human to mosquito and mosquito to human). Also, vectorial capacity is measured on a per day basis, whereas R_0 is measured over the course of a full infection. Vectorial capacity has previously been identified as equivalent to receptivity, but it can be difficult to estimate all of the parameters for vectorial capacity in the field *(16)*.

The basis of epidemics was explained with reference to the "growth rate", which defines the chain reaction that gives exponential growth in an epidemic, or can lead to its rapid decline. This rate is determined by R_0 and the generation time (Tg); also sometimes referred to as the serial interval, Tg is the average time between one person getting infected and that person infecting other people. When an epidemic begins to run out of people to infect, the growth rate declines because a substantial proportion of contacts for each infected case have already been infected. Therefore, the number of secondary cases per case drops below R_0 and instead becomes defined by the effective reproductive number (R_e), which is the product of R_0 and the proportion of the population that are still susceptible (s) (i.e. $R_e = s \times R_0$). Therefore, an epidemic will go into decline once s is less than $1/R_0$ because at this point R_e will be less than 1.

The threshold of R_e greater than 1 is required for self-sustaining local transmission. However, at R_e less than 1 there will still be small outbreaks, assuming there is some importation. The probability of such outbreaks becomes less likely as R_e gets smaller. The number of locally acquired cases therefore depends on both R_e and the number of importations. This means that receptivity and importation risk are both important in determining the chances of observing locally acquired cases.

Most work to date has been to estimate malaria R_0 as a measure of the intensity of transmission in a location experiencing ongoing transmission, based on:

- a modelled relationship with other malaria metrics (often within a geospatial framework);
- the relationship between aggregate numbers of imported and locally acquired cases; or
- "reconstruction" of potential chains of transmission using detailed data on each identified case or infection.

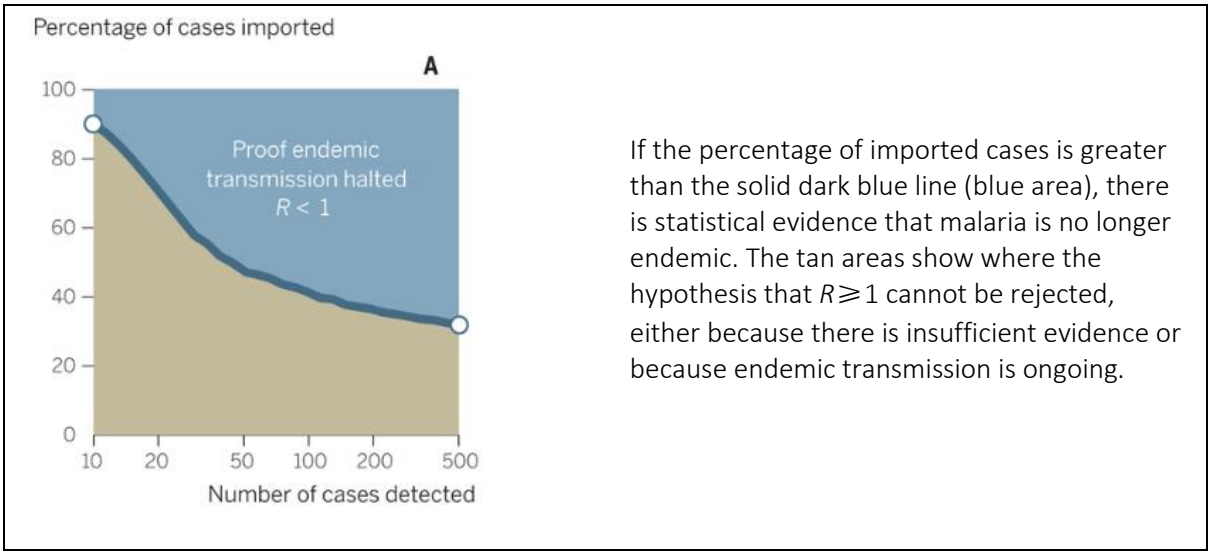
Much more work on this has been undertaken for other diseases, in particular for emerging diseases and outbreaks. Although less work has been done to date for malaria in elimination settings, the

methods used from assessing the relationship between aggregated numbers of imported and locally acquired cases remain relevant.

The methods used to aggregate case reports are based on how many cases each imported case is expected to generate. This draws on data on locally acquired and imported cases to specifically test whether R_e is greater than 1, and therefore whether there is self-sustaining local transmission. Simulations are used to derive the expected ratio of local to imported cases, to determine whether these are just above the threshold value of R_e equals 1. It can be scaled to any appropriate geographical level (e.g. country, province or district), depending on data availability.

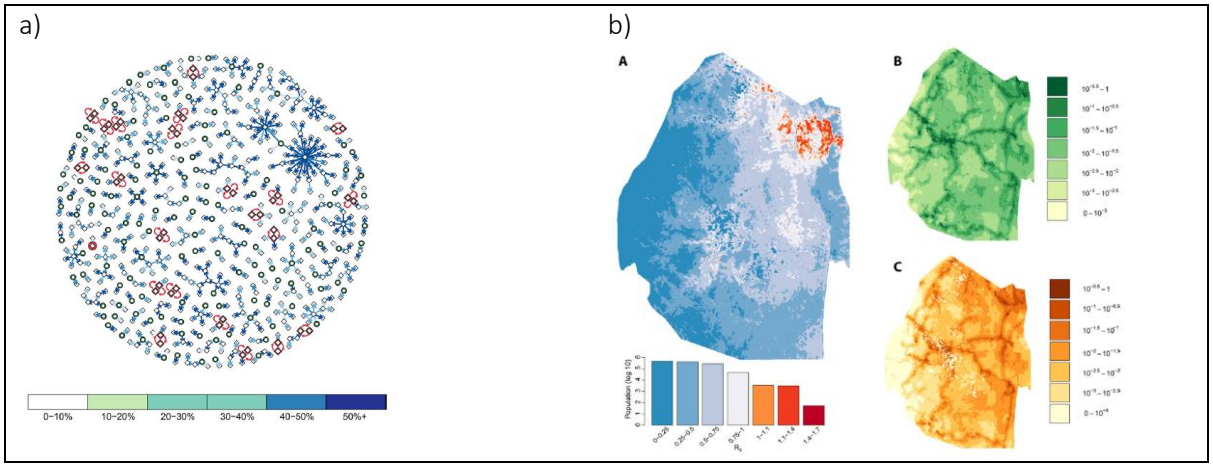
An example using this approach was presented for Eswatini *(17)*. R_e was estimated annually and was shown to be significantly less than 1 from 2012 onwards. Estimates were used to generate a simple graph that could be used in other locations. However, for elimination, individual information on the date of the case report is required to understand the potential times in the past that an individual could plausibly have been infected (i.e. considering the Tg distribution). Such information would help to ascertain which cases could have resulted from previous cases based on examining temporal overlap, which is useful for developing a map of potential transmission networks. A detailed network map developed for Eswatini by Reiner et al. *(18)* was presented. This can feed into regression models, with environmental covariates used to obtain maps of *R* and importation probability; multiplied together, these can give malariogenic potential (Fig. 5).

Fig. 4. The percentage of imported cases required to confirm that endemic malaria transmission has been halted



Sources: Churcher et al, 2014 and Reiner et al., 2015 *(18, 19)*.

Fig. 5. Maps for Eswatini showing a) consensus network plot of causal links and b) extrapolated R_C values to give estimates of A) vulnerability, B) receptivity and C) malariogenic potential



R_C: controlled reproductive number.
Source: Reiner et al., 2015 *(18)*.

An example of a methodologically different approach was presented for El Salvador *(20)*. The method relied on reconstructing transmission pathways, but also identified some "orphan" infections that do not appear to have a source. Spatial extrapolation similarly used demographic and environmental covariates, to map the probability of sustained transmission (i.e. R_e >1).

Limitations

The limitations of assessing the risk of re-establishment were presented by Professor Ghani. Primarily, where there are no locally acquired cases, it is not possible to reconstruct transmission events. The branching process methods used in the estimates produced for Eswatini were therefore considered more relevant to these settings. Instead of testing the null hypothesis of R_e being greater than 1, the same method could be used to obtain an upper 95% credible interval for R_e, conditional on having observed no outbreaks (or other similar metrics). The method can easily be extended to produce geographical maps similar to those presented above for Eswatini and El Salvador *(17, 18, 20)*.

Professor Ghani concluded that R_e/R_C (where R_c is controlled is an appropriate metric to estimate receptivity as elimination is approached. At its simplest, R_e/R_C can be estimated from counts of imported or locally acquired cases, or from case report data where such data are available. Both calendar time and geographical space can be used in assessment of risk (and potentially genetic information). Although methods development is ongoing, it has the potential to be synthesized in a form that could be accessible to NMCPs. However, it has not yet been applied or tested in areas or countries in which malaria has been eliminated.

4.1.4 Experiences of using the entomological surveillance planning tool to measure receptivity

Dr Adam Bennett presented on an entomological surveillance planning tool (ESPT) that is currently being developed, to support problem-solving and vector-control decision-making. The ESPT was developed in response to identified demand from NMCPs, owing to limited consolidated operational guidance for entomological surveillance. This was underscored by a growing need among programmes for deeper understanding of transmission dynamics and gaps in protection to inform response, with efficient and ethical entomology and vector control more important than ever.

The objectives of the ESPT are to:

- support gap-filling in operational guidance for entomological surveillance;
- align with and operationalize global normative guidance;

- develop minimum essential entomological indicators to generate data that are actionable and collectable;
- support NMCPs in making evidence-based decisions on vector control; and
- deepen the integration of entomological and epidemiological surveillance and response.

The ESPT is intended as a highly collaborative and iterative project that has been developed in alignment and in consultation with WHO. Version 1.0 was circulated in early 2018; version 2.0 is under development, based on feedback and pilots.

A number of potential use cases have been identified; for example:

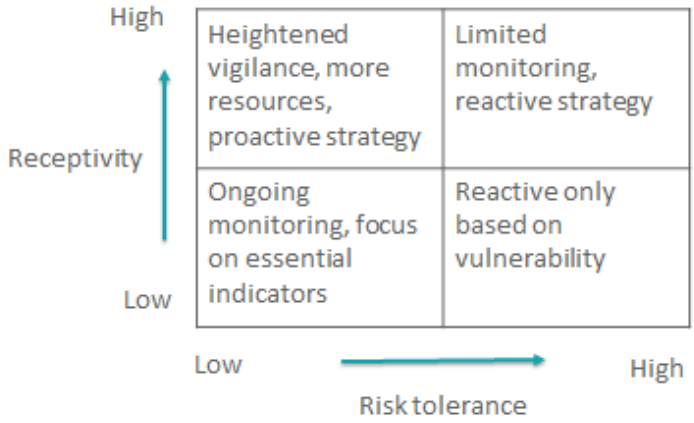
- planning annual NMCP entomological surveillance activities;
- developing a national entomological surveillance plan;
- developing and implementing training workshops;
- developing a protocol to answer a specific programmatic question;
- evaluating specific vector-control interventions in a programmatic setting;
- measuring receptivity (e.g. as part of prevention of reintroduction); and
- integrating entomological and epidemiological activities and data.

The ESPT is being piloted in five countries: Democratic Republic of the Congo, Mozambique, Myanmar, Namibia and Panama. Learnings from Mauritius thus far were presented, along with key outcomes and conclusions from work to date. In Mauritius, prevention of re-establishment strategy hinges on three activities: passenger screening (i.e. screening at ports of entry) – *vulnerability*; integrated vector management (IVM) and entomological surveillance – *receptivity*; and a strong passive surveillance system. IVM and entomological surveillance are needed to measure and maintain low receptivity. This is achieved through biweekly larval surveys and larviciding; sites include former malaria foci (routine) and high-risk areas around migrant workers' residence (proactive). Additional vector control includes enforced environmental management on personal property, and IRS and outdoor residual spraying at and around the port and airport every 6 months. Where an introduced malaria case is detected, focal larval surveys, larviciding and IRS are conducted within a 500 m radius of the case's residence, and anywhere the case stayed in the past 18–24 days. The presence of malaria vector(s) is used as a measure of receptivity, noting that climate and environment are implicit in the presence of vectors.

Numerous key questions were presented and discussed, including on minimal essential indicators, supplemental indicators, appropriate sampling methods, and frequency and location of sampling. It was emphasized that data that lead to action are vital; hence, all decision trees lead to an action in line with national strategy. Activities are also highly dependent on financial, technical and operational capacity; requirements for certification can serve as leverage to create sufficient capacity. The geographical size of areas monitoring receptivity matters; smaller pockets of malaria free areas in malaria endemic countries might implement monitoring based on vulnerability trigger, whereas larger malaria free regions or entire countries might implement routine monitoring (e.g. by historical peak or by month).

Ultimately, a ministry of health's (MoH's) prevention of re-establishment programme (and receptivity monitoring activities) will depend on the level of risk the country is willing to accept. Thus, a country that is risk averse would implement heightened vigilance and a proactive approach, whereas a country that is more risk tolerant would implement moderate vigilance and a more reactive approach (Fig. 6). The process of determining baseline risk and risk targets can be formalized – for example, through import risk analysis (as applied for zoonotic diseases and plant pests), and could be based on the quantitative or qualitative likelihood and implications of re-establishment, or the government's and public's attitude towards those potential outcomes.

