Malaria Policy Advisory Committee (MPAC) Meeting

14 - 16 September 2016
Salle A, World Health Organization, Geneva, Switzerland

PROVISIONAL PROGRAMME

Thursday, 15 September 2016			
	Session 5	**Open**	**for information**
08:30 – 09:30	Results of the Impact of Insecticide Resistance Project	Dr Tessa Knox	
09:30 – 10:30	Strategic Advisory Group (SAG) on malaria eradication	Dr Marcel Tanner Dr Kevin Marsh	**for decision**
10:30 – 11:00	*Coffee break*		

	Session 6	**Open**	**for discussion**
11:00 – 11:30	Consolidated Malaria Guidelines update/Presentation	Dr Peter Olumese Dr Martha Quinones	
11:30 – 12:30	Development of the Global Vector Control Response/ Presentation	Dr Steven Lindsay	
12:30 – 13:00	Proposed Evidence Review Group to review the cardiotoxicity of antimalarial medicines /Presentation	Dr Andrea Bosman	
13:00 – 14:00	*Lunch*		
	Session 7	**Open**	**for discussion**
14:00 – 15:30	Report of WHO technical consultation on detection and surveillance of HRP2/HRP3 deletions	Dr Jane Cunningham	
15:30 – 16:00	*Coffee break*		
	Session 8	**Open**	**for discussion**
16:00 – 17:00	Recommendations from the Surveillance Monitoring & Evaluation Taskforce /Presentation	Dr Richard Cibulskis	
17:00 – 17:30	Proposed Evidence Review Group to review *Plasmodium Knowlesi*	Dr Rabi Abeyasinghe	**for information**
18:00	*End of day*		

Malaria Policy Advisory Committee Meeting
14–16 September 2016, Geneva, Switzerland
Background document for Session 6

World Health Organization

Development of a guideline for malaria vector control

August 2016, Geneva, Switzerland

Introduction

Over the last 5 years, WHO has issued various documents containing recommendations for malaria vector control. These have taken the form of recommendations *(1, 2)*, guidance notes *(3–5)*, position statements *(6, 7)*, information notes *(8)* and operational manuals *(9–11)*. To guide the implementation of malaria vector control, WHO/GMP has now identified the need to further review the scientific evidence base, and to update and consolidate the existing recommendations into a single document (WHO Guideline). This Guideline on malaria vector control will be part of an umbrella document on malaria prevention, together with the updated Guideline for the treatment of malaria.

The proposed Guideline for malaria vector control will follow the methods, processes and procedures for the development of WHO Guidelines *(12)*. A transparent and explicit process using the available evidence base will ensure the Guideline's high quality. The Guideline will offer an analysis of the current evidence relating to malaria vector control to inform and guide technical decisions, and provide a framework for the development of specific malaria vector control guidelines by WHO Member States.

Objectives of the Guideline

The objectives of the proposed Guideline are as follows:

- To provide global, evidence-based recommendations on vector control strategies and tools for malaria control and elimination;
- To provide a framework for the development of specific and more detailed national vector control strategies and protocols, promoting the use of effective malaria control measures at the national level based on the best available evidence.

Target audience

Policy makers in the ministries of health in malaria-endemic or at-risk countries are the main target audience. Other groups that may find this Guideline useful are organizations and agencies partnering in malaria control in endemic countries.

WHO/HTM/GMP/MPAC/2016.12

Scope

The Guideline will include the following components or topics:

	Key topics for recommendations	Status of evidence
1	**Title: Core malaria vector control interventions**	
	Indoor residual spraying (IRS)	B
	Long-lasting insecticidal nets (LLINs)	B
	Combining core vector control interventions – IRS and LLINs	B
2	**Title: Complementary vector control interventions**	
	Larval source management (LSM)	A
	Space spraying	To be reviewed
	Personal protection (repellents and other tools)	To be reviewed
	Environmental management measures not included in LSM (e.g. house improvements)	To be reviewed
3	**Title: Issues and challenges in implementation**	
	Risk associated with scaling back vector control	C
4	**Title: Vector control by eco-epidemiological settings** (13)	
	Tropical African savannah	D
	Plains and valleys outside Africa	
	Forest and forest fringes	
	Highlands and desert fringes	
	Wetland and coastal fringes	
	Urban and peri-urban areas	
5	**Title: Vector control under special circumstances**	
	Humanitarian emergencies (complex health emergencies)	D
	Outbreaks or epidemic situations	
	Malaria elimination settings	
	Residual transmission settings	
	Hard-to-reach populations: migrants, forest workers, cross- border populations	
6	**Title: New tools and methods for malaria vector control**	
	LLINs treated with PBO	C
	Other novel methods	No evidence yet

A: Systematic review available and GRADE (Grading of Recommendation, Assessment, Development and Evaluation) tables included
B: Systematic review available, GRADE needs to be updated
C: Systematic review and modelling of evidence not suitable for GRADE table
D: Technical Expert Group (TEG) consensus decision based on evidence of interventions

Composition of proposed groups:

WHO Guideline Steering Group

A WHO Guideline Steering Group comprised of members from different relevant WHO departments has been established to oversee the Guideline review process.

Guideline Development Group

The Guideline Development Group (Vector Control Technical Expert Group - VCTEG) will advise on the content of the Guideline (PICO1, relevant outcomes for decision making, evidence, risks/benefits, and recommendations according to GRADE).

External Review Group

An External Review Group will review the scoping documents, the PICO questions and the draft final Guideline document.

The list of proposed members for each of the above groups is given in Annex 1.

Review process and timelines

• June/16	Establishment of a WHO Guideline Steering Group (GSG). This is a WHO in-house committee comprised of members from relevant WHO departments involved in the development of guidelines related to malaria vector control.
• July-Aug/16	Meetings of the WHO GSC to discuss the scope of the Guideline and to formulate PICO questions
• Aug-Sept/16	Draft of the Guideline proposal and submission to the Guidelines Review Committee (GRC)
• Sept-Oct/16	Identification of evidence needs and commission of systematic reviews
• Jan-Feb/17	Development of GRADE tables and summary tables
• March/17	Formulation of recommendations based on the available evidence (VCTEG meeting)
• April/17	External electronic consultations, as needed
• March-June/17	Development of the draft Guideline
• June-July/17	Peer review (external review group) and editing
• Aug/17	Submission to the WHO Guidelines Review Committee
• Sept/17	Revision based on GRC comments, and seeking of final departmental and WHO approvals

[1] PICO – population, intervention, comparator, outcomes expected

Budget

The total budget for the production of this Guideline is US$ 300 000.00, with budget lines as follows:

Content development

• Evidence retrieval, systematic reviews and GRADE tables	$ 85 000.00
• GDG meeting	$ 100 000.00
• Writing, editing/proofing and translations	$ 75 000.00
• Layout and printing	$ 30 000.00
• Communications and distribution	$ 10 000.00

References

1. WHO recommendations for achieving universal coverage with long-lasting insecticidal nets in malaria control. September 2013 (revised March 2014). Geneva: World Health Organization; 2013 (http://www.who.int/malaria/publications/atoz/who_recommendations_universal_coverage_llins.pdf)

2. Conditions for use of long lasting insecticidal nets treated with a pyrethroid and piperonil butoxide. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/use-of-pbo-treated-llins.pdf)

3. WHO guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets. Geneva: World Health Organization; 2014 (http://www.who.int/malaria/publications/atoz/who-guidance-combining-irs_llins-mar2014.pdf)

4. Control of residual malaria parasite transmission. Guidance note September 2014. Geneva: World Health Organization; 2014 (http://www.who.int/malaria/publications/atoz/guidance-control-residual-transmission/en/)

5. WHO guidance note for estimating the longevity of long-lasting insecticidal nets in malaria control. Geneva: World Health Organization; 2013 (http://www.who.int/malaria/publications/atoz/who_guidance_longevity_llins/en/)

6. Interim position statement. The role of larviciding for malaria control in sub-Saharan Africa. Geneva: World Health Organization; 2012 (http://www.who.int/malaria/publications/atoz/interim_position_statement_larviciding_sub_saharan_africa.pdf)

7. The use of DDT in malaria vector control. WHO position statement. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/69945/1/WHO_HTM_GMP_2011_eng.pdf)

8. Risk associated with scale back of vector control after malaria transmission has been reduced. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/scale-back-vector-control.pdf)

9. Indoor residual spraying: an operational manual for indoor residual spraying (IRS) for malaria transmission control and elimination. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/177242/1/9789241508940_eng.pdf)

10. Larval source management: a supplementary measure for malaria vector control - an operational manual. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/85379/1/9789241505604_eng.pdf)

11. Malaria control in humanitarian emergencies - an inter-agency field handbook. 2nd edition. Geneva: World Health Organization; 2013

12. WHO handbook for guideline development. 2nd edition. Geneva: World Health Organization; 2014.

13. Malaria vector control and personal protection. WHO Technical Report Series 936. Report of a WHO Study Group. Geneva: World Health Organization; 2006 (http://apps.who.int/iris/bitstream/10665/43425/1/WHO_TRS_936_eng.pdf)

Annex 1. Composition of the groups for the development of the Guideline

WHO Guideline Steering Group

- Rabindra Abeyasinghe (WPRO)
- Birkinesh Ameneshewa (AFRO)
- Caroline Barwa (EMRO)
- Florence Fouque (VES/TDR)
- Haroldo Bezerra (PAHO)
- Abraham Mnzava (EVC/GMP)
- Peter Olumese (HTM/GMP/DTV)
- Martha L. Quinones (EVC/GMP) – Responsible technical officer
- Rajpal Yadav (WHOPES/NTD)
- Raman Velayudhan (VEM/NTD)
- Michael MacDonald (WPRO/SEARO)