Fig. 6. Representation of the influence of receptivity and risk tolerance on response actions



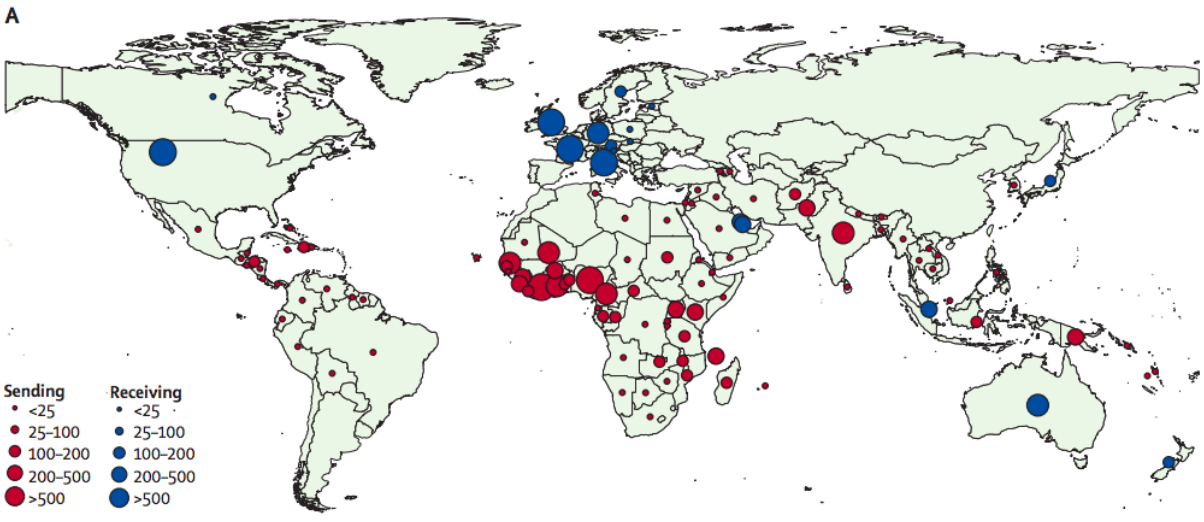
Excerpt from presentation by A. Bennett.

4.2 Proposed methods for assessing vulnerability

4.2.1 Approaches to assessing vulnerability to imported parasites

Dr Andy Tatem presented on measuring and mapping of vulnerability to malaria. Human movements contribute to the transmission of malaria on spatial scales that exceed the limits of mosquito dispersal. Identifying the sources and sinks of imported infections due to human travel, and locating high-risk sites of parasite importation, could support the targeting of limited resources. Dr Tatem presented the literature on approaches to identifying importation routes that contribute to malaria epidemiology on regional, national and subnational scales. Historical and current examples of human mobility were shown that highlight today's increasing volume of worldwide mobility; the rise has been particularly marked recently in low- and middle-income countries. Maps showing the geography of imported malaria to nonendemic countries indicated that this is a significant issue *(21)*; the effects of such importation were presented, with clear examples of resurgence in countries across all WHO regions *(22)*. Further country-specific examples of importation risks and origins were presented for Cabo Verde, China and Le Reunion.

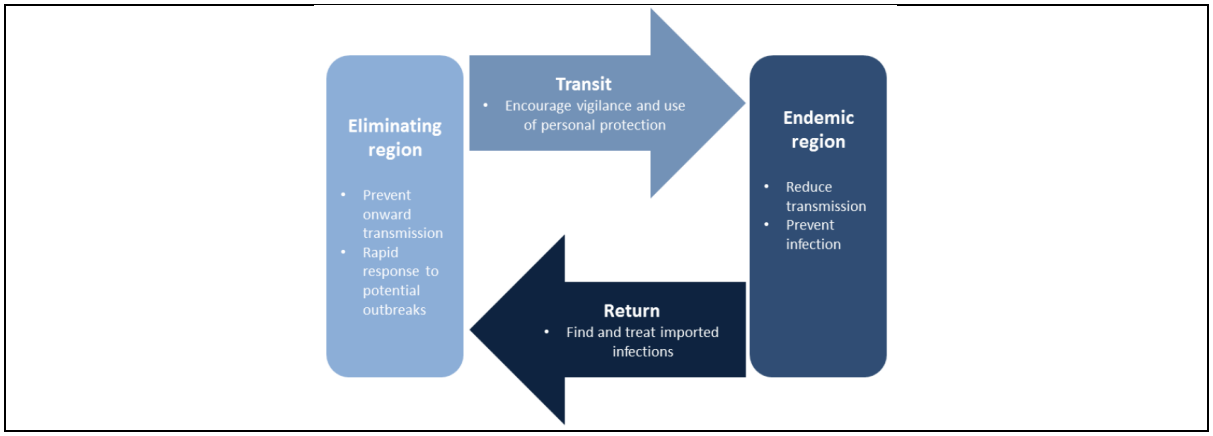
Fig. 7. Origins, destinations and flows of imported cases of malaria from endemic to nonendemic countries – average annual number of malaria cases (all species) between 2005 and 2015 exported from endemic to nonendemic countries (red) and imported cases to nonendemic from endemic countries (blue)



Excerpt from presentation by A. Tatem.

Outcomes of a qualitative assessment of malaria parasite importation into Zanzibar, United Republic of Tanzania indicate that the potential pathways by which parasites might be imported were residents infected while visiting endemic areas, infected visitors bitten by resident mosquitoes, infected migrants and infected migrant mosquitoes *(23)*. The importance of importation of malaria parasites into receptive areas that can lead to onward transmission was discussed in the context of elimination efforts in southern Africa, where there is extensive interconnectivity between high-burden and low-burden areas. Dr Tatem noted also that importation from high-risk areas places a significant burden on the health care system, absorbing human and financial resources. Thus, even if conditions are such that local transmission eventually dies out, importation can lead to considerable numbers of local cases. Further examples were presented from El Salvador, Equatorial Guinea, Eswatini, Uganda and the Thailand–Myanmar border. For instance, in patients who had recently travelled to areas of higher transmission intensity than their home areas were nearly seven times more likely to have confirmed malaria *(24)*. The four stages of human movement and corresponding objectives of interventions were presented *(25)*.

Fig. 8. Human management and intervention objectives



In terms of measuring parasite movement and connectivity, the advantages and disadvantages of different approaches were presented (with examples), as summarized in Table 1.

Table 1. Summary of advantages and disadvantages of different data types for assessing vulnerability

Data type	Advantages	Disadvantages
Surveillance data: data on imported cases collected through routine or active case detection	• Provides a direct measurement of imported cases, demographics and other characteristics • Can be spatially and temporally detailed	• Can be sparse, incomplete and inaccurate • Asymptomatic carriers are typically missed • Treatment seeking rates, informal populations and private clinics may lead to missed cases • Varying amounts of information are captured • Identification of imported versus local cases is challenging • Recall biases • Definitions changing or inconsistent temporally and spatially

Data type	Advantages	Disadvantages
Parasite genetics: measures diversity and relatedness of parasite genetic samples, enabling direct measurement of parasite connectivity	• Most direct measure of parasite importation and connectivity • Overcomes issues of asymptomatic people and treatment seeking in surveillance data	• Few efforts to systematically collect and few genotype representative samples at sufficient spatial scale and density to provide useful data • Difficult to detect relevant spatial signal in parasite genetic data using traditional population genetic methods, particularly in areas such as sub-Saharan Africa that have high levels of population diversity and polyclonal infections
Travel history surveys and participatory mapping: household surveys, border surveys and expert opinion on movement patterns	• Captures movements that may be missed by surveillance system	• Recall and other biases • Expensive to undertake for large areas
Census-based migration: assembly of population and housing census data on place of residence 1–5 years ago; spatial interaction modelling for filling gaps	• Global extent and consistent measure; covers complete population • Shows strong correlations to shorter scale movements, both domestic and international • Data on imported cases are collected through routine or active case detection	• Permanent migrations only • Bias to longer spatial scales • Affected by conflicts • Coarse spatial scale
Air and sea traffic data: statistics on passengers (or flights and passenger ships) travelling between airports or ports	• Captures relevant movements where flights and ships are the primary method of introduction	• Not so useful where land travel is prevalent
Call detail records: geolocated data from mobile phone calls	• Massive sample size • Impossible to achieve with travel history surveys • National-scale data • Long time series • Relatively reliable source of destinations and lengths of stay for travel • Provides information on social networks and wealth • Cross-border measurements feasible	• Bias in representation of national population movements • Coverage gaps in the most rural areas • No demographic information • No information on activities, malaria protection etc. during travel
Internet and social media location histories: geolocated data from smartphone devices; for example, Google location history (GLH)	• Spatially precise • Long time series • Captures domestic and international data • Rapidly increasing volume of data	• Huge biases • No demographics • Variations by device • Changing sample over time

Data type	Advantages	Disadvantages
	• Exploring potential for connectivity and for mobility modelling penetration	
GPS tracking: volunteers are given Global Positioning System (GPS) trackers or smartphones to monitor movement patterns	• Precise, detailed data on movements, overcomes recall bias problems • Useful for validation of other methods	• Expensive • Limited to small areas and small samples • Limitations to long-term measurement
Infrastructure: georeferenced data on transport links that form the basis of regional mobility	• Global coverage • Consistent data • Indicative of connectivity and mobility • Useful alternative measure of the connectivity and access that drive vulnerability	• No measure of actual movements • Few time series

Numerous examples of the use of movement data for mapping transmission foci were presented, including for mapping transmission foci *(e.g. 26, 27-29)*. Dr Tatem concluded that a strong surveillance system, capturing imported cases and related information, is central to assessing vulnerability. Alternative sources of data and modelling approaches can complement and add value. However, no source of mobility data is perfect, and integration of multiple types of data will probably provide the most complete picture. Data on parasite movements and connectivity can be analysed in multiple ways to answer different types of questions facing programmes. Dr Tatem identified a number of other questions of interest, such as the appropriate standard metric for vulnerability, the best data sets for the different needs, and how to integrate the different data sets to draw on the strengths of each one.

Conclusions

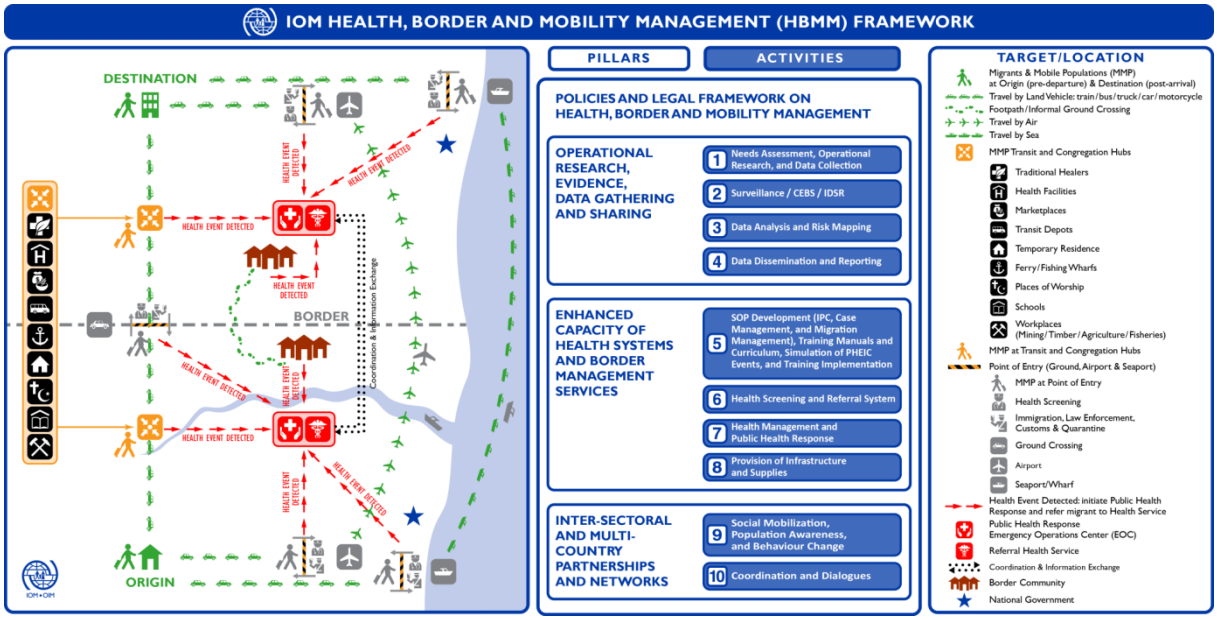
After considering the information presented, the ERG identified the core priority on vulnerability as it pertains to malariogenic potential to be identification of the points of entry and the numbers of people coming from areas of malaria endemicity to areas where transmission had been interrupted. Discussions centred on whether surveillance data are sufficient to determine this, or whether there can be full reliance on mobile data or other data sources for some or all areas. A number of limitations of mobile data were indicated, such as not being able to detect movement between countries owing to differences in mobile providers and the need for service roaming functions, and the fact that multiple service providers may complicate access to a complete data set. Although data collected through routine or active case detection provide a direct measurement of imported cases and hence should be the central component of surveillance, these show the number but not the risk of importations because of limited knowledge on the denominator. Therefore, mobile data could be of supplementary use to show the actual volume and patterns of human movement, to determine how these relate to importation risk.

The ERG concluded that there is utility in comparison of multiple types of data, to give confidence that other types of data can be used in settings where the surveillance system is not yet sufficiently strong and the surveillance data are not yet of an acceptable standard to support elimination and prevention of reintroduction.