Guideline Development Group (Vector Control Technical Expert Group – VCTEG)

Name	Region	Affiliation	Gender
NMCP manager			
Dr Chioma N. AMAJOH	African	Community Vision Initiative, Abuja, Nigeria	F
Dr Pierre CARNEVALE	European	Directeur de Recherches C.E., Portiragnes, France	M
Dr John CHIMUMBWA	African	International Malaria Consultant, Lusaka, Zambia	M
Professor Maureen COETZEE	African	Wits Research Institute for Malaria, University of Witwatersrand, Johannesburg, South Africa	F
Prof. Dr Marc COOSEMANS	European	Department of Parasitology, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium	M
Dr Josiane D. ETANG	African	Organisation de Coordination pour la Lutte, Contre les Endémies en Afrique Centrale (OCEAC), Yaoundé, Cameroun	F
Dr Jeffrey HII	Pacific	International Malaria Consultant, 7 Brunswick Place, Wights Mountain, Brisbane, Australia	M
Dr Jonathan LINES	European	London School of Hygiene and Tropical Medicine, London, United Kingdom	M
Dr Melanie RENSHAW	African	ALMA, Nairobi, Kenya	F
Dr Mark ROWLAND	European	London School of Hygiene and Tropical Medicine, Department of Disease Control, London, United Kingdom	F

Name	Region	Affiliation	Gender
Dr Joshua YUKICH	African	Tulane University, School of Public Health, Department of Global Health Systems and Development, New Orleans, USA	M

External Review Group

Name	Region	Affiliation	Gender
Steve LINDSAY	European	School of Biological and Biomedical Sciences, Durham University, UK	M
Christen FORNADEL	Americas	USAID - President's Malaria Initiative	F
Charles MBOGO	African	Malaria Public Health Department, Nairobi, Kenya	M
Willem TAKKEN	European	Wageningen University, Wageningen, The Netherlands	M
Graham WHITE	Americas	University of Florida IFAS, Gainesville, FL, USA	M
Patricia GRAVES	West-Pacific	James Cook University, Cairns, Queensland, Australia	F

Guideline for vector control

Entomology and Vector Control Unit

Global **Malaria** Programme

World Health Organization

Guideline for vector control

Entomology and Vector Control Unit

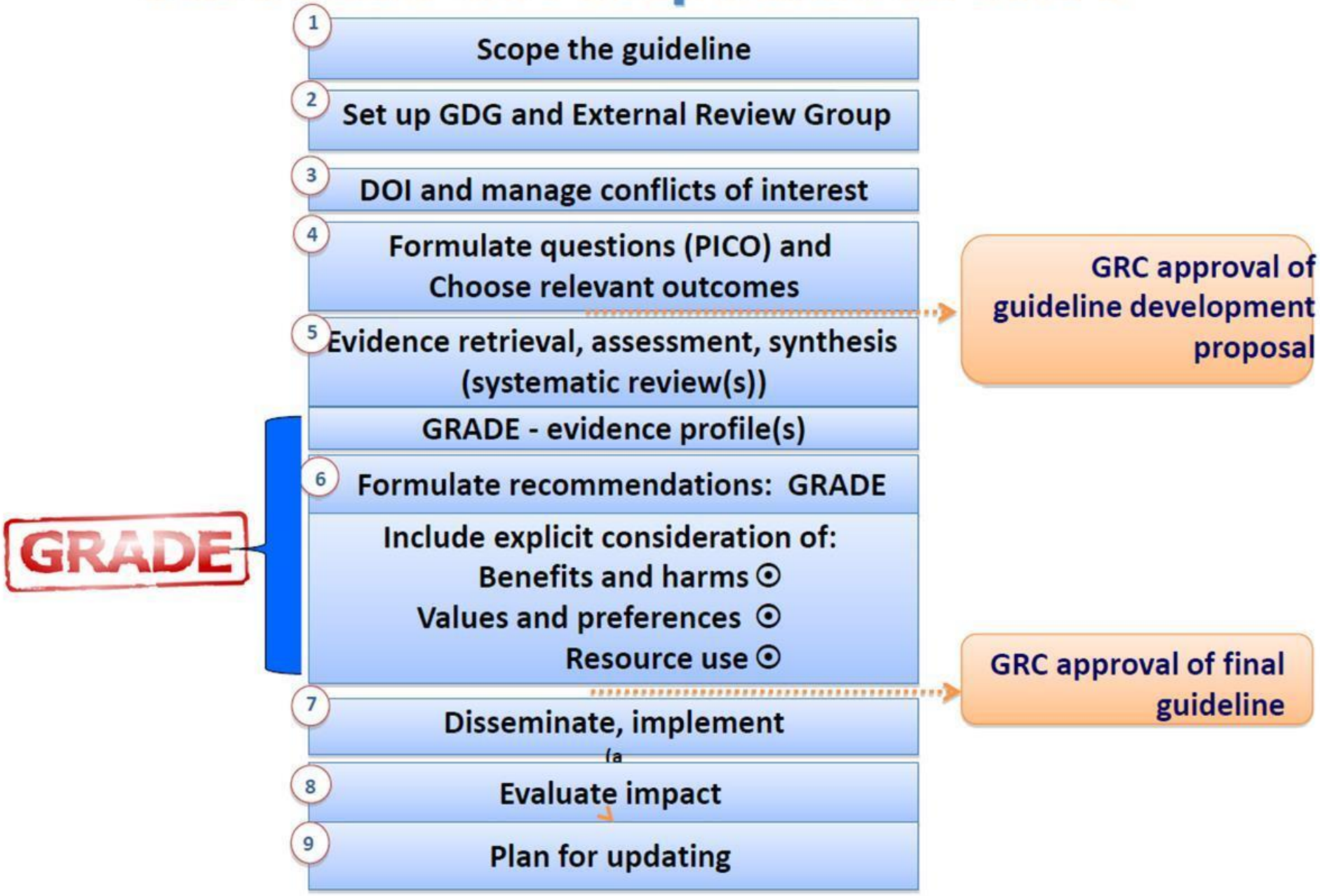
Global **Malaria** Programme

World Health Organization

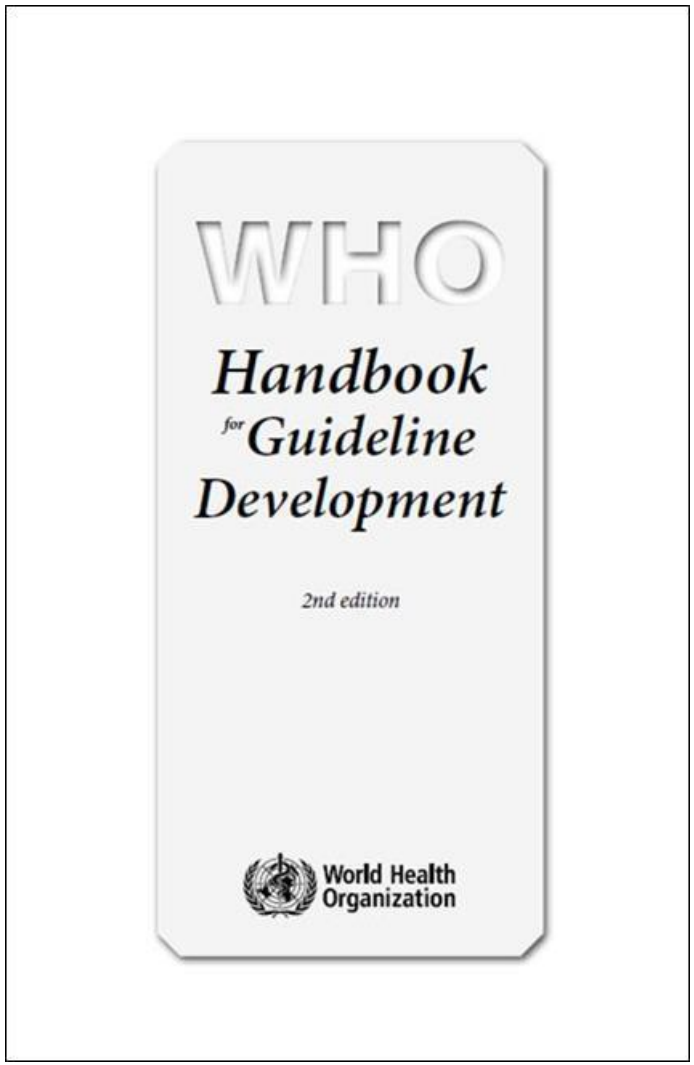
Principles for WHO Guidelines

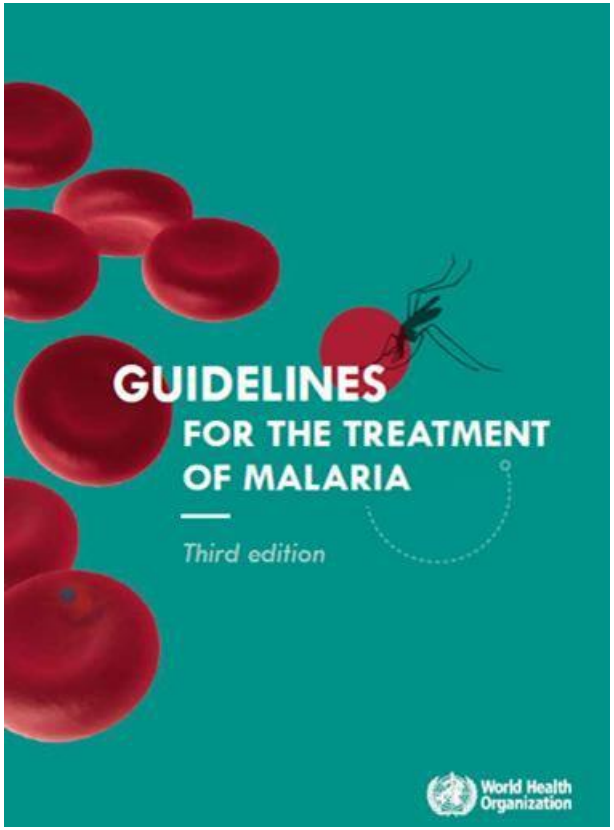
- Well-defined scope and target audience
- Broad and representative guideline development group
- *A priori* development of key question for systematic reviews
- Systematic and comprehensive evidence retrieval, synthesis
- Quality assessment of the body of evidence for each question
- Formulation of recommendations based on the evidence and other explicit considerations.
- Disclosure and management of all secondary interests (COI)
- Adherence to WHO reporting standards
- Usable document: relevant, applicable, user-friendly
- Include a plan for implementation and updating

Guideline development at WHO



WHO process for guideline development





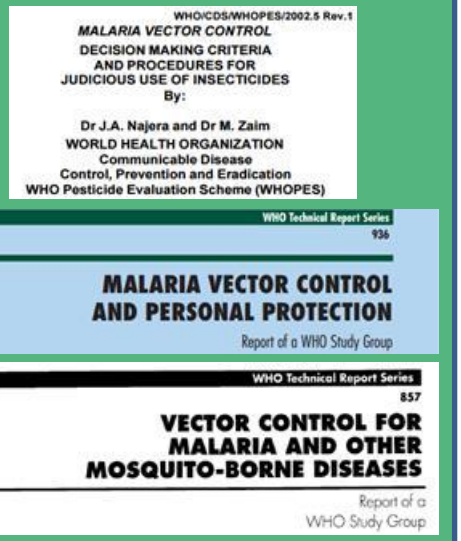
WHO documents with recommendations for malaria vector control

RECOMMENDATIONS

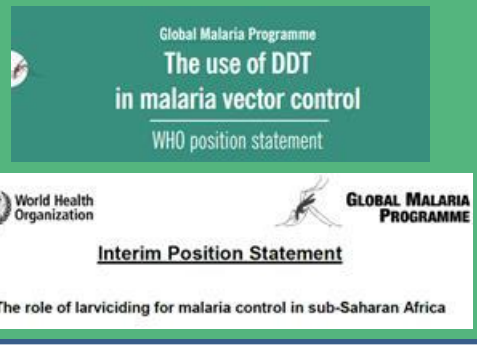
GUIDANCE NOTES

OPERATIONAL MANUALS

REPORTS OF WHO STUDY GROUPS - DOCUMENTS



POSITION STATEMENTS



INFORMATION NOTE

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Steering Group

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Birkinesh Ameneshewa (AFRO)
Caroline Barwa (EMRO)
Florence Fouque (TDR)
Haroldo Bezerra (PAHO)
Abraham Mnzava (EVC/GMP)
Peter Olumese (HTM/GMP/DTV)
Martha L. Quinones (EVC/GMP)
Rajpal Singh (NTD)
Raman Velayudhan (NTD)
Michael Macdonald (WPRO/SEARO)

The role of the Steering Group is to:

- Provide administrative **support for guideline development**;
- Draft the **scope** of the guideline and key questions in **PICO** format. PICO is an acronym for population, intervention (or exposure), comparator and outcome.
- Identify the systematic review team and guideline methodologist(s);
- Develop and finalize the **planning proposal** for submission to the guideline review committee (GRC);
- Oversee evidence retrieval, assessment and synthesis;
- Select members of the GDG and the external review group (ERG);
- Collect and assess disclosures of interest and manage conflicts in collaboration with the Director of the technical unit and in consultation with the Office of Compliance, Risk Management and Ethics, as needed;
- Organize GDG meetings;
- **Draft recommendations** based on the decisions of the GDG;
- **Draft the final guideline**, in collaboration with the technical writer;
- Oversee peer review, review comments and revise the draft guideline as appropriate;
- **Submit the final guideline to the GRC** and revise as indicated to meet GRC requirements;
- Oversee publication and dissemination of the guideline; and
- Monitor new information, user needs and requests that inform when an update may be needed.

GDG and ERG

Guideline Development Group: Vector Control Technical Expert Group - VCTEG
The role of the GDG is to:

- Provide input into the **scope** of the guideline;
- Assist the steering group in developing the **key questions** in PICO format;
- Choose and rank priority **outcomes** that will guide the evidence reviews and focus the recommendations;
- Examine the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles or other assessments of the **quality of the evidence** used to inform the recommendations and provide input;
- Interpret the evidence, with explicit consideration of the overall balance of benefits and harms;
- **Formulate recommendations** taking into account benefits, harms, values and preferences, feasibility, equity, acceptability, resource requirements and other factors, as appropriate; and
- Review and approve the final guideline document before submission to the GRC.

External Review Group
The role of the External Review Group is to:

- Review the final guideline document at the end.
- May provide some input along the process.

Budget

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Thank you

Malaria Policy Advisory Committee Meeting
14–16 September 2016, Geneva, Switzerland
Background document for Session 6

World Health Organization

Working paper on the development of the global vector control response

September 2016, Geneva, Switzerland

Global vector control response at a glance (*version 1.3)*

Vision

- A world free of vector-borne diseases that affect humans.

Goal

- To reduce the burden and threat of vector-borne diseases through sustainable, effective vector control.

Rationale

- Vector-borne diseases (VBDs) constitute around 22% of the total burden of all infectious diseases and 29% of emerging diseases;
- VBD transmission is changing rapidly due to environmental factors such as urbanization, globalization and climate;
- Substantive investments in vector control have contributed significantly to global reductions in some VBDs, particularly malaria and onchocerciasis;
- New investments and approaches are needed to protect populations at risk for other VBDs including emerging and re-emerging diseases;
- Improved delivery of vector control services through strengthened health systems and intersectoral collaboration will enhance efficiency and impact against VBDs, and lead to significant reductions in disease and economic burden.

Objectives

- To strengthen vector control as a key strategy for VBD reduction and prevention, including environmental management in urban and rural development initiatives;
- To establish and enhance intersectoral collaboration for integrated action;
- To develop locally adaptive systems for efficient vector surveillance and control;
- To enhance and link entomological and epidemiological evidence in order to optimize the planning and implementation of vector control;
- To ensure government and partner commitment to vector control through legislation, policy and planning.

WHO/HTM/GMP/MPAC/2016.10

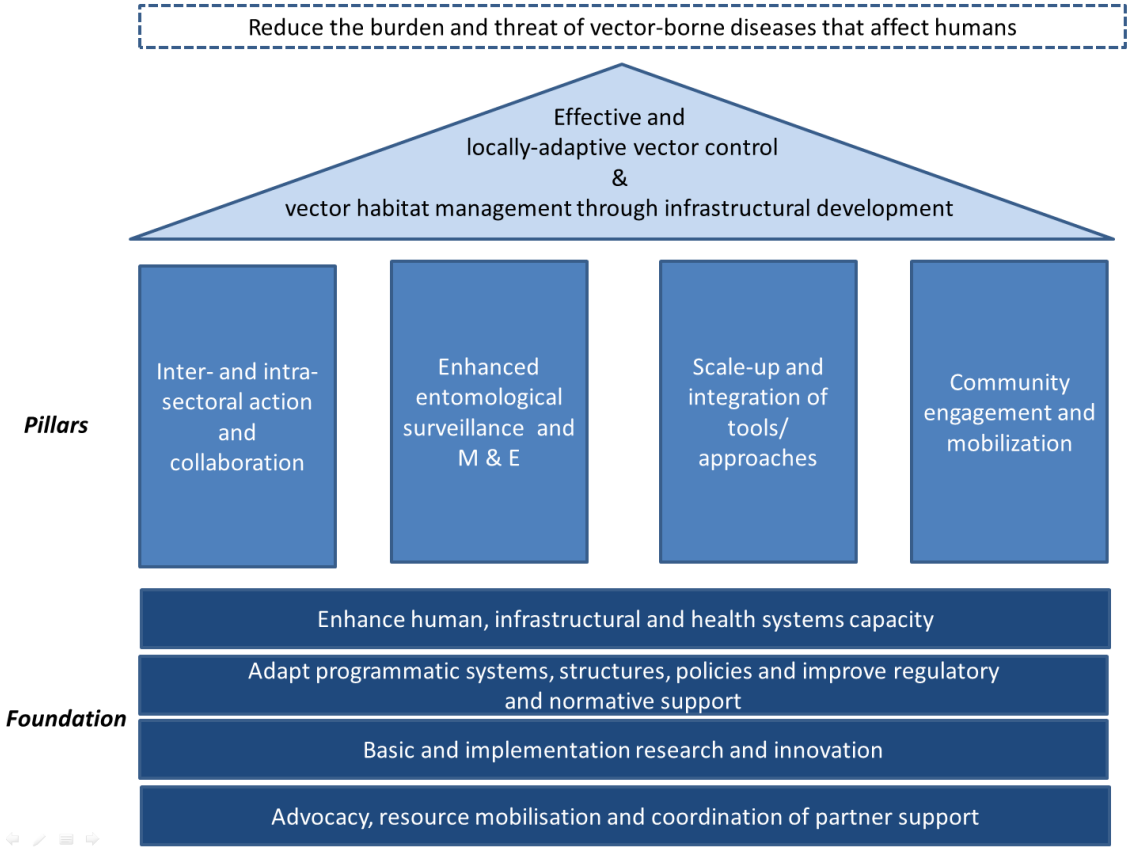
Foundation

- Enhance human, infrastructural and health systems capacity;
- Adapt programmatic systems, structures, policies and improve regulatory and normative support;
- Basic and implementation research and innovation;
- Advocacy, resource mobilisation and coordination of partner support.