4.2.2 Vulnerability assessment through tools developed by the International Organization for Migration

Dr Carlos van der Laat and Mr Nawar Sattar Tashbid presented on the International Organization for Migration (IOM) Health, Border and Mobility Management (HBMM) framework and population mobility mapping *(30)*. Originally developed for Ebola virus outbreaks, the HBMM framework empowers governments and communities to prevent, detect and respond to the spread of infectious diseases and other potential health threats along the mobility continuum (i.e. at origin, transit, destination and return points), with particular focus on border areas. At the core of HBMM is the understanding that the mobility continuum extends beyond the physical or regulated border areas, such as the official points of entry (PoEs) as articulated within the International Health Regulations (IHR) 2005, to include pathways and spaces of vulnerability. Grounded on this understanding, the scope of HBMM ranges from the collection and analysis of information on mobility patterns, to disease surveillance and health threat response mechanisms at spaces of vulnerability along mobility pathways. Thus, HBMM ultimately contributes to health system strengthening that is sensitive to mobility dynamics, notably at the primary health care level.

Fig. 9. Overview of the IOM HBMM framework



Excerpt from presentation by C. van der Laat.

The IOM has identified vulnerability to malaria based on the key areas of service access, knowledge, health care seeking behaviours, exposure and other risk factors. As with mobility, the definition of vulnerability considers it to be a known social determinant of health, a direct contributor to the spread of diseases, and a continuum wherein to better understand vulnerability is to enable better prevention, detection and response to public health threats. According to the IOM definition, spaces of vulnerability are human mobility bridges in areas of high-risk exposure to diseases, where human mobility connects communities and defines common spaces of vulnerability (e.g. those that can have increased risk of exposure to malaria). It was clear that the IOM concept of vulnerability differs from the malaria-specific definition provided in *WHO malaria terminology (1)*. The former considers "spaces of vulnerability" as being related to the places within the migration cycle where migrants are at greater risk for disease; it focuses on the space, the community or the site where migrants gather, such as the market or the church. This reiterates the ambiguity in the use of the term "vulnerability" to refer to what could more accurately be referred to as "importation risk".

IOM undertake three phases to ensure that better mobility information has a positive impact on public health:

1. Identify geographical areas of interest with human mobility dynamics and patterns, and other vulnerabilities that may increase the impact of public health risk of international, national and community concern.
2. Collect data – assess the characteristics, vulnerabilities and extent of human mobility into, from and between identified areas of interest, including their congregation points. This includes carrying out vulnerability and capacity assessments for disease surveillance and response at spaces of vulnerability (e.g. health facilities, PoEs and "at-risk" communities).
3. Analyse mobility patterns in the context of the public health event, to guide resource and response needs.

Examples were presented on identification of migration routes and risks in Ghana through data collected via participatory mapping with stakeholders at the national and subnational levels. Mapping of results was through the software ArcGIS and Illustrator, to define mobility corridors, connectivity and mobility trends. The Ghana case study was of particular interest to the ERG members, with further inquiries on methodology. Dr van der Laat and Mr Tashbid clarified that the initial step of national mapping required about US$ 30 000 for convening, printing of basemaps and payment of experts in facilitation, note taking and ArcGIS. The stakeholder consultation included 25–30 people from different backgrounds (i.e. different actors in public health) working for about 2–3 days, with the total exercise taking less than 1 week. From this, key priority districts were identified for further participatory mapping, with local mappings to identify key community areas of vulnerability. Direct observations could then be made, and public health interventions could be developed and implemented.

A similar approach is being undertaken with support of the IOM in several other countries in Africa; preliminary results were presented for Côte d'Ivoire, Democratic Republic of the Congo, Liberia and Sierra Leone. Sites are defined based on clear administrative and geographical boundaries for consistency and replicability, as well as the feasibility of covering those sites. Their selection is based on existing information on health risks and epidemiology, population mobility dynamics indicated by locally available information, and the accessibility and availability of resources. Examples of similar undertakings were presented for the response to the international emergency of public health concern declared for Ebola and Zika, as well as for cholera outbreaks.

The main areas identified as requiring work were the need to:

- improve tools, methodologies and practice for assessing and understanding local mobility dynamics;
- link prevention, treatment and surveillance data, and initiatives across migration routes and borders;
- strengthen multisectoral engagement; and
- promote migrant inclusion in national, state and provincial health service planning, and all malaria services.

4.3 NMCP experience with assessing receptivity and vulnerability

4.3.1 Malaysia

Dr Jenarun Jelip presented on Malaysia's experience with assessing receptivity. Vulnerability assessments were presented later in the meeting, but are summarized here for continuity, along with the overall use of this information for stratification and intervention. Vulnerability in the Malaysian

context referred to importation risk, but also included the likelihood of malaria infection given the characteristics of the population.

Malaysia has 14 states with 147 districts and more than 55 000 localities, covering an area of 329 847 km². In 2017, the population was estimated at 32 million, and is multiracial, with a multitude of ethnic groups. In 2003, Malaysia achieved an annual parasite index (API) of less than 1 per 1000 population. The latest national stratification was undertaken in 2015, and was based on disease burden (i.e. by API); it indicated that 97.3% of the localities in Malaysia were free of malaria. The MoH therefore decided to use receptivity and vulnerability as measures for risk of malaria reintroduction. Methods were developed to measure these parameters, and these methods formed the main component of the national *Guideline for prevention of malaria re-introduction*, which was published in 2016. The definitions of receptivity and vulnerability that were applied, as well as the definition of malaria focus, were guided by the WHO *Framework for malaria elimination (4)*.

Measurement of receptivity

Parameters included in the receptivity index are indicated in Table 2; each is assigned a weighting factor, and an overall receptivity score is then generated. A standardized form is used for the preliminary ecological assessment for *Anopheles* reproduction – which in Bahasa Malaysia is "*Penilaian Awal Kesesuaian Ekologi Pembiakan Anopheles*" (PAKEPA). The PAKEPA form has four parts:

- case information (if available);
- basic data on locality;
- receptivity variables and possible vector species; and
- vulnerability level and conclusion from an entomological risk assessment (ERA) or entomological investigation (EI).

Table 2. Receptivity assessment used in Malaysia

No.	Parameters		Weighting factor	NOTE
1	PAKEPA (preliminary ecological assessment)	Suitable	2	Select one
		Not suitable	0	
2	Discovery of *Anopheles* spp. larvae	• In permanent pool	4	
		• In non-permanent pool	3	
3	Distance from positive breeding to household	• <2 km	3	
		• >2 km	1	
4	Discovery of *Anopheles* spp. resting outdoor	• Density >2 pmh	3	Select one
		• Density <2 pmh	2	
5	Discovery of *Anopheles* spp. resting indoor	• Density >2 pmh	5	Select one
		• Density <2 pmh	3	
6	Discovery of *Anopheles* spp. biting outdoor	• HBR >1 pmh	5	Select one
		• HBR >1 pmh	3	
7	Discovery of *Anopheles* spp. biting indoor	• HBR >1 pmh	9	Select one
		• HBR >1 pmh	7	
8	Discovery of parous *Anopheles* spp.	• Parity rate ≥80%	5	Select one
		• Parity rate 30–80%	3	
		• Parity rate ≤30%	1	
9	Discovery of *Anopheles* spp. with sporozoite and/or oocyst		10	

pmh: per man hour (Excerpt from presentation by J. Jelip).

Since it is almost impossible to measure receptivity for each of the 55 000 localities in Malaysia, those with similar ecology are grouped together and considered "one ecosystem". One locality within the ecosystem is then selected as the reference, and the PAKEPA is conducted there. The PAKEPA classification for the reference locality is then generalized to all localities within the ecosystem. Ecosystems are dynamic; hence, constituent localities can alter over time as a result of ecological changes.

Entomologists used PAKEPA classification of a locality to determine the need for a complete ERA/EI; these assessments are conducted by the health staff in charge of the respective area, with validation by the entomologist. In Malaysia, there are currently 114 entomologists working at headquarters (4), state (43) and district (62) level, or in the Institute for Public Health (3) or Public Health Laboratory (2); the presence of this professional staff underpins the system.

A preliminary study was conducted in 129 localities in Sabah State to pretest this receptivity assessment tool. Based on data from this preliminary study, thresholds were identified to stratify the localities. The thresholds were decided in such a way that a manageable number of localities were classified as having a low, medium or high receptivity index, with low being less than 6, medium being 6–17 and high being greater than 17.

Appropriate vector-control strategies were identified based on the receptivity index, such as larval source management to be applied where PAKEPA is equal to 2, and where there are *Anopheles* in permanent and non-permanent pools that are found within 2 km of a household. IRS is applied where *Anopheles* spp. are found resting or biting indoors (irrespective of density), or where *Anopheles* spp. are discovered harbouring sporozoites or oocysts. ITNs or IRS are likewise recommended under these conditions, as well as where the parity rate is equal to or greater than 80%. Personal protection measures and insecticide-treated curtains are recommended in the case of outdoors resting or biting *Anopheles* spp., and where sporozoites or oocysts have been found. Space spraying is also used where higher densities of vectors and sporozoites or oocysts are found, irrespective of whether this is for mosquitoes found resting or biting indoors or outdoors.

Measurement of vulnerability

Parameters included in the vulnerability index are indicated in Table 3; each is assigned a weighting factor, and an overall receptivity score is then generated. A preliminary study was conducted in 957 localities in Sabah State to pretest this vulnerability tool. Based on the observed data from this preliminary study, thresholds were identified to stratify the localities; thresholds were decided in such a way that a manageable number of localities are classified as having a high vulnerability index, with low being less than 21, medium being 21–26 and high being greater than 26.

Table 3. Vulnerability assessment used in Malaysia

No.	Parameters	Weighting factor	Possible scenario
1	Malaria case with gametocyte in the previous 6 months	10	
2	Imported human malaria in the previous 6 months	9	
3	Locality with high risk of malaria	8	• Plantation, logging • Aboriginal settlement (Peninsular Malaysia) • Penan settlement • Refugee camp or detention camp • Illegal entry routes
4	Presence of illegal immigrant population (PATI) from malaria endemic countries	7	
5	Presence of legal immigrant population (PADI) from malaria endemic countries	6	
6	Presence of local high-risk population	5	• Aboriginal community • Penan community • People living in houses with incomplete walls • People with no access to health services • People without public transportation facilities
7	People involved in high-risk activities	4	• Hunting • Fishing • Jungle recreation activities • Security force • Wildlife protection • Forestry • Land surveyor
8	Local people working in high-risk sector in malaria endemic countries	3	• Logging • Road construction • Dam construction • Mining
9	Localities at immediate border with malaria endemic area	2	
10	Construction projects of more than 2 months duration	1	

Excerpt from presentation by J. Jelip.

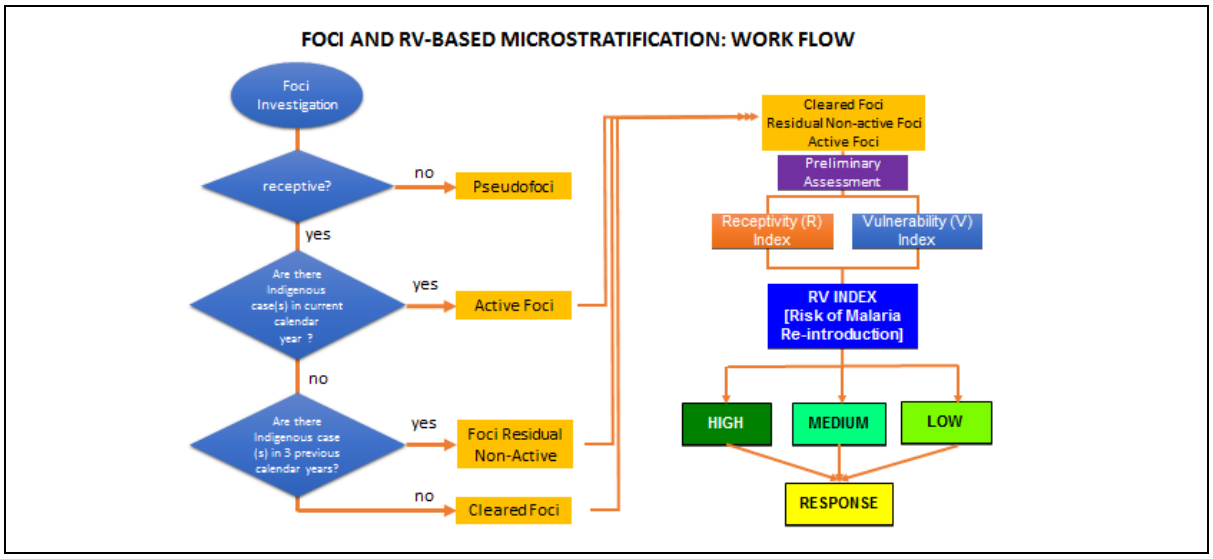
Stratification of reintroduction risk

The receptivity and vulnerability indices are multiplied together to produce a stratification of reintroduction index. This is then used to classify the malaria reintroduction risk as low (≤2), medium (3–5) or high (≥6).

An overview of the work flow for stratification based on the receptivity and vulnerability assessments is presented below (Fig. 10). The foci type and reintroduction risk index are then used to determine the appropriate interventions (Table 4).

Information to determine receptivity and vulnerability is entered online using MyFoci v2.0 software,[1] which automatically calculates some indices (e.g. receptivity, vulnerability and reintroduction matrix) and hence appropriate interventions.

Fig. 10. Work flow of foci and receptivity/vulnerability-based microstratification



Excerpt from presentation by J. Jelip.

Table 4. Response based on foci type and reintroduction risk index

TYPE OF FOCI	RV INDEX	INTERVENTIONS
Pseudofoci	–	• Case management (imported or relapse) • Passive case detection
Active foci	HIGH	
	MEDIUM	
	LOW	
Residual non-active foci	HIGH	• Epidemiological surveillance • Consider active case detection • Vector control (continuation) • Entomological risk assessment after six cycles of vector control
	MEDIUM	
	LOW	
Cleared foci	HIGH	• Epidemiological surveillance • Integrated vector management • Epidemic risk assessment every two cycles of vector control
	MEDIUM	
	LOW	• Case management (imported or relapse) • Passive case detection

4.3.2 Bhutan

Mr Rinzin Namgay presented on receptivity and vulnerability assessments for Bhutan, which has experienced a significant decline in malaria since a peak of 39 852 cases in 1994. In 2017, only 62 cases were reported. Most of the cases from 2013 to 2016 were non-Bhutanese; however, of the 62 cases in 2017, 38 were Bhutanese and 24 were non-Bhutanese. There has been no local transmission of *P. falciparum* in Bhutan since 2016. Contributing to the marked reduction in the number of malaria

[1] See http://myfoci.jknsabah.gov.my

cases were the massive deployment of rapid diagnostic tests (RDTs) and artemisinin-based combination therapies (ACTs) down to community level, and large-scale LLIN campaigns with two rounds of focal IRS, along with enhanced malaria surveillance. By 2010, the country had moved into the elimination phase. Bhutan is progressing well towards the stated goal of the National Malaria Strategic Plan 2015–2020, which is to interrupt indigenous transmission by 2018. However, there is an example from Samtse wherein after 5 years with no transmission, local transmission recommenced; this indicates how malaria can resurge.

Measurement of receptivity

The parameters considered in the receptivity assessment in Bhutan are shown in Table 5. The programme has three entomologists and five insect collectors, with malaria technicians in health centres being responsible for basic entomological services. The border populations live in close proximity and intermingle; therefore, a division by administrative boundaries makes little biological sense. The limits of malaria transmission are probably due to the interaction of extrinsic incubation period (EIP) and the longevity of the vectors.

Table 5. Malaria receptivity and its relevance and mitigation in Bhutan

Receptivity index	Relevance	Mitigation measures
Topography: low altitude, plain, forested foothills	Yes for proliferation and vectorial roles	High LLIN and IRS coverage in risk areas
Climate: more rain, humid, favourable temperature	Yes for vector proliferation and survival; people do not use nets during the hot season	High LLIN and IRS coverage in risk areas with IEC campaigns
Environment alteration: development, forestation or deforestation	Yes for vector proliferation and transmission	Control coverage and IEC
Border malaria: sporadic cases appear in border villages only	Yes – no reservoirs detected by RACD nor any imported cases to link	In addition to LLIN and IRS, fogging is done
Housing type: especially among people with a low income, migrant workers, cattle herders and crop guarders	Yes for more human–vector contact	LLIN coverage; IRS is often not applicable in temporary structures

IEC: information, education and communication; IRS: indoor residual spraying; LLIN: long-lasting insecticidal net; RACD: reactive case detection (Excerpt from presentation by R. Namgay).

Receptivity assessments indicate that seven districts fall in the high receptivity category, nine have pockets of receptivity and four have no receptivity for malaria. In terms of vulnerability, a number of vulnerable population types have been identified, along with their relevance to malaria transmission and mitigation measures for their protection from malaria (Table 6).

Measurement of vulnerability

Table 6. Malaria vulnerability and its relevance and mitigation in Bhutan

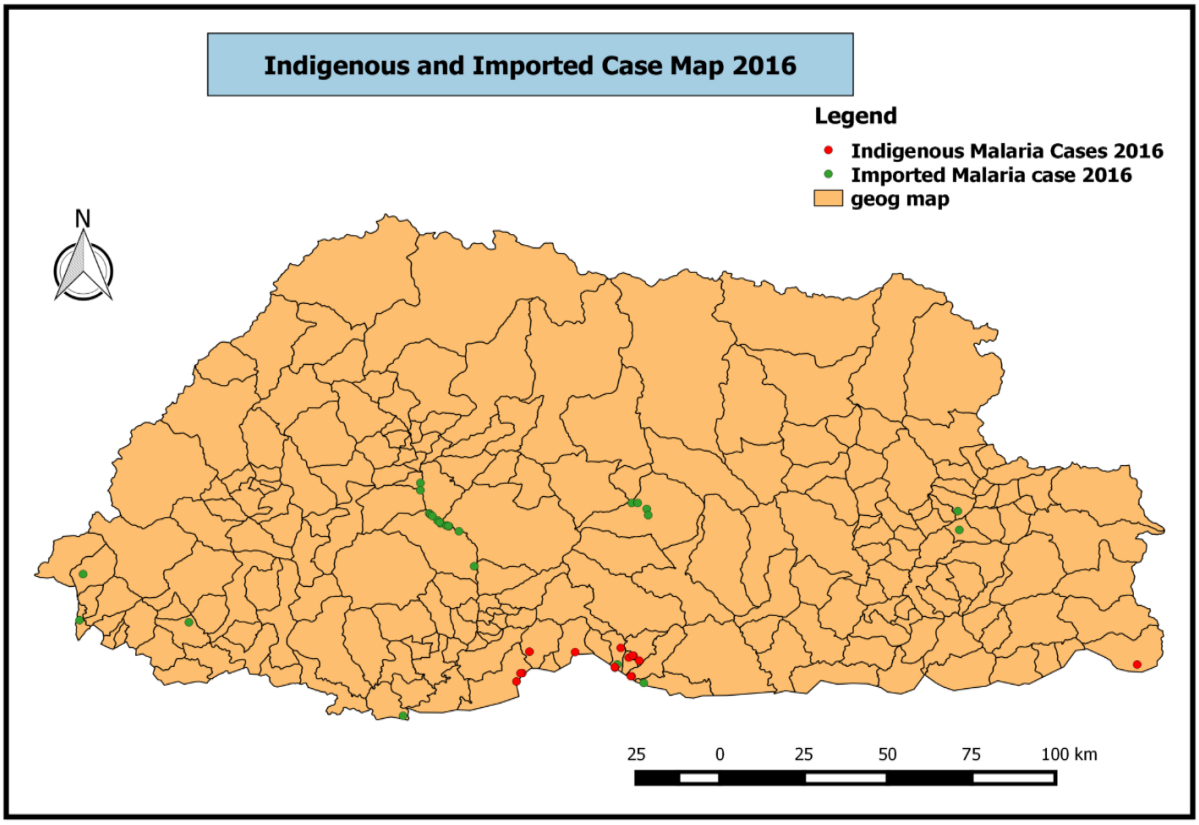
Vulnerable population type	Relevance	Mitigation measures
Migrant workers: hydroelectricity projects, public and private constructions (contractors bring workers in batches and are responsible for them getting screened)	65 000–70 000 per year (as per MoL)	• Mandatory screening at entry points by eight private clinics and report to VDCP • Rescreening at work site by health centres and VDCP • LLIN provision
Tourists: mostly to northern Bhutan	Unknown	No screening till now
Outgoing populations: UN peace keepers, students, business people, workers, pilgrims to India and Nepal	Programme trying to obtain information from relevant sources	Screening during return and rescreening after 1–2 weeks will be established
Uniform patrolling personnel: army, police, forest guards and community peace keepers		Odorous repellents supplied by programme
Visits: family visits across the border	Unknown	No screening unless reported to health centres

LLIN: long-lasting insecticidal net; MoL: Ministry of Labor; UN: United Nations; VDCP: Vector-borne Disease Control Programme (Excerpt from presentation by R. Namgay).

Anyone can access free malaria diagnosis, treatment and 3 days admission in health centres in Bhutan. Day workers and other population along border areas are registered as N3 in the malaria register, since they have not spent nights in Bhutan. However, these populations often do not consent to admission for 3 days, and cannot be traced for the requisite follow-up required to day 42. Therefore, completion of the course of treatment is often compromised.

The number of workers screened at the entry point by private clinics was outlined; the total was 2057 and 2537 in consecutive years, with wide variation in the number originating from neighbouring regions of India and elsewhere. Private clinics do not treat malaria; hence, all positive cases were referred to public health facilities. Geomaps of the number of indigenous and important cases were presented for 2016; they indicated that imported cases were predominantly from migrant workers from hydroelectricity projects in Punatsangchu I, Punatsangchu II, Mangdachu and Kholongchu (Fig. 11).

Fig. 11. Geomap of indigenous versus imported cases of malaria in Bhutan, 2016



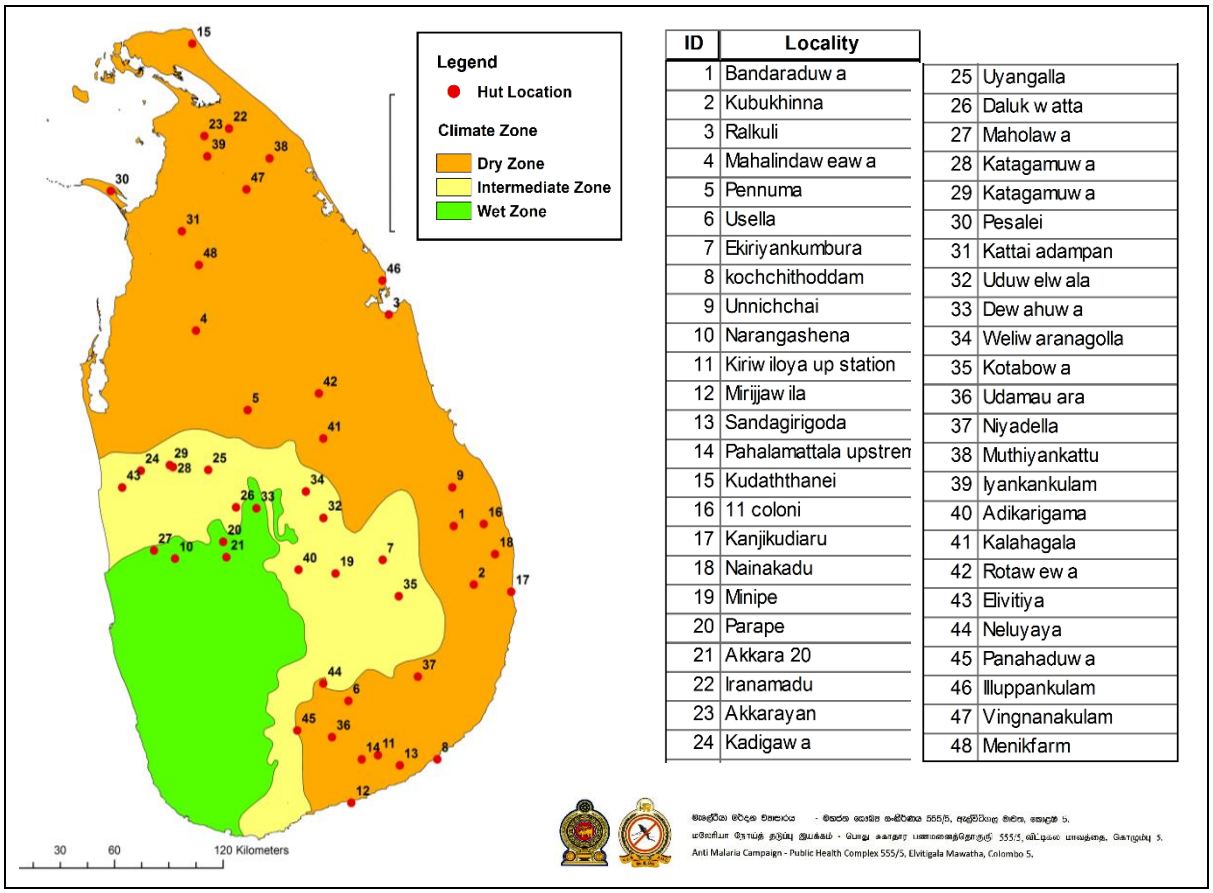
Excerpt from presentation by R. Namgay.

4.3.3 Sri Lanka

Ms Mihirini Hewavitharane presented on the experience from Sri Lanka on the assessment of receptivity and vulnerability for prevention of reintroduction of malaria. There has been no local transmission of malaria in Sri Lanka since October 2012, with the country certified as malaria free in 2016. Historical malaria transmission patterns in the country are considered a reflection of receptivity. Malaria was typically endemic in the dry and intermediate rainfall zones of the country with the wet zone becoming prone to malaria during exceptional dry conditions caused by a failure of the monsoons. The climatic pattern is determined by the monsoonal wind patterns in the surrounding oceans; 55% of the rainfall is monsoonal and the mean annual rainfall is 900–6000 mm. Based on the rainfall patterns and amount, the country is divided into three main climatic zones: dry, intermediate and wet zones. The climate of Sri Lanka is conducive to vector mosquito breeding and malaria transmission.

Malaria vectors in Sri Lanka have diverse breeding habitats, resting and biting behaviours, and seasonal patterns of abundance. They therefore vary in their potential for transmission of malaria. The principal malaria vector species present in the country has been *An. culicifacies*, with *An. subpictus* the secondary vector and *An. annularis* and *An. varuna* potential vectors. *An. stephensi* was recently found to be present in six districts of Sri Lanka. Extensive entomological information is collected on a routine basis in the country, through sentinel surveys, spot surveys and case-based reactive surveys. Sentinel sites are distributed throughout the three zones of the country, with sites in the wet zone positioned along the margins with the intermediate zone (Fig. 12).