Pillars

- Inter- and intra-sectoral action and collaboration;
- Enhanced entomological surveillance, and vector control monitoring and evaluation;
- Scale-up and integration of tools/approaches;
- Community engagement and mobilization;

Figure 1. Global vector control response to reduce the burden and threat of VBDs through sustainable and effective vector control.



Background

Vector-borne diseases account for 22% of the estimated global burden of all infectious diseases. Major vector-borne diseases include those caused by parasites (malaria, leishmaniasis, lymphatic filariasis, onchocerciasis, African sleeping sickness, Chagas disease) and viruses (dengue fever, Zika virus disease, Chikungunya, yellow fever, Japanese encephalitis). Together these diseases claim more than 700 000 lives every year and exact an enormous toll on affected communities and economies. Many of those who survive are left permanently disabled, disfigured, maimed or blind.

The world has recently witnessed a significant re-emergence of vector-borne diseases. This has included reoccurrence in some areas following an absence of up to 70 years, geographic spread to new areas, extension of the transmission season in endemic areas, and the identification of new clinical complications. These changes have been driven by increased global travel and trade, together with environmental challenges such as burgeoning urbanization and climate change, which affect the reach of vector populations and the diseases they spread.

History provides clear examples of where rigorous vector control has significantly reduced transmission and disease, such as for dengue and yellow fever in the Americas in the 1950s and 1960s. More recently, impressive global reductions in malaria have been attributable in large part to the massive scale-up of insecticidal bed nets and indoor residual spraying. However, a critical lack of human, infrastructural and financial capacity has hampered sustained and successful vector control; many countries continue to experience a high burden of vector-borne diseases. Progress has been hindered by a shortage of the resources needed to gather entomological information to ensure informed, data-driven vector control, as well as limited capability to implement rigorous and sustained control measures and mount additional response as needed. The result is that the full impact of vector control has yet to be realized, despite being the best proven option for the prevention of most vector-borne diseases.

Need for a Global Vector Control Response

There has never been a more urgent need to reorient vector control to ensure the efficient and sustainable reduction of the burden and threat of VBDs. World Health Day 2014 focused on diseases transmitted by vectors, and with the unprecedented global spread in 2015–2016 has clearly highlighted the challenges faced by Member States. The transmission and risk of VBDs are changing quickly due to unplanned urbanization, increased movement of people and goods, environmental changes and biological challenges, such as the resistance of vectors to insecticides. Particularly in tropical and subtropical towns and cities, rapid urbanization has placed large populations at risk of the emergence and expansion of arboviral diseases. The health sector must be resilient to detect early and respond rapidly to these changes. Strengthening capacity in vector control programmes as well as intersectoral collaboration with community engagement will improve efficiencies in reducing the public health and socioeconomic impact of VBDs. Incorporating environmental management approaches into urban and rural development will help to further reduce the burden and threat of VBDs.

The Sustainable Development Goals (SDGs) provide the health sector with a framework through which it can harmonize approaches to disease control and prevention with other sectors. The SDGs support a multipronged attack on VBDs, particularly in tropical and subtropical towns and cities. Although the use of insecticides has had significant impact against VBDs, these should be supplemented with new approaches, including environmental management that reduces the suitability of urban environments as vector habitats. Other exciting new advances will facilitate improved vector control. These include enhanced surveillance systems and management structures; new classes of insecticides with novel modes of action; highly effective and efficient vector traps; and other non-insecticidal approaches such as the release of sterilized, genetically-

modified or *Wolbachia*-infected vectors incapable of transmitting pathogens. Convincing evidence has shown that combinations of treatment, vaccination and vector control can drive down a vector-borne disease more effectively and with longer lasting results than any single method on its own. This response seeks to optimize the vector control component of disease-specific strategies.

Response development process

Following the support expressed by Member States at the Sixty-ninth World Health Assembly and the Executive Board at their 139th meeting for the development of a global vector control response for the post-2015 period, the WHO Secretariat gathered input from experts representing national VBD control and elimination programmes, health ministries, research organizations and implementing partners. The process is being co-led by the WHO Global Malaria Programme (GMP), WHO Department of Control of Neglected Tropical Diseases (NTD) and the Special Programme for Research and Training in Tropical Diseases (TDR). WHO is being supported by a Steering Committee which is comprises of leading VBD experts, scientists and representatives of countries in which VBDs are endemic. The first meeting of the Steering Committee was held in August 2016 with the second meeting to be convened in October 2016. The WHO GMP Malaria Policy Advisory Committee, NTD Scientific and Technical Advisory Group, and TDR Scientific and Technical Advisory Committee will be consulted electronically for detailed inputs on the second draft of the global vector control response in late September 2016. Regional and national consultations will also be conducted between September 2016 and January 2017. An advanced draft of the response will be discussed by the WHO Executive Board at their 140th meeting to be held in January 2017. It is anticipated that the response will be included in the agenda for discussion at the Seventieth World Health Assembly in May 2017.

Table 1. Milestones, targets and activities

To reduce the burden and threat of vector-borne diseases affecting humans, through the following:

	Activity	Milestones				Target
		2018	2019	2020	2025	2030
1	National inter-ministerial task-force for multi-sectoral engagement in vector control established and functioning	At least 50% of countries	At least 75% of countries	100% of countries	100% of countries	100% of countries
2	Regional and national VBD strategic plans aligned with Global Vector Control Response	1 region and at least 10% of countries	2 regions and at least 25% of countries	4 regions and 50% of countries	All regions and countries	All regions and countries
3	National vector control needs assessment conducted	At least 50% of countries	At least 75% of countries	100% of countries	100% of countries	100% of countries
4	National public health entomology workforce established and maintained to meet identified needs	At least 10% of countries	At least 25% of countries	At least 50% of countries	At least 75% of countries	100% of countries
5	Relevant staff from Ministries of Health and/or their supporting institutions trained in public health entomology	At least 10% of countries	At least 25% of countries	At least 50% of countries	At least 75% of countries	100% of countries
6	National entomological surveillance systems strengthened and integrated with health information systems to guide vector control	At least 10% of countries	At least 25% of countries	At least 50% of countries	At least 75% of countries	100% of countries
7	National agenda for basic and implementation research on entomological surveillance and vector control established and/or progress reviewed	At least 10% of countries	At least 25% of countries	At least 50% of countries	At least 75% of countries	100% of countries
8	Regional and/or national institutional networks to support training and education for vector control established and functioning	1 region and at least 10% of countries	2 regions and at least 25% of countries	4 regions and 50% of countries	All regions and countries	All regions and countries
9	Global and/or regional registries of appropriate experts to support entomological surveillance and vector control established and up-to-date	Global and 1 region	Global and 2 regions	Global and 4 regions	Global and all 6 regions	Global and all 6 regions

Note: table shows draft milestones/targets only; these are to be refined based on feedback from regional offices on current 'baseline' situation.

Update on the ongoing development of a Global Vector Control Response

Malaria Policy Advisory Committee

15th September 2016

Global **Malaria** Programme
Department of Control of **Neglected Tropical Diseases**
Special Programme for **Research and Training** in Tropical Diseases

World Health Organization

High level acknowledgement of the importance of vector control

… above all, the spread of Zika, the resurgence of dengue, and the emerging threat of Chikungunya are the price being paid for **a massive policy failure that dropped the ball on mosquito control in the 1970s**.

Margaret Chan

DG WHO

Opening Address

69 WHA

May 2016

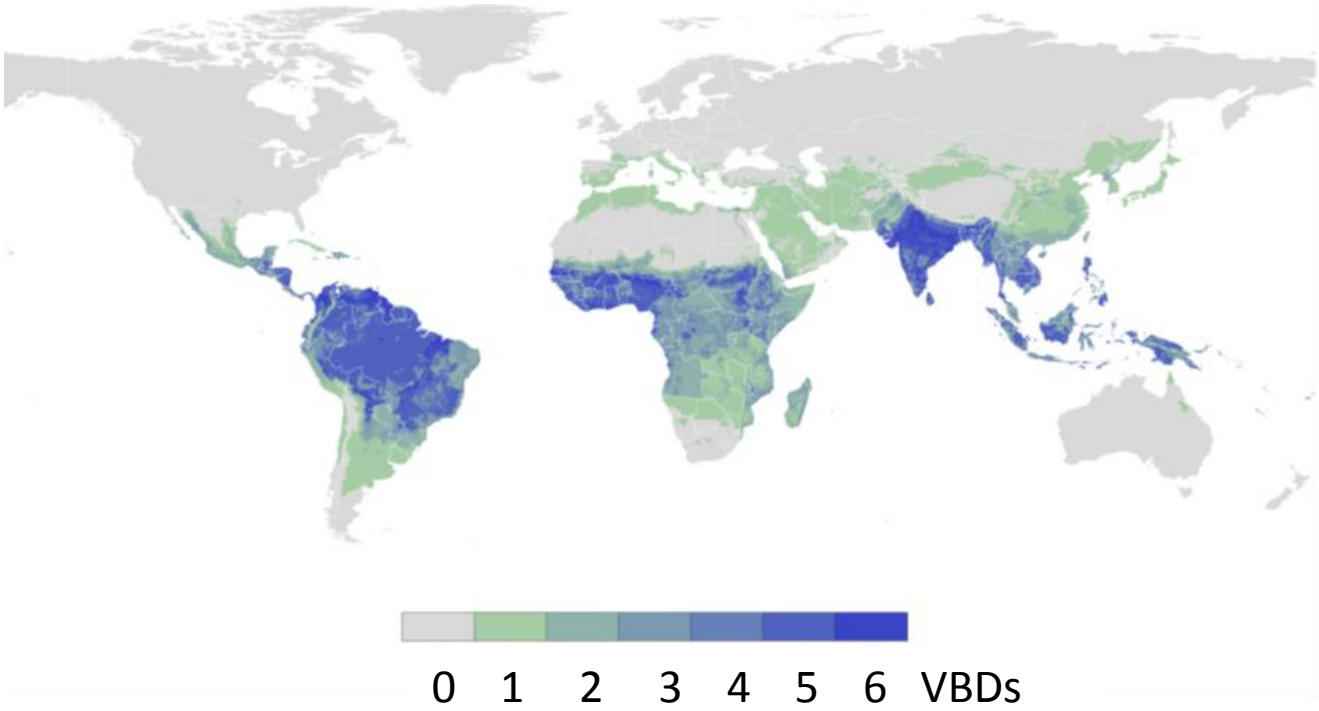
Background

Global burden of VBDs

Disease	Cases (in thousands)	DALYs	Deaths
Malaria	214,000 (range: 149,000 –303,000)	Not available	438,000 (range: 236,000 – 635,000)
Dengue	58,419 (23,611 – 121,920)	1,143 (728 – 1978)	9,100 (95% UI: 5,600 – 10,800)
Cutan./Muco. Leishmaniasis	3,915 (3,300 – 4,670)	42 (19 - 80)	-
Visceral leishmaniasis	114 (94 – 141)	4,242 (3,488 – 5,045)	62,500 (52,300 – 73,300)
Yellow Fever	2 (1 – 5)	31 (25 - 37)	500 (400 – 600)
Chagas	9,434 (9,241 – 9,628)	339 (184 - 846)	10,600 (4,200 – 33,00)
HAT	20 (11 – 34)	390 (211 – 615)	6,900 (3,700 – 10,900)
Lymphatic filariasis	43,850 (36,941 – 52,906)	2,022 (1,096 – 3,294)	-

Estimates from Global burden of disease (2013) except [1] WHO World Malaria Report 2015

Global distribution of some major VBDs

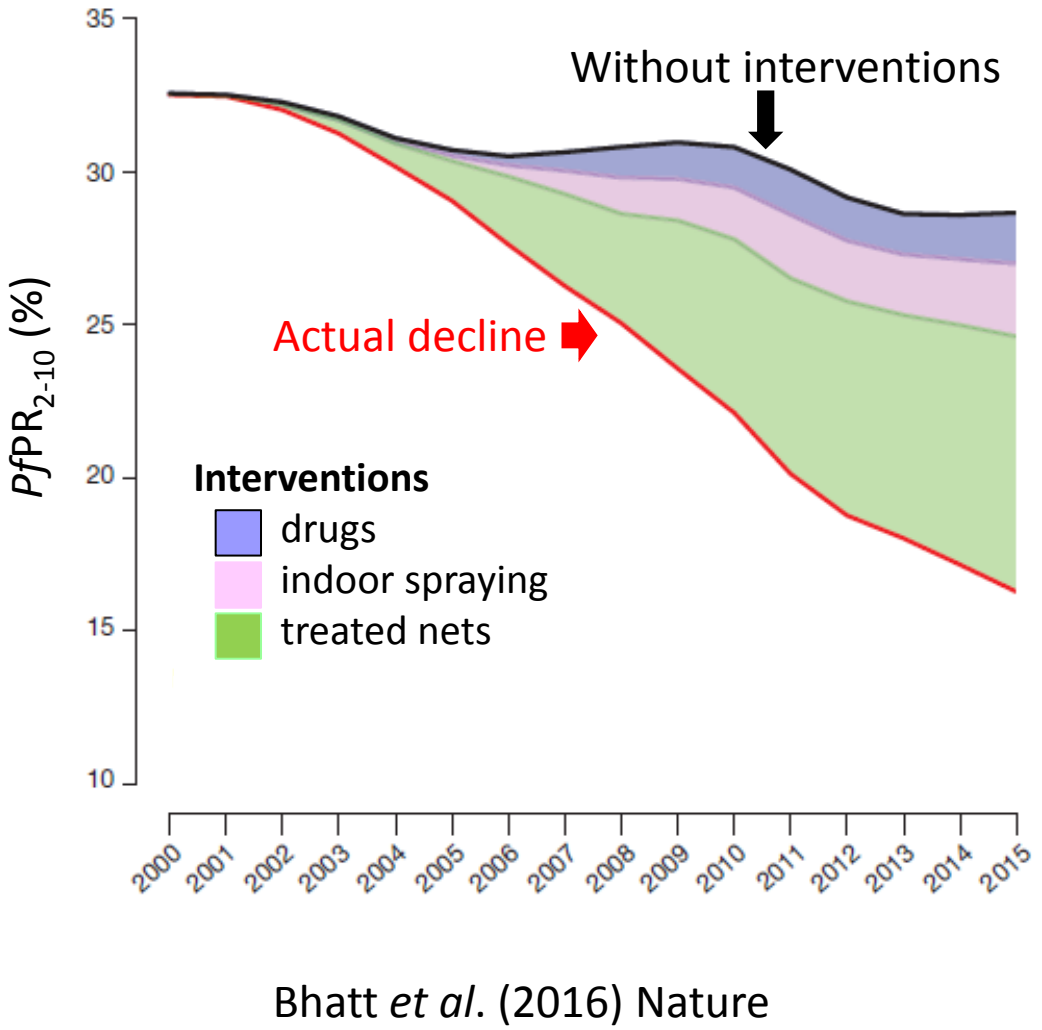


Combined global distribution of malaria, dengue, lymphatic filariasis, leishmaniasis, Japanese encephalitis, yellow fever and Chagas disease.

Today more than **80% of the world's population is at risk** from at least one VBD, with more than half at risk from two or more.

Golding et al. (2015) PLoS NTDs

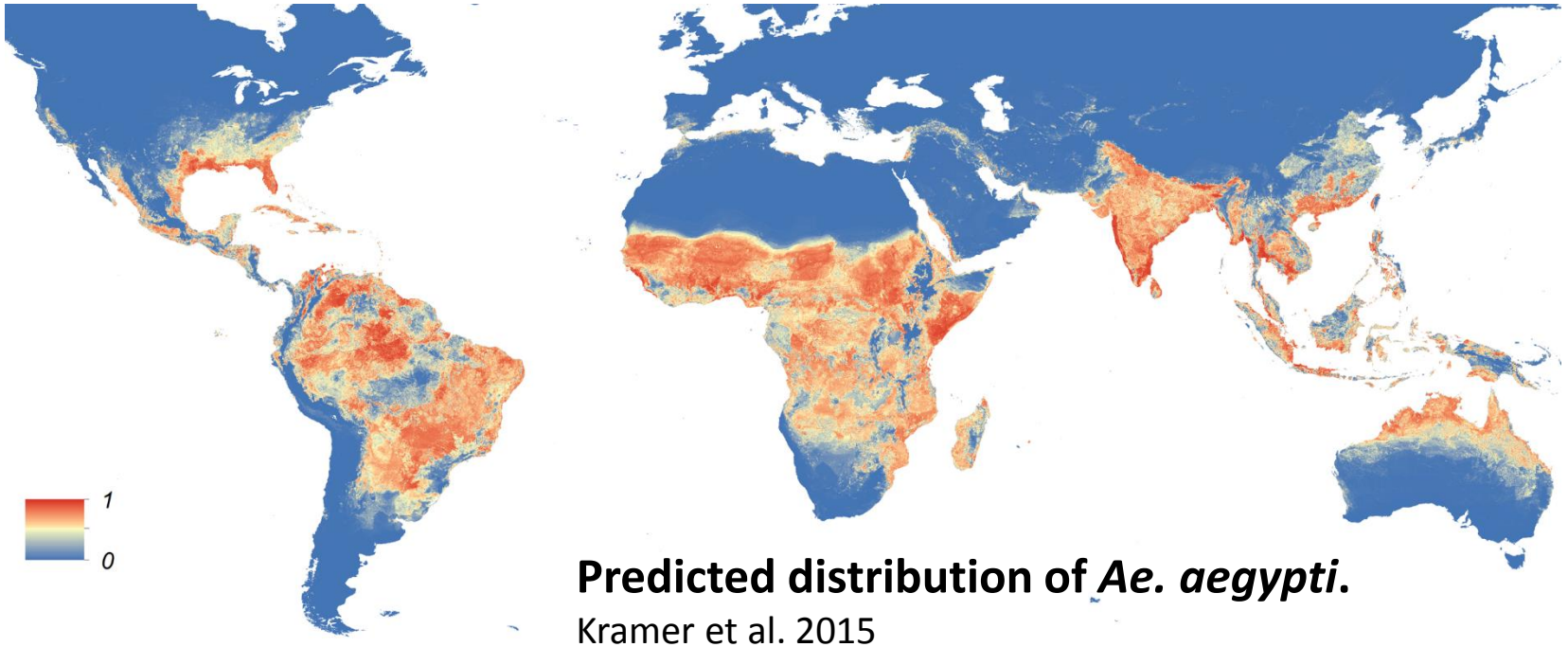
The future of malaria control



Bhatt *et al*. (2016) Nature

- Greatest reduction in malaria in sub-Saharan Africa achieved using vector control
- Sub-Saharan Africa accounted for 89% of cases and 91% of deaths in 2015
- Current activities are insufficient to eliminate malaria from SSA – particularly in a pyrethroid-resistant Africa
- Need for improved implementation, additional tools & strategies

Aedes-borne diseases: an increasing challenge



Predicted distribution of *Ae. aegypti*.
Kramer et al. 2015

- Vector spread to probably all towns and cities in the tropics & sub-tropics
- Best vector of Zika, dengue, chikungunya, yellow fever & potentially, novel human viruses
- Vector control of *Aedes* inadequate in most countries
- Improved implementation plus new tools and approaches are needed