Fig. 12. Distribution of entomological sentinel sites in 2017



ID	Locality
1	Bandaraduw a
2	Kubukhinna
3	Ralkuli
4	Mahalindaw eaw a
5	Pennuma
6	Usella
7	Ekiriyankumbura
8	kochchithoddam
9	Unnichchai
10	Narangashena
11	Kiriw iloya up station
12	Mirijjaw ila
13	Sandagirigoda
14	Pahalamattala upstrea
15	Kudaththanei
16	11 coloni
17	Kanjikudiaru
18	Nainakadu
19	Minipe
20	Parape
21	Akkara 20
22	Iranamadu
23	Akkarayan
24	Kadigaw a
25	Uyangalla
26	Daluk w atta
27	Maholaw a
28	Katagamuw a
29	Katagamuw a
30	Pesalei
31	Kattai adampan
32	Uduw elw ala
33	Dew ahuw a
34	Weliw aranagolla
35	Kotabow a
36	Udamau ara
37	Niyadella
38	Muthiyankattu
39	Iyankankulam
40	Adikarigama
41	Kalahagala
42	Rotaw ew a
43	Elivitiya
44	Neluyaya
45	Panahaduw a
46	Illuppankulam
47	Vingnanakulam
48	Menikfarm

Excerpt from presentation by M. Hewavitharane.

Measurement of receptivity

Entomological tools and indicators monitored in Sri Lanka to determine receptivity for prevention of reintroduction are:

- *Anopheles* spp. composition and densities (including seasonal fluctuations) measured monthly by larval surveys, cattle-baited trap collections, cattle-baited hut collections, indoor hand collections and pyrethrum spray catches;
- larval density by aquatic habitats measured via larval surveys;
- vector species behaviour in terms of indoor/outdoor resting measured via hand collections indoors and outdoors and pyrethroid spray catches;
- vector species human biting behaviour in terms of endophagy/exophagy and human biting rate measured monthly via human landing catches indoors and outdoors;
- mosquito age as indicated by parity rates for mosquitoes collected by human landing catches and ovary dissections;
- vector incrimination as indicated by sporozoite detection via salivary gland dissection and molecular techniques;
- insecticide resistance from knock-down and corrected mortality rate in susceptibility tests at sentinel sites; and
- bio-efficacy levels of insecticides used in vector-control interventions via bioassays on sprayed walls or nets.

The mean larval densities and adult densities of *An. culicifacies* in different districts have been used as an indication of receptivity, to identify receptive and non-receptive districts following elimination. Even after elimination of malaria some districts remain highly receptive, while some have moderate to low levels of receptivity. This information has been used for risk management and resource assignment for the districts.

However, it was well acknowledged that programmes require a quantitative measurement for receptivity for application in the prevention of reintroduction phase. This should support reorientation towards sustaining malaria eliminated status through a suitable entomological surveillance system which supports the decision-making. The large quantity of entomological data collections required reorganization in a way that would help in the assessment of malariogenic potential, and to reorient entomological surveillance and response. This requires identification of the geographical distribution and relative density of vector species and, particularly, identification of newly introduced vector species. It is also important to determine whether potential vectors have regained high vectorial efficiency in receptive areas, and to track the reaction of vectors to vector control to recommend measures to prevent reintroduction.

A workshop was therefore convened to provide guidance on the broad principles of entomological surveillance during the prevention of reintroduction of malaria phase and to supply information needed to produce risk assessments on malaria in receptive and vulnerable areas (Table 7). It also aimed to provide recommendations in the development of implementation strategy for routine entomological surveillance, and to initiate risk mapping. The outcome was a two-staged approach: it involved assessment of the history of malaria transmission (including outbreaks) and relative abundance of vectors and potential vectors (larvae and adults) and other entomological data collected in the last 3 years in order to generate a preliminary stratification of the areas according to receptivity risks (of high, medium and low); and the update of the map based on entomological data collected during spot checks (reactive), during spot checks (proactive) conducted in high, moderate and low vulnerable areas with no entomological data, and from spot checks at sites where vulnerability risk has increased.

Table 7. Receptivity measuring guide for Sri Lanka

No.	Factor	Possible scenario	Weighting
1	Presence of potential breeding places – primary, secondary or potential vectors	Permanent Semi-permanent Temporary Unavailable	3 2 1 0 (max. 6)
2	Discovery of the primary vector – *An. culicifacies* (larva) during the period of previous year	Yes No	3 0
3	Discovery of the secondary vector – *An. subpictus* (larva) during the period of previous year	Yes No	2 0
4	Discovery of the potential vector – *An. varuna, An. annularis*, (larva) during the period of previous year	Yes No	1 0
5	Discovery of the primary vector – *An. culicifaices* (adult) during the period of previous year	Yes No	3 0
6	Discovery of the secondary vector – *An. subpictus* (adults) during the period of previous year	Yes No	2 0
7	Discovery of the potential vector – *An. varuna, An. annularis*, (adults) during the period of previous year	Yes No	2 0
8	Human biting behaviour of primary vector – *An. culicifaices*	Positive Negative	4 0

No.	Factor	Possible scenario	Weighting
9	Human biting behaviour of secondary vector – *An. subpictus*	Positive Negative	3 0
10	Human biting behaviour of potential vector – *An. varuna, An. annularis*	Positive Negative	2 0
11	Resting behaviour of primary vector – *An. culicifacies*	Endophilic Exophilic	3 2
12	Discovery of parous vectors	Yes No	2 0
13	Conducive environment conditions or presence of developmental projects creating more breeding sites	Yes No	2 0

Excerpt from presentation by M. Hewavitharane.

Information from receptivity measurements as in Table 7 was used to generate a vulnerability level of high, moderate and low risk (Fig. 13a), where low is less than 4, medium is 4–8 and high is greater than 12.

If infected *Anopheles* spp. are detected then receptivity categorization should be "high", regardless of other factors. Similarly, if life stages (larva or adult) of *An. stephensi* are detected, receptivity categorization should be "high", regardless of other factors. If more than one possible scenario is present, then all are considered for the weighting.

The approach presented is an initial attempt to quantify receptivity, but further technical guidance and refinement may be needed. It took into account only the presence of vectors, vector bionomics and environmental factors conducive to vector breeding and abundance. Thresholds were identified based on weighted measures and varied from 0 to 36; however, the resulting stratification and assessment approach have not been validated. The stratification is currently conducted by Sri Lanka's MoH, although it would be preferable for this to be devolved to the locality. At present, there are also no comprehensive entomological surveillance data available from the previously nonendemic yet currently highly vulnerable areas, such as Western Province.

Measurement of vulnerability

In Sri Lanka, the principal evidence in favour of a case being imported is considered to be one of the following:

- travel history overseas to a malaria endemic country in the recent past;
- a past history of malaria when the person was overseas, in which case a relapse would also be considered if the malaria was *P. vivax* or *P. ovale*;
- absence of a malaria infection or evidence of malaria transmission in the location of the patient's residence in Sri Lanka after the patient's return, particularly based on the case investigation and entomological surveillance conducted in response to a case; or
- a malaria infection in a co-traveller.

Risk management requires an assessment of vulnerability for a given area in a certain period of time. Therefore, steps were taken to assess vulnerability, taking into account the importation of malaria cases, as well as high-risk groups in the country after malaria elimination. An effort to quantify vulnerability in the country in a more standard manner was attempted in late 2017 (Table 8).

Table 8. Vulnerability measuring guide for Sri Lanka

No.	Factor	Weightage	Possible scenario (and weightage)
1	Number of imported malaria cases in the previous 3 years	0.5 per case	In the absence of specific guidelines for countries in elimination or prevention of reintroduction on effective ways of vulnerability mapping, the geographical distribution of imported malaria cases over the recent years has been considered as a proxy measure
2	Locality with high risk of importing malaria	4 (maximum)	• Ports of entries (2) • Illegal entry routes (2) • Tourist areas (1) • Asylum camps (1) • Detention camps (1) • Resettlement areas (1) • Camps for security forces (1)
3	Presence of immigrant population from malaria endemic countries	5	• Illegal (3) – fishers, agricultural workers from India, etc. • Legal (2) – foreign workers
4	Local people working in high-risk sector in malaria endemic countries	4 (maximum)	• Gem traders and miners (2) • Businesspeople (1) • UN peace-keeping missions (1) • Professionals (1)
5	Local people returning from malaria endemic countries within 1 year	2	• Pilgrims (1) • Returnees from safari (1)
6	Localities at close proximity to India – risk of importing infected mosquitoes	2	Coastal borders with anchorage facilities

Excerpt from presentation by M. Hewavitharane.

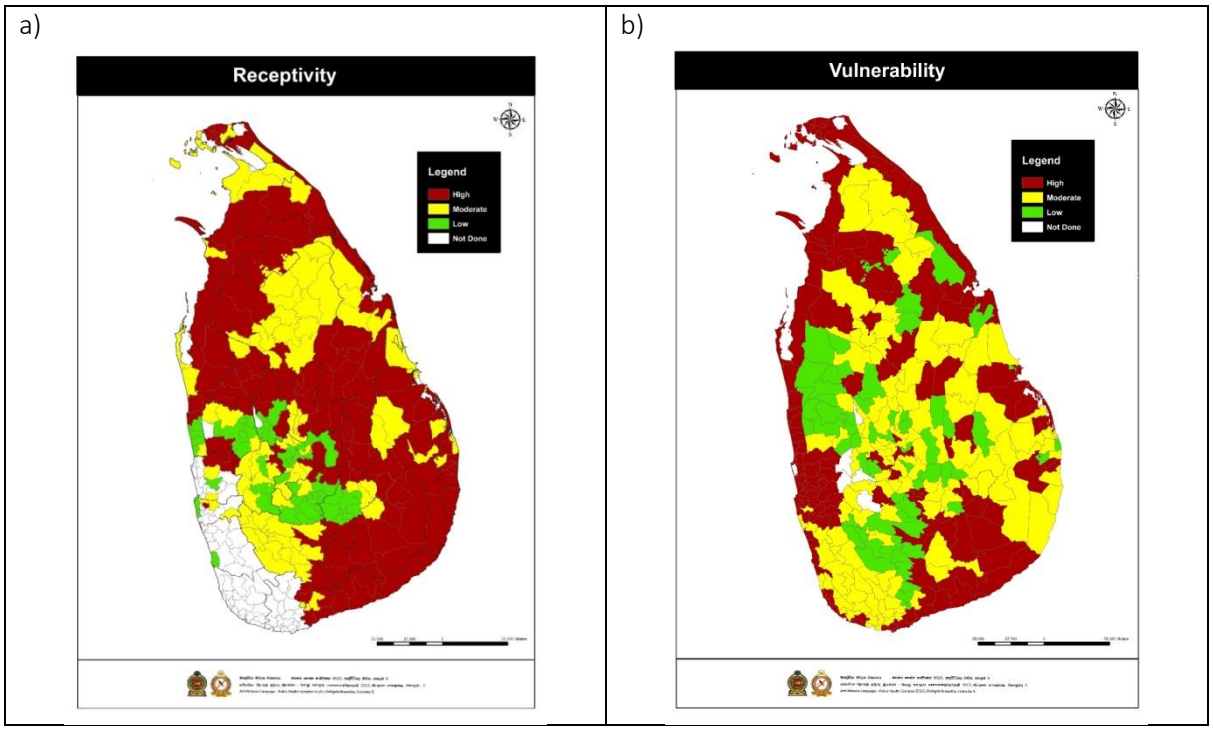
Most of the imported malaria cases were identified as Sri Lankans returning from travel to malaria endemic countries, with foreign nationals coming to Sri Lanka constituting 28–38% of imported malaria cases during the past 5 years. Most cases of imported malaria were contracted in South-East Asia, with India as the single largest source. Travel is quite extensive between India and Sri Lanka, owing to Sri Lankan business travellers, pilgrimage and Indian migratory labour. Pakistan contributed to imported malaria, with almost all cases being asylum seekers. The African continent accounted for most of the cases during the past 2 years, with Sri Lankans travelling there for business, tourism and peace-keeping missions; there were also cases imported by foreigners. Within Sri Lanka, most of the imported cases were reported from the Western Province, which is a previous nonendemic area. This is in contrast to the districts reporting indigenous malaria in 2011 and 2012. Thus, it can be concluded that highly vulnerable districts and receptive districts are quite distinct, with little overlap between them.

The identified high-risk groups for Sri Lanka were foreigners, especially those from India (workers), Pakistan (asylum seekers) and China (workers); Sri Lankans with a travel history to a malaria endemic country; travellers returning from Africa for occupation (gem business) and leisure tours; travellers returning from Asia (e.g. pilgrims, businesspeople or those travelling for study or leisure); armed forces personnel returning from peace-keeping missions and training; and Sri Lankan refugee returnees from India.

Information from vulnerability measurements as in Table 8 was used to generate a vulnerability level of high, moderate and low risk (Fig. 13b), where low is less than 2, moderate is equal to 2 or greater but lower than 4, and high is equal to 4 or greater.

A number of challenges and gaps were identified for vulnerability assessments. Imported malaria has been considered as a reasonable proxy for measuring vulnerability, but it requires a higher degree of vigilance. It requires sustained efforts for an active surveillance strategy to detect imported cases, strong awareness of the system among health staff and communities, involvement of international partnerships, intersectoral collaboration between local institutions, field vigilance and sustained financial commitment. However, there are difficulties with locating high-risk groups such as pilgrims.