Rationale for a Global Vector Control Response

- Vector-borne diseases (VBDs) constitute around 22% of the total burden of all infectious diseases and 29% of emerging diseases;
- Transmission patterns are changing rapidly;
- Substantial investments in vector surveillance and control enabled well-documented examples of success;
- New investments are required to boost capacity for a) improved implementation of existing interventions and b) evidence-based development of use of new tools and approaches

Development of a Global Vector Control Response (GVCR)

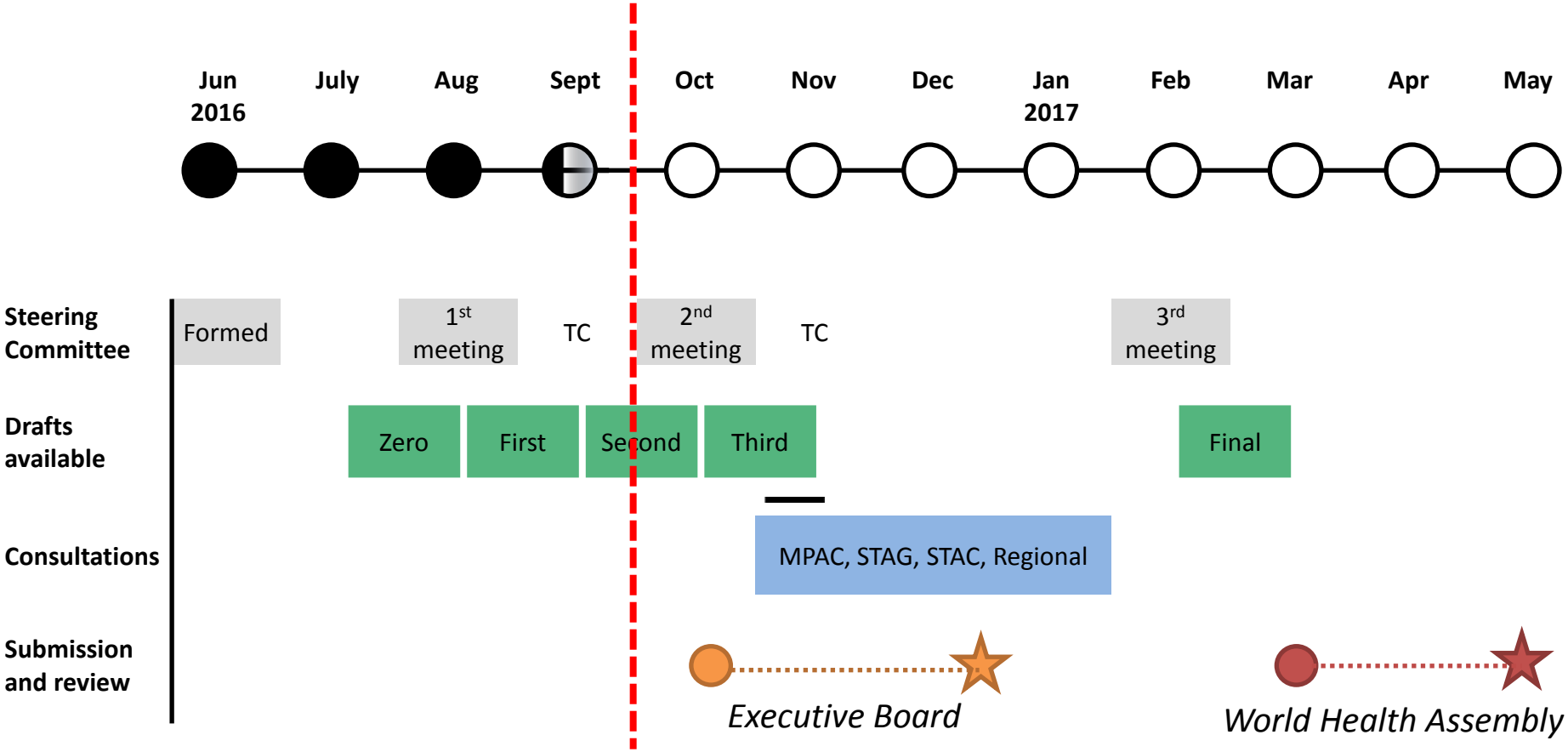
Led by:

WHO Global Malaria Programme
WHO Department for Control of Neglected Tropical Diseases
Special Programme for Research and Training in Tropical Diseases

GVCR: Development timeline

Status

GVCR Second draft currently under formulation: to be available 26 September 2016



GVCR: Involved in development thus far

Lead	GMP, NTD, TDR
Steering Committee	Co-Chairs: Prof. Thomas Scott, Dr Ana Santelli Regional advisors & other experts
WHO regional advisors & entomology / vector control focal points	AFRO, EMRO, EURO, PAHO, SEARO, WPRO
National programmes	Consultation meeting (16 national programmes + research & academia)
Research & academia	Pan-African Mosquito Control Association 3rd meeting, Lagos (~150 delegates of national programmes, research, academia)

Global Vector Control Response
2nd Draft

Vision: A world free of human vector-borne diseases.

Goal: Reduce the burden and threat of vector-borne diseases.

Integrated vector management

- IVM is a rational decision-making process for the optimal use of resources for vector control.
- Proper uptake has generally been poor due to :
  1. Complexity of communicating IVM
  2. Limited human capacity to advocate, plan and implement
  3. Fragmented global and national architecture that restricts multi-disease approach (e.g. disease-specific strategies and financing)
  4. Insufficient political buy-in for reorientation and harmonization

= IVM needs to be repackaged to be **simple, practical and actionable**

Challenges

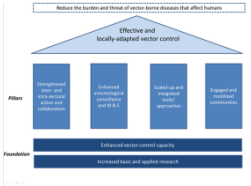
- Capacity of public health entomologists at sub-national, national, regional and global levels;
- Funding;
- Implementation of vector control;
- Monitoring and evaluation of vector control;
- Basic and applied research, outside malaria;
- Multiple locally-adapted and integrated approaches;
- Emergence of new diseases;
- Threats to present interventions e.g. insecticide resistance.
- Environmental change.

Opportunities

- Sustainable development goals;

- Success in malaria;
- Global strategy for dengue;
- Emergency responses;
- Cost savings;
- Collateral impact;
- New tools and approaches.

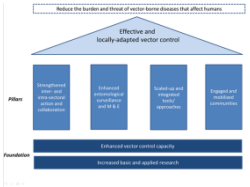
Foundation



Resilient and sustainable vector control systems requires:

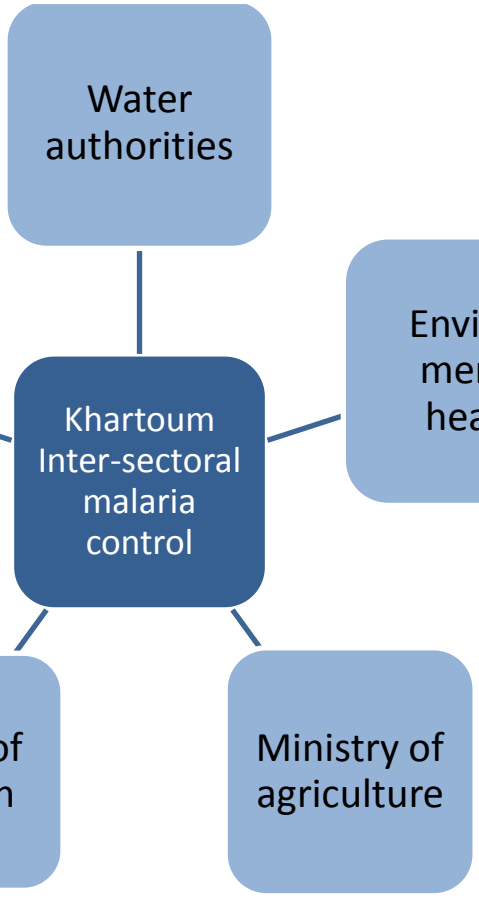
- Enhanced capacity for vector surveillance and control within all locally relevant sectors (including human, infrastructural, and health systems);
- Improved basic and applied research.