Fig. 13. Map of a) receptivity and b) vulnerability for Sri Lanka



Excerpt from presentation by M. Hewavitharane.

Composite index

A composite index was developed that combined the receptivity and vulnerability index (Table 9).

Table 9. Classification of Sri Lanka MoH areas according to receptivity and vulnerability

	Receptivity		
Vulnerability	**Low**	**Moderate**	**High**
Low	(Low risk)	(Low risk)	(Moderate risk)
Moderate	(Low risk)	(Moderate risk)	(Moderate risk)
High	(Moderate risk)	(Moderate risk)	(High risk)

Excerpt from presentation by M. Hewavitharane.

Periodic updates of receptivity and vulnerability assessments are required because of changes in the ecosystem. There is a need to develop and validate thresholds that inform appropriate stratification, and it would be best if such efforts were guided locally rather than centrally. Further technical guidance and refinement are required.

4.4 Proposed methods for assessing infectivity

Elimination of malaria vectors is generally unattainable; hence, the strategic objective of vector control is conventionally to reduce vectorial capacity below the threshold for sustained malaria transmission. Despite the interruption of transmission of malaria in many countries, and from extensive areas within other countries, *Anopheles* malaria vectors remain entrenched throughout most of their natural ranges. Endemic anthropophilic *Anopheles* spp. mosquitoes are mostly susceptible to exotic strains of human malarias, although some *Anopheles* show refractory parasite–vector interactions, depending on the imported *Plasmodium* species and strain.

Such parasite–vector specificities influence the receptivity of an area to local malaria transmission in the event of an imported infection. The phenomenon of "anophelism without malaria" was recognized by early malariologists, whereby *Anopheles* mosquitoes existed in regions that were not malarious, although they could have been, given the climatic and ecological conditions. Information on these specificities may therefore be of use in guiding programmatic responses, such as to de-prioritize vector control where an imported case is caused by a parasite strain to which local vectors are known to be refractory.

4.4.1 Review of mosquito susceptibility to imported exotic malaria parasites

Professor Graham White presented results from a systematic review of literature on the susceptibility of endemic *Anopheles* spp. mosquitoes to imported exotic strains of human malaria parasites. This susceptibility, or potential to become infective, is termed "vector competence", and is defined as the "*ability of the mosquito to support completion of malaria parasite development after zygote formation and oocyst formation, development and release of sporozoites that migrate to salivary glands, allowing transmission of viable sporozoites when the infective female mosquito feeds again" (1)*. The review catalogues species reports from various countries classified as malaria endemic, approaching elimination or malaria free, and includes a summary table of examples of the range of *Anopheles* competence to human malaria parasites. A concise overview of *Anopheles* competence or incompetence to *P. falciparum* and *P. vivax* originating from different malaria zones was also presented (Annex 4).

Professor White stressed the importance of understanding the bionomics and behaviour of all the vector species responsible for *Plasmodium* transmission to humans, rather than reliance on information generalized to species complex or group level. For vector control and surveillance, it is essential to distinguish between similar species having differential vectorial capacity or contrasted vector competence.

The ERG discussed the alarming recent expansion of *An. stephensi* as an urban malaria vector from the Indian subcontinent to Sri Lanka and the African continent, first in Djibouti and then in Ethiopia, and indicated that this issue requires further consideration and potential intervention by WHO.

Because the 12 main malariological regions are defined by their competent species of malaria vectors, the ERG concluded that there are no broadly applicable demonstrated regional incompatibilities between human malaria parasites and their vector species. Hence, the working assumption should be that none of the proven malaria vectors are refractory to specific *Plasmodium* parasite strains. Further investigations of interactions between strains of *Plasmodium* and *Anopheles* spp. are warranted; if clear cases of incompetence or low competence are identified, this may be informative for decision-making on the level of response required to decrease vectorial capacity.

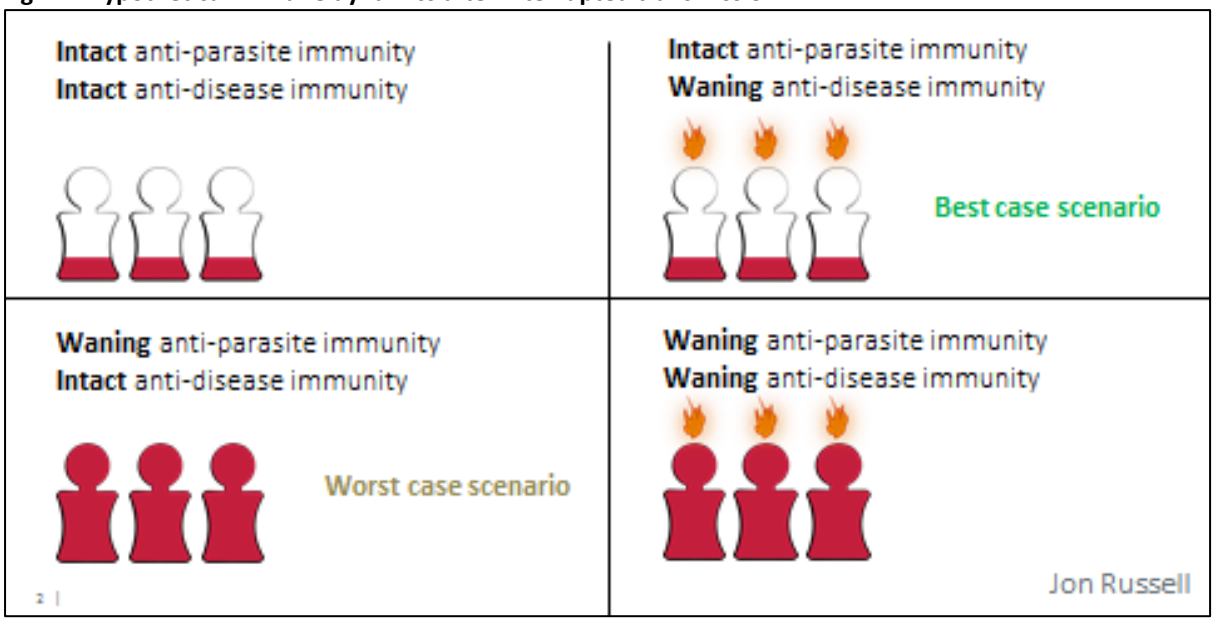
The ERG was informed of the approach taken in China, whereby the response to imported cases caused by *Plasmodium* spp. originating from countries of South-East Asia is given higher priority than the response to those imported from Africa, putatively based on differential competence of the main vector *An. sinensis*. The scientific evidence used to inform this approach was not reviewed by the ERG. Therefore, it was recommended that a case study be conducted to examine and document the evidence for refractoriness of *An. sinensis* to Afrotropical malarias, such as the well-established incompetence of European *Anopheles* spp. to transmit African strains of *P. falciparum (31, 32)*.

4.5 Stratification and intervention mixes

Dr Jaline Gerardin presented on the effectiveness of intervention mixes, as stratified by vulnerability and receptivity. This included a consideration of hypothetical immune dynamics after the interruption of transmission, based on two predominant components of malaria immunity: anti-parasite immunity (or immunity to high parasite density) and anti-disease immunity (or immunity to developing symptoms, even though infected) (

Fig. 14). These types of immunity are considered separately here to isolate their impact on human infectiousness (anti-parasite immunity) and the ability of the surveillance system to detect new infections (anti-disease or anti-symptom immunity). If both components of immunity remain intact through elimination, then it would be expected that an outbreak would result in multiple lower density infections for which individuals are largely asymptomatic. Conversely, if both components of malaria immunity wane through elimination, then it would be expected that higher density infections would result in symptomatic cases. Noting that immunity is complex, in fact the result could also be low-density infections leading to visible symptoms, or high-density infections leading to numerous asymptomatic individuals.

Fig. 14. Hypothetical immune dynamics after interrupted transmission



Excerpt from presentation by J. Gerardin.

Analyses based on earlier data from Garki, Nigeria, indicated that asexual parasite densities for new infections tend to increase with an increase in the malaria free interval (comparing <80 days with >365 days) for individuals aged more than 5 years, 5–11 years and more than 11 years *(33)*. In this analysis, individuals are considered to experience a "malaria free interval" when they are slide negative during a routine cross-sectional prevalence survey. However, it is possible these individuals

may not be malaria free but rather free from patent infection, or that they may be experiencing short infections during the 1 month between surveys. Analyses using recent field data from Tororo, Uganda, did not identify a clear trend in the detection of new infections with fevers following a malaria free interval of between 0 and 600 days, for those aged more than 5 years, 5–11 years or more than 18 years *(34)*. Although data were relatively sparse (especially for adults) and further investigations are underway, this finding indicates that new infections may not be significantly more likely to be symptomatic after a malaria free interval of less than 2 years. Therefore, should importations happen in an area with previously high levels of population immunity, transmission may be fairly easily re-established owing to individuals who are largely asymptomatic but have higher density infections and are more infectious (i.e. the bottom left quadrant of

Fig. 14). Such immune dynamics in the short term (i.e. 2–3 years) could present operational challenges to maintaining elimination, but much more evidence is needed.

Results from a modular agent-based model using Epidemiological MODeling software (EMOD) were presented *(35)*. Used for simulation modelling of other diseases (e.g. HIV and tuberculosis), the malaria model was developed to support data-driven malaria control and elimination efforts. It combines detailed vector population dynamics and interactions with human populations, and includes microsimulations for human immunity and within-host parasite dynamics. The model builds on the work of Ross and MacDonald, leverages the Garki model, and incorporates current modelling efforts to model multiple vector species simultaneously interacting with a human population. Simulation modelling presented drew on data from the Lake Kariba region, which borders Zambia and Zimbabwe, because this represents a setting with diverse transmission dynamics for which a relatively rich data set is available *(36, 37)*.

Outcomes of the simulation modelling from the Lake Kariba region indicated that in an area with historically limited vectorial capacity, good case management (i.e. 50–75% of symptomatic cases treated) alone was sufficient to prevent resurgence, and fair case management (i.e. 50% treatment rate) could be compensated by good reactive case detection (i.e. 50% of treated cases receive follow-up). However, in an area with a historically high transmission before recent elimination, vector control must be maintained along with continuing excellent case management rates and reactive case detection. Modelling also indicated that reactive IRS may be as effective as, or more effective than, routine IRS, even when it results in 10-fold fewer houses being sprayed. Treatment rates, vector-control coverage and appropriate radius of reactive activities necessary to maintain elimination in these areas depend on the degree of household clustering, in that denser areas require more intense interventions.

It was also indicated that the current use of “asymptomatic individuals” is not useful from a programmatic perspective, because it is difficult to define given differences in factors such as what would be considered “symptoms” (e.g. is this limited to fevers only or does it consider other effects such as anaemia), the time of day of testing and health care seeking behaviour.

5. Conclusions

The ERG considered malariogenic potential to be an important concept and noted the urgent requirement for a clear definition of the term and of its components. In particular, it was noted that the definition of “receptivity” as appears in the WHO malaria terminology document is ambiguous and circular. The ERG also felt that use of the term “vulnerability” is at odds with its use in common parlance in the fields of health and development. The ERG discussed the appropriate scope and wording of definitions, and reached consensus on the proposed definitions. These definitions are included below, and in the recommendations section.

5.1 Receptivity

In terms of assessing receptivity, the ERG identified three methods based on the evidence presented:

- historical data
- entomological composite methods
- R_0/R methods.

Discussion points and conclusions related to each of these methods, as well as their utility in determining malariogenic potential, are outlined below.

Historical data

Many programmes use data from recent years to assess receptivity of areas as elimination is approached, and to prioritize surveillance to prevent re-establishment following malaria elimination. Data from more than 3 years ago are not used for receptivity estimates in Bhutan, Malaysia and Sri Lanka because it was indicated by the presenters that older data may not accurately reflect the current situation owing to ongoing changes in the ecosystems (including health systems). The ERG agreed that the appropriate duration (i.e. number of years) of data to be used will depend on the context and changes in the ecosystem, and should be decided upon by the individual programme. However, the ERG felt that older data can provide a useful baseline for assessment of receptivity. Data should be examined in the context of the interventions in place at the time and how these have changed since, and should consider changes in the ecosystem. Examples of such data types include entomological data, API, parasite prevalence and case counts; such data would need to have been collected before the implementation of current control measures to be informative about what might happen in the absence of such interventions. Data from serological surveys may be useful, although this approach has not yet been standardized and validated – a review of the evidence from such surveys was deemed to be beyond the scope of the meeting.

Entomological composite methods

The examples presented by Malaysia and Sri Lanka were developed by countries with significant entomological capacity. Data collected included adult vector occurrence and density; immature vector aquatic habitat availability and occupancy, and larval density; adult vector biting and resting behaviour; insecticide resistance frequency and status; and sporozoite rates. However, the ERG noted that this level of entomological surveillance may not be realistic in all countries undertaking prevention of re-establishment of malaria activities. On the basis of the evidence considered, the ERG concluded that a smaller number of key entomological indicators should be monitored as a minimum, in the context of prevention of re-establishment. These indicators are described in *Malaria surveillance, monitoring & evaluation: a reference manual (2)*; they are vector adult occurrence (high priority), resistance (moderate priority) and aquatic habitat surveys (but only if larval source management is considered or ongoing). It was also noted that investigating the identity of principal and secondary vectors should be a priority in settings where vector incrimination has not been comprehensively conducted or where such studies date back to the control phase of the programme. Programmes should also consider reducing insecticide resistance monitoring frequency to once every 2 years in prevention of re-establishment settings. Overall, it was thought that further investigation into key components of vectorial capacity following earlier work by Dye *(16)* would be valuable, to further focus entomological surveillance efforts.

Once transmission has been interrupted, adjustment of entomological surveillance strategies will be required to guide appropriate response, such as selection of vector-control intervention (e.g. selection of insecticides for IRS depending on resistance status). This is especially important if a programme is considering scaling back vector-control interventions based on enhanced capacity for focal response and a review of the malariogenic potential of the area.

The ERG felt that baseline entomological data can also be informative for identifying high-risk areas but that the selection of sites for ongoing surveillance should be further informed by changes in the ecosystem and context. The appropriate sampling frame (i.e. number and location of sites) for a representative sample will depend on the context and available resources. The ERG indicated that clearer WHO guidance on sentinel site selection and frequency or timing of surveillance would be of use in ensuring that the appropriate approach and extent of monitoring is undertaken. Specific situations or concerns may warrant intensified surveillance to guide response, such as if invasive species are suspected or identified, as for *An. stephensi*.

R_0/R_e methods

The methods of estimating risk from the basic reproductive number and the effective reproductive number capture both vector and human aspects. Counts of imported versus locally acquired cases (and their ratio) were noted as being useful where the quality of surveillance data is high. Probabilistic methods can be used to link local cases to imported cases based on plausible distance in time and space, to determine the risk of re-establishment. However, a more standardized definition to classify imported cases is required for these methods to provide estimates of risk that can be compared between countries.

Selection of receptivity measures

The ERG noted that there has been no validation or comparison of the three potential measures of receptivity, nor an examination of their complementarity. An aggregate approach considering historical transmission data, entomological data and calculation of effective reproductive numbers from the ratio of imported to indigenous cases importation risk may be required, even within a single country. Guidance on the minimum quality of data required would be useful. The ERG indicated that further development of these methods is required to make them applicable and informative for programmatic use.

5.2 Importation risk

Because "vulnerability" also refers to the potential for being harmed and is used in public health to refer to disadvantaged or at-risk populations, the ERG recommended that the term should not be used to refer to importation risk, especially when a clear and unambiguous term is available.

The ERG acknowledged that there are multiple methods and measures for importation risk, the relevance of which will be heavily dependent on the local context. However, it is important that the unit of interest for importation risk – including cross-border and subnational movement – be the same as or able to be correlated to the unit at which receptivity is assessed. The primary measure should be case-based surveillance that determines travel history as related to malaria risk. The surveillance system may not encounter all imported cases, and attempts should be made to capture all cases if possible, including population movement to and from areas (e.g. residents returning from endemic countries).

Participatory focus group discussions and key informant interviews exemplified in the presentation from the IOM can be used to identify major human movement patterns and factors related to malaria importation risk. Human movement patterns can be similar across areas; thus, programmes may be able to generalize imported cases from one area to other areas that have similar population influxes. Importation of infected mosquitoes is likely to be an issue, mainly at land boundaries geographically adjacent to those with ongoing malaria, or along major human or goods transportation routes.

Efforts to describe malaria importation risk should ensure that data are captured from other sectors of the health system (e.g. other ministries and local government authorities), including data on movement of visitors, the military, peace-keeping forces and migrants. Where possible, stratification by occupational risk, age, gender, season and economic status should be considered. Census population surveys can give an indication of general levels of influx and connectivity to endemic

countries, and hence can provide a proxy for risk of importation. Mobile phone data may be of use for determining population movement, although this will require close engagement with service providers and utility will depend on mobile phone ownership and use within and between countries.

The utility of border screening to measure importation risk is unclear. A review of the data – for example, comparison of infections identified through border or workplace screening compared with passive case detection at clinics – is needed to ascertain whether border screening is informative.

5.3 Infectivity

The ERG noted that the proposed updates to the definitions would mean that mosquito vector competence (or infectivity) is included as a component of vectorial capacity and would therefore be a component of receptivity. The variations in receptivity of *Anopheles* mosquito species (and populations) to exotic *Plasmodium* species (and strains) revealed by the literature review may mean that this compatibility is a driver of receptivity – or lack of receptivity – of the local ecosystem to transmission of particular parasite strains, such as a strain from another continent. This parasite–vector infectivity specificity should be adequately acknowledged in related WHO documents, including the vector competence entry in the WHO malaria terminology document.

Further information on infectivity may be gleaned from an examination of outbreak data from countries that eliminated malaria, after determining the origin of the imported parasite strains and the number of resultant infections transmitted by local mosquitoes. For this, the surveillance system must capture the origin of cases, and programmes would need to review their data periodically to ascertain which imported cases led to onward transmission (or otherwise). In particular, the generation and use of vector competence data in China to guide action (e.g. de-prioritization of responses to Africa *P. falciparum* imported cases) may present a good example that may be applied elsewhere.

5.4 Malariogenic potential

The ERG noted that the components of malariogenic potential – receptivity and importation risk – have some overlap in the way they are measured. A pragmatic approach should be taken during the assessment of malariogenic potential; the approach should use surveillance data to validate assumptions of receptivity and importation risk, and use these to refine estimates. For instance, adjustment of receptivity estimates should be informed by examining transmission in relation to importation risk; for example, when the importation risk is high but onward transmission is low, then receptivity may be relatively low. The priority should be measurement of receptivity in areas with high importation risk, and vice versa.

Further work will be needed to define relevant thresholds for receptivity and risk of importation to inform programmatic decisions. Modelling may be helpful to inform relevant thresholds. Ongoing modification of thresholds and classifications will be required due to local specificities; this should be informed by local information rather than predetermined on a national basis.

6. Recommendations

On the basis of the evidence reviewed and discussed, the ERG recommended the following to MPAC:

1. Update the *WHO malaria terminology* document *(1)* be updated as follows:
    a. Add or update terms as shown in the table below.

Action	Term	Definition and comments
Add	Malariogenic potential	Likelihood of local transmission that is the product of receptivity, risk of importation of malaria parasites and infectivity of imported parasites. *Note: The concept of malariogenic potential is most relevant for elimination and prevention of re-establishment when indigenous transmission is mostly or entirely eliminated.*
Update	Receptivity	Degree to which an ecosystem in a given area at a given time allows for the transmission of *Plasmodium* spp. from a human through a vector mosquito to another human. *Note: This concept reflects vectorial capacity, susceptibility of the human population to malaria infection, and the strength of the health system, including malaria interventions. Receptivity can be influenced by ecological and climatic factors.*
Update	Vulnerability	Likelihood of malaria infection based on living conditions or behavioural risk factors, or likelihood of increased risk of severe morbidity and mortality from malaria infection.
Update	Importation risk	Risk or potential influx of parasites via infected individuals or infected *Anopheles* spp. mosquitoes. *Note: "Infected individuals" includes residents infected while visiting endemic areas as well as infected immigrants.*
Add	Infectivity	Ability of a given *Plasmodium* strain to establish an infection in an *Anopheles* mosquito species and undergo development until the mosquito has sporozoites in its salivary glands.

    b. Align all cross-references to these terms throughout the WHO malaria terminology document, with the final agreed upon definitions for the terms listed above.
2. Update the WHO *Malaria surveillance, monitoring & evaluation: a reference manual (2)* to:
    a. more clearly articulate the importance for entomological surveillance to identify principal versus secondary vectors, given ongoing and likely temporal and spatial changes in vector distribution and abundance; and
    b. provide more detailed guidance on site selection, and on the frequency and timing of entomological surveillance, to inform assessment of receptivity.
3. Revise other current WHO guidance documents in line with points (1) and (2), to ensure consistency.
4. Give priority to further development of methods for assessing malariogenic potential (receptivity, importation risk and infectivity) to ensure that these are applicable and informative for programmatic use. This includes:

a. comparison of methods for the three potential measures of receptivity for selected countries, to ascertain comparability within countries, between countries or between neighbouring regions, to inform their use in receptivity assessments;

b. comparison of entomological parameters, as well as each of their associations with parasitological indicators, to identify key components that should be included in assessment of receptivity;

c. examination of outbreak data from certified countries, to determine the origin of the imported parasite strains and the number of resultant infections;

d. comparison of existing data on infections identified through border or workplace screening with those identified through passive case detection at clinics, to ascertain whether information from passive case detection provides an accurate picture of importation risk; and

e. examination of examples where countries can generalize data on imported cases for populations in specific regions to other areas with similar population movement or influxes.

5. After relevant and feasible methods for measurement of the components of malariogenic potential have been identified, interpret these measurements and develop thresholds to guide programmatic decision-making regarding maintenance of vector control and intensified surveillance.

6. Further evaluate the issue of infectivity with respect to the mosquito and parasite factors that may reduce vector competence for different strains of *Plasmodium,* to determine whether there are programmatic implications for these findings. This may require additional review of evidence in future.

The ERG members also suggested that WHO consider developing a more standardized approach to classifying imported cases that is appropriate across different settings, as there is currently ambiguity on this issue. This topic was, however, considered beyond the scope of the current ERG.

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Abbreviations

AIDS	acquired immunodeficiency syndrome
API	annual parasite index
DOI	declaration of interest
EI	entomological investigation
ERA	entomological risk assessment
ERG	evidence review group
ESPT	entomological surveillance planning tool
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Global Malaria Programme
HBMM	Health, Border and Mobility Management
HIV	human immunodeficiency virus
IOM	International Organization for Migration
IRS	indoor residual spraying
ITN	insecticide-treated mosquito net
IVM	integrated vector management
LLIN	long-lasting insecticidal net
MoH	ministry of health
MPAC	Malaria Policy Advisory Committee
NMCP	national malaria control programme
PAKEPA	*Penilaian Awal Kesesuaian Ekologi Pembiakan Anopheles*
PA*Pf*$PR_{2–10}$	population-adjusted *Plasmodium falciparum* prevalence in children aged 2–10 years
*Pf*PR	*Plasmodium falciparum* prevalence
Pf$PR_{2–10}$	*Plasmodium falciparum* prevalence in children aged 2–10 years
PoE	point of entry
R_0	basic reproductive number
R_e	effective reproductive number
R_C	controlled reproductive number
Tg	generation time
WHO	World Health Organization

Annexes

Annex 1. Agenda

Tuesday, 2 October 2018		
09.00 – 09.10	Opening remarks and welcome	Pedro Alonso
09.10 – 09.20	Declaration of interests	Jan Kolaczinski
09.20 – 09.40	Background, objectives and expected outcomes WHO guidance on prevention of re-establishment	Jan Kolaczinski and Kim Lindblade
Part I: Proposed methods for assessing receptivity		
9.40 – 10.30	Systematic review of assessment of receptivity	Josh Yukich
10.30 – 10.45	Discussion	Chair
11:15 – 11:45	Bayesian geospatial approaches to assessment of receptivity	Abdisalan Noor
11.45 – 12.00	Discussion	Chair
12.00 – 12.30	Estimation of R0 to assess receptivity	Azra Ghani
12.30 – 12.45	Discussion	Chair
13.45-14.15	Experiences with the entomological surveillance planning tool to measure receptivity	Adam Bennett
14:15-14:30	Discussion	Chair
14.30 - 15.30	National programme experiences with assessing receptivity • Malaysia • Bhutan • Sri Lanka	Jenarun Bin Jelip Rinzin Namgay Mihirini Hewavitharane
15.45 – 16.00	Discussion	Chair
16.00 – 16.30	Initial conclusions on assessing measures of receptivity	Chair
Wednesday, 3 October 2018		
Part II: Proposed methods for assessing vulnerability		
09.00 – 09.45	Approaches to assessing vulnerability to imported parasites	Andy Tatem
09.45 – 10.00	Discussion	Chair
10.00 – 10.30	Assessment of vulnerability through tools developed by the International Organization for Migration	Carlos Van Der Laat
10.30 – 10.45	Discussion	Chair
11.15 – 12.15	National programme experiences with assessing vulnerability • Malaysia	Jenarun Bin Jelip Rinzin Namgay Mihirini Hewavitharane

	• Bhutan • Sri Lanka	
12.15 – 12.30	Discussion	Chair
12.30 – 13.00	Initial conclusions on assessment of vulnerability	Chair
Part III: Proposed methods for assessing infectivity		
14.00 – 14.45	Systematic review of the susceptibility of mosquitoes to imported exotic malaria parasites	Graham White
14.45 – 15.30	Discussion and initial conclusions on infectivity	Chair
Part IV: Stratification and intervention mixes		
16.00 – 16.30	Effectiveness of intervention mixes stratified by vulnerability and receptivity	Jaline Gerardin
16.30 – 16.45	Discussion	Chair
16.45 – 17.00	Programme of work for the following day	Jan Kolaczinski
Thursday, 4 October 2018		
Part V: Group discussion		
09.00 – 10.30	Conclusions on: • assessment of receptivity and approaches to identifying meaningful thresholds • assessment of vulnerability and approaches to identifying meaningful thresholds • review of infectivity • priority research questions	Chair
11.00 – 13.00	Continue discussion, as above	Chair
Part VI: Closed session (ERG members and WHO Secretariat only)		
14.00 – 15.00	Finalization of recommendations	Chair
15.00 – 15.30	Meeting closure	Jan Kolaczinski and Kim Lindblade

Annex 2. List of participants

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Annex 3. Declarations of interest

All ERG members and technical experts participating in the meeting submitted declaration of interest (DOI) and confidentiality undertaking forms. DOI forms were assessed by the WHO Secretariat. The following participants declared interests that required further consideration and discussion with the WHO Office of Compliance, Risk Management and Ethics.