Pillars of Action



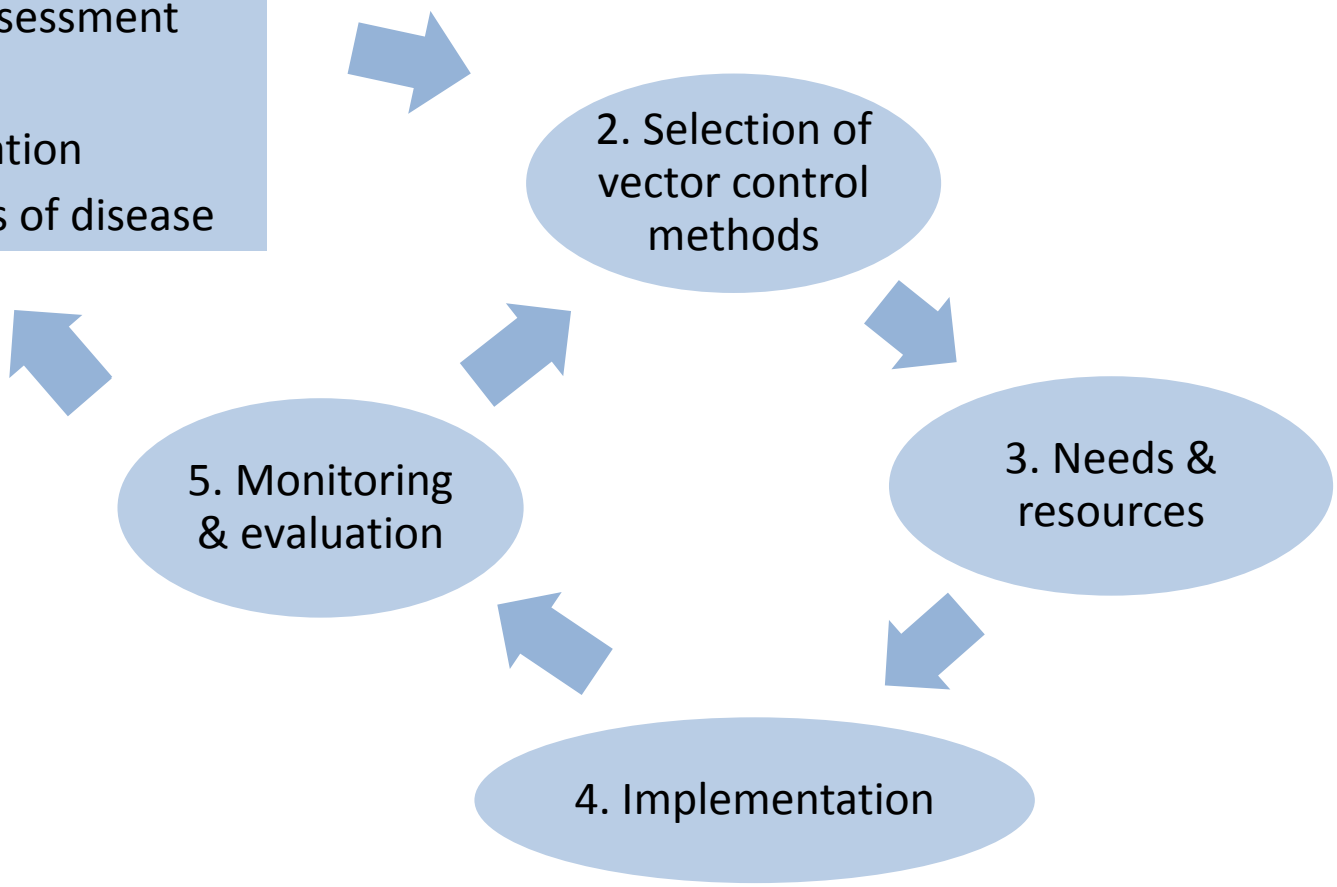
- Inter- and intra-sectoral action and collaboration;
- Enhanced entomological surveillance, and vector control monitoring and evaluation;
- Scale-up and integration of tools/approaches;
- Community engagement and mobilization.

Example of inter-sectoral collaboration for vector control



Framework for planning & implementation

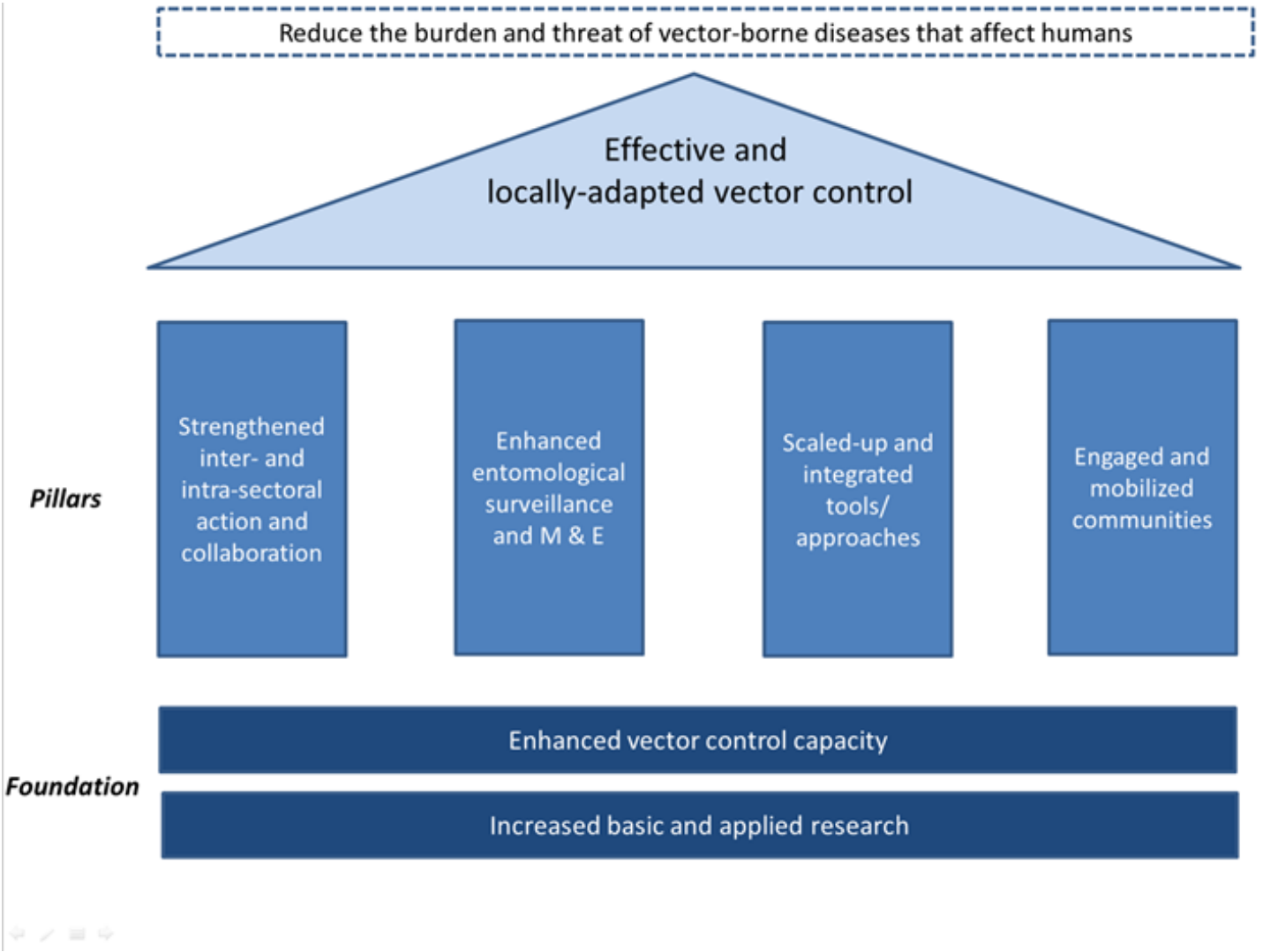
1. Disease situation
- Epidemiological assessment
- Vector assessment
- Ecological stratification
- Local determinants of disease



Enabling factors

- Country leadership;
- Resource mobilization;
- Advocacy;
- Regulatory support;
- Policy and normative support.

GVCR overview



Milestones, targets and activities

	Priority activities
1	National inter-ministerial task-force for multi-sectoral engagement in vector control established and functioning
2	National vector control needs assessment conducted
3	National-public health entomology workforce established and maintained to meet identified needs
4	Relevant staff from Ministries of Health and/or their supporting institutions trained in public health entomology
5	National entomological surveillance systems strengthened and integrated with health information systems to guide vector control
6	National agenda for basic and implementation research on entomological surveillance and vector control established and/or progress reviewed
7	National and regional VBD strategic plans aligned with Global Vector Control Response
8	National and/or regional institutional networks to support training and education for vector control established and functioning
9	Regional and global registries of appropriate experts to support entomological surveillance and vector control established and up-to-date

Milestones, targets and activities

To reduce the burden and threat of vector-borne diseases affecting humans, through the following:

	Priority activities	Milestones				Target
		2018	2019	2020	2025	2030
		Proportion of countries at risk or experience transmission of VBDs				
1	National inter-ministerial task-force for multi-sectoral engagement in vector control established and functioning	≥ 50%	≥ 75%	100%	100%	100%
2	National vector control needs assessment conducted	≥ 50%	≥ 75%	100%	100%	100%
3	National public health entomology workforce established and maintained to meet identified needs	≥ 10%	≥ 25%	≥ 50%	≥ 75%	100%
4	Relevant staff from Ministries of Health and/or their supporting institutions trained in public health entomology	≥ 10%	≥ 25%	≥ 50%	≥ 75%	100%
5	National entomological surveillance systems strengthened and integrated with health information systems to guide vector control	≥ 10%	≥ 25%	≥ 50%	≥ 75%	100%
6	National agenda for basic and implementation research on entomological surveillance and vector control established and/or progress reviewed	≥ 10%	≥ 25%	≥ 50%	≥ 75%	100%
7	National and regional VBD strategic plans aligned with *Global Vector Control Response*	≥ 10% (≥ 1 region)	≥ 25% (≥ 2 regions)	≥ 50% (≥ 4 regions)	100% (all regions)	100% (all regions)
8	National and/or regional institutional networks to support training and education for vector control established and functioning	≥ 10% (≥ 1 region)	≥ 25% (≥ 2 regions)	≥ 50% (≥ 4 regions)	100% (all 6 regions)	100% (all 6 regions)
9	Regional and global registries of appropriate experts to support entomological surveillance and vector control established and up-to-date	≥ 1 region (+ global)	≥ 2 regions (+ global)	≥ 4 regions (+ global)	All 6 regions (+ global)	All 6 regions (+ global)

NOTE 1: progress in activities to be tracked through indicators as defined in Table 2.
NOTE 2: these are draft milestones/targets only - to be refined based on regional feedback on current 'baseline' situation

MPAC inputs to GVCR

- 2nd draft to be completed **26 September 2016**
  - To be circulated to MPAC (GMP), STAG (NTD) and STAC (TDR)
  - ➢ Electronic feedback required by **9 October 2016**
  - Due to time constraints, national/regional consultations to be conducted leveraging planned meetings

Concluding points

- Country leadership of prevention and control efforts is critical.
- Policies and activities should not be limited to the health sector and should always be evidence-based.
- Action within countries and between countries should be harmonized and strengthened.
- Adoption of novel tools when validated for operational use is encouraged.
- Aim is to ensure all countries can achieve success, irrespective of their current capacities and resources.
- Emphasis on integrated, community-based approaches.