Professor Azra Ghani is employed by the School of Public Health, Imperial College London in the United Kingdom of Great Britain and Northern Ireland. She reported the following potential conflicts of interest related to the topic of the meeting:

a. Received travel support (airfare) for meetings with GlaxoSmithKline in Belgium between 2011 and 2015.

b. Conducted mid-term independent evaluation of United Kingdom Department for International Development malaria programme for Oxford Policy Management, with over US$ 5000 received in 2013.

c. Conducted consultancy projects with Global Fund for which she received over US$ 5000 between 2016–2017.

d. Received academic grant funding from multiple organizations (Bill & Melinda Gates Foundation, Innovative Vector Control Consortium, Malaria Vaccine Initiative, Medical Research Council (Gambia), Medicines for Malaria Venture, National Institutes of Health, Wellcome Trust) of over US$ 5000 over 3 years.

e. Serves as a Charity Trustee for Malaria No More United Kingdom without funding provided.

In an email exchange on 27 September 2018, Professor Ghani clarified that none of the research funding she receives relates directly to the subject of the meeting, except for the Wellcome Trust, but that funding is provided for a PhD student and the funders have no direct relationship with her. All the declarations (a–e) were considered insignificant potential conflicts of interest because they are unlikely to affect the expert's judgement.

Dr Justin Cohen works for Clinton Health Access Initiative, Boston, United States of America (USA) and reported two potential conflicts of interest related to the topic of the meeting:

a. Employed as Senior Director for Global Malaria in which capacity he and his team are paid to assist governments with issues related to the topic of the meeting.

b. Received several grants from the Bill & Melinda Gates Foundation, United Kingdom Department for International Development and Malaria No More United Kingdom to assist governments with work related to the topic of interest.

In an email exchange on 28 September 2018, Dr Cohen clarified that there is a grant of over US$ 5000 from the Bill & Melinda Gates Foundation and over US$ 5000 from the US Centers for Disease Control and Prevention (CDC) Foundation with, among others, specific outputs related to mapping malaria risk and mapping parasite movement. This interest was considered significant and relevant. Dr Cohen was therefore subject to partial exclusion from the decision-making process and excluded from the closed session during which recommendations were finalized on the afternoon of Wednesday 4 October 2018.

Dr Adam Bennett works for the Global Health Group Malaria Elimination Initiative (MEI) at the University of California, San Francisco, USA. Dr Bennett reported one potential conflict of interest:

a. As Program Lead at MEI and an Assistant Professor of Epidemiology and Biostatistics, his research focuses primarily on modelling spatial and climatic variability in the context of surveillance, monitoring and evaluation for vector-borne disease control interventions. He leads the MEI's surveillance efforts to develop and recommend new and efficient strategies for identifying, tracking and targeting malaria cases in elimination settings.

Dr Bennett's potential conflicts of interest were considered personal and nonspecific but financially significant. As he is not an ERG member, he was already to be excluded from the closed session during which recommendations were finalized on the afternoon of Wednesday 4 October 2018. Therefore, no further action was required.

Further "due diligence" internet research was conducted on profiles of all ERG members and technical experts. Nothing significant was found that was not already disclosed through DOIs.

Note: 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 expert's organization, from any single malaria-related company exceeds US$ 10 000 in a calendar year. Likewise, a shareholding in any one malaria-related company in excess of US$ 1000 would also constitute a "significant shareholding".

Last update: 10 March 2016

Annex 4. Overview of evidence on Anopheles spp. and Plasmodium spp. compatibility for different malaria zones

Summary of *Anopheles spp*. competence or incompetence for *P. falciparum* in the 12 malaria zones. Excerpt from presentation by G. White.

***P.falciparum* origin**	**vector competence (+) or incompetence**											
Malaria Zones	1: North American	2: Central American	3: South American	4: North Eurasian	5: Medi-terranean	6: Desert	7: Afro-tropical	8: Indo-Iranian	9: Indo-Chinese	10: Malaysian	11: Chinese	12: Austra-lasian
1: North American	all+?	–	–	–	–	–	–	–	–	–	–	–
2: central American	*freeborni*	all? except *pseudopunctipennis*		+	+	+	+	+	+	*dirus maculatus*	+	+
3: South American	+	+	all+?	+	+	+	+	+	+	+	+	+
4: North Eurasian	+	+	+	all+?	+	+	+	+	+	+	+	+
5: Medi-terranean	+	+	+	+	all+?		+	+	+	+	+	+
6: Afro-Arabian Desert	+	+	+	*atroparvus*	+	all+?	+	+	+	+	+	+
7: Afrotropical	+	+	+	*atroparvus claviger labranchiae messae plumbeus sacharovi subalpinus*	*claviger plumbeus sacharovi*	+	all+?	+	+	+	+	+
8: Indo-Iranian	+	+	+	*atroparvus messeae*	+	+	+	all+ except *culicifacies* B	*maculatus*	+	+	+
9: Indo-Chinese	+	+	+	*atroparvus*	+	+	*coluzzii gambiae*	*stephensi*	*barbirostris campestris cracens*	+	+	+
10: Malaysian	+	+	+	+	+	+	+	+	*maculatus*	all+?	+	+
11: Chinese	*freeborni*	+	+	+	+	+	*gambiae*	*culicifacies stephensi*	*dirus*	+	all+?	+
12: Australasian	+	+	+	+	+	+	+	+	+	+	+	all+?

Summary of *Anopheles spp*. competence or incompetence for *P. vivax* in the 12 malaria zones. Excerpt from presentation by G. White.

***P.vivax* origin**	***Anopheles* competence (+) or incompetence or [very low susceptibility]**											
Malaria Zones	1: North American	2: central American	3: South American	4: North Eurasian	5: Mediterranean	6: Desert	7: Afrotropical	8: Indo-Iranian	9: Indo-Chinese	10: Malaysian	11: Chinese	12: Australasian
1: North American	all+?	–	–	–	–	–	–	–	–	–	–	–
2: central American	*freeborni quadrimaculatus*	*pseudo-punctipennis*	albitarsis	*atroparvus*	+	+	*gambiae*	*culicifacies stephensi*	*dirus maculatus*	+	+	*farauti*
3: South American	*freeborni quadrimaculatus*	*pseudo-punctipennis*	all+?	*atroparvus*	+	+	*gambiae*	*culicifacies stephensi*	*dirus maculatus*	+	+	+
4: North Eurasian	+	+	+	all+?	+	+	+	+	+	+	+	+
5: Mediterranean	+	+	+		all+?	+	+	+	+	+	+	+
6: Afro-Arabian Desert	+	+	+	*atroparvus*	+	all+?	+	+	+	+	+	+
7: Afrotropical	+	+	+	+	+	+	all+?	+	+	+	+	+
8: Indo-Iranian	*freeborni*	[*albimanus*]	+	*atroparvus*	+	+	*gambiae*	all+ except *culicifacies* B	*dirus maculatus*	*balabacensis*	+	+
9: Indo-Chinese	*freeborni*	+	+	*atroparvus messeae sacharovi*	+	+	*gambiae*	*culicifacies stephensi*	*barbirostris campstris cracens*	+	+	+
10: Malaysian	+	+	+	+	+	+	+	+	+	all+?	+	+
11: Chinese	*freeborni*	+	+	+	+	+	*gambiae*	*culicifacies stephensi*	*dirus maculatus*	+	all+?	+
12: Australasian	*freeborni quadrimaculatus*	[*albimanus*]	+	*atroparvus*	+	+	*gambiae*	*culicifacies stephensu*	*dirus maculatus*	*balabacensis maculatus*	+	all+?

ASSESSMENT OF MALARIOGENIC POTENTIAL TO INFORM ELIMINATION STRATEGIES AND PLANS TO PREVENT RE-ESTABLISHMENT

Malaria Policy Advisory Committee Meeting
Geneva, Switzerland
10 – 12 APRIL 2019

Global **Malaria** Programme

World Health Organization

Background

- Malariogenic potential is a critical factor in determining strategies to achieve elimination and prevent re-establishment of transmission
- WHO recommends that countries approaching elimination or working to prevent re-establishment of malaria stratify their geographical units by malariogenic potential, to help in targeting appropriate interventions
- WHO also recommends that this assessment should determine whether vector control can be withdrawn after transmission is interrupted in an area
- There is a lack of guidance on methods to measure the components of malariogenic potential and on thresholds relevant for programmatic decisions

ERG Objectives

1. To review current **definitions** of receptivity, vulnerability and malariogenic potential contained in the WHO glossary and, if required, recommend improvements to ensure that the definitions are valid and appropriate;

2. To review available **methodologies** for assessing receptivity and recommend appropriate and valid methodological approaches, including data requirements, for national malaria programmes to use to measure receptivity in their respective countries;

3. To advise WHO on **options for classifying receptivity** according to programmatically relevant categories aimed at guiding interventions to prevent re-establishment of transmission;

ERG Objectives

4. To review the validity and practicality of available methods for assessing vulnerability and recommend appropriate and valid **methodological approaches**, including data requirements, for national malaria programmes to use to **assess vulnerability** in their respective countries;

5. To review data on the regional receptivity ('**infectivity**') of endemic anophelines to exotic strains of human malaria;

6. To advise WHO on **approaches to combining measures** of receptivity, vulnerability and infectivity to guide national malaria programmes in designing strategies to prevent re-establishment of transmission.

MPAC Conclusions, April 2018

- ERG convening endorsed
- Use the ERG to standardize terminology to avoid confusion
- Maintain the focus of the ERG on those countries nearing elimination and moving to prevent re-establishment of transmission at either the subnational or national level
- Acknowledge the impact on vulnerability and receptivity that has already occurred
- Important to emphasize of the final objective (6) that will provide national programmes with the guidance needed

ERG Convened 2-4 October 2018

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ERG Conclusions

- Update terms
- Methods to assess receptivity have not been cross-validated or compared.
- Reduced infectivity of local mosquitoes to exotic parasite strains should be further investigated, to help inform response strategies to imported cases.
- Measures of importation risk have not been cross-validated or compared in a systematic way.
- Development of programmatic thresholds for malariogenic potential will require additional investigation and modelling

ERG Recommendation 1: Proposed changes to the WHO Malaria Terminology

Malariogenic Potential (Add)

- Likelihood of local transmission that is the product of receptivity, risk of importation of malaria parasites and infectivity of imported parasites.

Note: The concept of malariogenic potential is most relevant for elimination and prevention of re-establishment when indigenous transmission is mostly or entirely eliminated.

Receptivity (Update)

- Degree to which an ecosystem in a given area at a given time allows for the transmission of Plasmodium spp. from a human through a vector mosquito to another human.

Note: This concept reflects vectorial capacity, susceptibility of the human population to malaria infection, and the strength of the health system, including malaria interventions. Receptivity can be influenced by ecological and climatic factors.

Vulnerability (Update)

- Likelihood of malaria infection based on living conditions or behavioural risk factors, or likelihood of increased risk of severe morbidity and mortality from malaria infection.

Importation Risk (Update)

- Risk or potential influx of parasites via infected individuals or infected *Anopheles* spp. mosquitoes.

Note: “Infected individuals” includes residents infected while visiting endemic areas as well as infected immigrants.

Infectivity (Add)

- Ability of a given *Plasmodium* strain to establish an infection in an *Anopheles* mosquito species and undergo development until the mosquito has sporozoites in its salivary glands.

ERG Recommendations (continued)

2. Update the WHO *Malaria surveillance, monitoring & evaluation: a reference manual* to:
   - more clearly articulate the importance for entomological surveillance to identify principal versus secondary vectors, given ongoing and likely temporal and spatial changes in vector distribution and abundance; and
   - provide more detailed guidance on site selection, and on the frequency and timing of entomological surveillance, to inform assessment of receptivity.

3. Revise other current WHO guidance documents in line with recommendations 1 and 2, to ensure consistency.

ERG Recommendations (continued)

4. Prioritize further development of methods for assessing malariogenic potential to ensure that these are applicable and informative for programmatic use:

   - compare methods for the three potential measures of receptivity for selected countries, to ascertain comparability within countries, between countries or between neighbouring regions, to inform their use in receptivity assessments;
   - compare entomological parameters, as well as each of their associations with parasitological indicators, to identify key components that should be included in assessment of receptivity;
   - examine outbreak data from certified countries, to determine the origin of the imported parasite strains and the number of resultant infections;
   - compare existing data on infections identified through border or workplace screening with those identified through passive case detection at clinics, to ascertain whether information from passive case detection provides an accurate picture of importation risk; and
   - examine examples where countries can generalize data on imported cases for populations in specific regions to other areas with similar population movement or influxes.

ERG Recommendations (continued)

5. Once methods for measurement of the components of malariogenic potential have been identified, interpret these measurements and develop thresholds to guide programmatic decision-making regarding maintenance of vector control and intensified surveillance.

6. Further evaluate the issue of infectivity with respect to the mosquito and parasite factors that may reduce vector competence for different strains of *Plasmodium,* to determine whether there are programmatic implications for these findings. This may require additional review of evidence in future.

MPAC Guidance Requested

- Endorsement of changes to the WHO Malaria Terminology
- Suggestions for pursuing comparisons of different measures of receptivity