Malaria Policy Advisory Committee Meeting

14–16 September 2016, Geneva, Switzerland
Background document for Session 6

Proposed Evidence Review Group to review the cardiotoxicity of quinoline antimalarial medicines

Dr Andrea Bosman, WHO Global Malaria Programme
Dr Shanthi Pal, WHO Essential Medicines and Health Products
August 2016, Geneva, Switzerland

Background

A prolonged QTc interval is a risk factor for ventricular tachyarrhythmias, such as torsades de pointes (TdP), which can cause sudden cardiac death, particularly when the QTc interval is over 500 msec. However, the relation between QTc prolongation and TdP is not entirely clear, as only some patients with prolonged QTc intervals develop life-threatening ventricular tachyarrhythmias. This could be related to genetic disorders, pathological conditions, or drug interactions with concomitant medications that prolong the QTc interval.

As a drug side effect, TdP has been a major liability, causing the withdrawal of medications from the marketplace. Yet, the relations between the drug-induced prolongation of QTc intervals and predictors of ventricular tachyarrhythmias that can cause sudden cardiac death are not well understood. Compounds that have been linked to clinical observations of TdP include amiodarone, fluoroquinolones, methadone, lithium, chloroquine, erythromycin, amphetamine, ephedrine, pseudoephedrine, methylphenidate and phenothiazines. Some antiarrhythmic medications, such as sotalol, procainamide and quinidine, may induce TdP as a side effect. The following factors have been associated with an increased risk of TdP: hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, heart failure, left ventricular hypertrophy, hypothermia, subarachnoid hemorrhage and hypothyroidism.

The US-FDA is investing in a research programme designed to identify better predictors of drug-induced TdP, with the aim of progressively moving away from Thorough QT (TQT) study requirements for registration. This programme is expected to be completed over the next two years, and involves *in vitro* studies assessing the effects of drugs on multiple ion channels, as well as early clinical studies with exposure –response analysis using detailed ECG collection. The programme also includes ECG studies of multichannel block by multiple drugs in order to differentiate a pure hERG potassium channel block associated with a high torsade risk, and a combined hERG potassium channel and inward current block (calcium or late sodium) that may lower torsade risk *(1)*.

The case of antimalarial medicines

Several quinoline antimalarial medicines are associated with a prolonged QTc interval, namely chloroquine, quinine, mefloquine and piperaquine (in fixed-dose combination with dihydroartemisinin). WHO recommends all of these medicines for the treatment of malaria. Quinidine is associated with higher levels of cardiotoxicity and is no longer used for malaria

WHO/HTM/GMP/MPAC/2016.9

treatment. Halofantrine causes a marked increase in QTc prolongation and has been associated with over 30 reports of sudden cardiac death. As a result, WHO does not recommend halofantrine for the treatment of malaria.

Many studies on the effects of antimalarials on prolonged QT intervals may systematically overestimate drug-induced effects when comparing pre- and post-treatment ECGs, as the resolution of fever and fasting (which influence the heart rate) are associated with the prolongation of the QTc interval. The QT should be corrected according to the heart rate, preferably using the Fridericia correction (QTcF), in order to improve the detection of patients at increased risk of ventricular arrhythmia.

Chloroquine belongs to the 4-aminoquinoline group and has been the most widely used antimalarial over the last 60 years. Several hundred tons have been dispensed for treatment and prophylaxis; in the past, it was even distributed as medicated salt. At higher doses, often in combination with other agents, it has also been used for the treatment of rheumatoid arthritis, systemic lupus erythematosus and other chronic conditions.

Piperaquine is a bisquinoline compound, also of the 4-aminoquinoline group. In the 1960s, it was deployed on a large scale in China, where an estimated 140 million adult doses were deployed for large-scale malaria prophylaxis, treatment and mass drug administration. In view of increasing levels of drug resistance and in line with WHO recommendations, dihydroartemisinin-piperaquine in fixed-dose combination is increasingly being deployed in malaria-endemic countries, including for mass drug administration.[1]

In 2011, based on findings from Thorough QT (TQT) studies, the European Medicine Authority gave marketing authorization to Eurartesim™, outlining a series of contraindications and requirements for ECG monitoring (SmPC available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001199/WC500118113.pdf)

Plan for WHO review of the cardiotoxicity of antimalarial medicines

In collaboration with the WHO Department of Essential Medicines and Health Products, and following the EMA's and US-FDA's recommendations for experts, the WHO Global Malaria Programme consulted a small group of expert cardiologists and QTologists on how best to proceed with the review of the cardiotoxicity of antimalarial medicines.

Although more research is needed to identify the predictors of drug-induced TdP, the experts recommended that WHO analyse a large individual patient data series to document sudden cardiac death following drug exposure. Documented TdP in ECG recordings, even in a single case, should be taken as a strong indicator of the mechanisms of drug-induced death. The analysis should include not only the quinoline antimalarial medicines, but also concomitant medicines able to prolong the QTc interval. There was general consensus that the search and analysis of drug-associated "syncope" was unnecessary, as it would be influenced by too many confounders.

The WHO secretariat presented the rationale, objectives and proposed methods of the Evidence Review Group (ERG) at the Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), held in June 2016 in Geneva. The advisory committee endorsed the objectives and proposed list of studies, and experts recommended the findings be presented at the next annual meeting in 2017.

1 Administration of antimalarial treatment to every member 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. Mass drug administration is usually performed in order to reduce the parasite reservoir of infection radically and thus reduce transmission in a population.

The specific objectives of the ERG meeting will be the following:

- To evaluate the risk of sudden unexplained death following exposure to quinoline antimalarials (from data available to Vigibase, WWARN, Liverpool STM, and pharmaceutical companies);
- To assess the dose-response effect and risk factors of QTc prolongation from pharmacokinetic/pharmacodynamic (PK/PD) studies of the main ACTs used in Africa, i.e., artemether-lumefantrine, artesunate-amodiaquine and dihydroartemisinin-piperaquine
- To analyse the PK/PD effect of piperaquine in healthy volunteers compared to malaria patients, based on comparative clinical trials of dihydroartemisinin-piperaquine, arterolane-piperaquine and artefenomel-piperaquine
- To identify evidence gaps and provide recommendations for additional studies, including meta-analyses of individual patient dose-response effects and risk factors for QTc prolongation following exposure to different antimalarial medicines.

WHO will review data from the global database (Vigibase™) of suspected drug safety reports maintained at the Uppsala Monitoring Center in Sweden. The database contains approximately 13 million reports of suspected adverse drug reactions (ADRs), so-called Individual Case Safety Reports (ICSRs), collected by the national drug authorities of 124 countries for more than 100 000 different medicinal products. In addition to this review, in consultation with malaria research, a list of possible studies and reviews was compiled with timelines for completion for consideration and review by the WHO Evidence Review Group on cardiotoxicity of antimalarials in October 2016 (see Annex 1).

The conclusions of the ERG and draft recommendations will be presented to the Malaria Policy Advisory Committee (MPAC) in March 2017 and to the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) in April 2017.

References

1. Johannesen L, Vicente J, Mason JW, Sanabria C, Waite-Labott K, Hong M et al. Differentiating drug-induced multichannel block on the electrocardiogram: randomized study of dofetilide, quinidine, ranolazine, and verapamil. Clinical Pharmacology & Therapeutics 2014;96:549–58.

ANNEX 1 - List of studies on cardiotoxicity antimalarials with timelines

	Actions	Responsible group (contact person)	Objectives	Status	Timeline	WHO ERG presentation (Oct 2016)
1	Vigibase analysis of reports of serious adverse events	Shanti Pal	1. Define risk of sudden death and torsade de pointes associated with halofantrine	Completed		Yes
			2. Define risk of cardiac SAEs associated with DHA-PPQ	Ongoing	Mid-August	Yes
			3. Analysis of risk of unexplained sudden death following any antimalarial	Ongoing	End of August	Yes
2	Literature reviews	Nick White	Meta-analyses of: 1. Cardiac safety reports, and 2. Sudden deaths reported with targeted antimalarial drugs: quinine; chloroquine; piperaquine; mefloquine; lumefantrine; amodiaquine; sulfadoxine-pyrimethamine; halofantrine; primaquine	Publication in preparation	End of September	Yes
3	SAE Liverpool safety database	Cheryl Pace	To analyse serious adverse events and their relationship with antimalarial drugs and doses	Ongoing	End of September	Yes
4	DHA-piperaquine population PK/PD analysis	Joel Tarning	To assess the piperaquine exposure–QT relationship, and the effects of confounders including malaria disease severity, using PK/PD data from the following studies: 1. INESS multicenter Phase IV study PK/PD data	Ongoing	End of September	Yes
		Joel Tarning	2. Healthy volunteer study (n=16), Thailand	Completed		Yes
		Eva Maria Hodel, Anja Terlouw, Joel Tarning	3. ADJUST study, Malawi	Ongoing	Preliminary ADJUST analysis Sept. 2016	Yes
5	Review of cardiotoxicity safety data from pharmaceutical companies	GSK, Novartis, Roche, Sanofi, Shing Poon, Sigma Tau, SunPharma	To review available proprietary data on antimalarial cardiotoxicity to determine any association with drug, dose or confounders To encourage pharma to contribute raw data to a pooled analysis of all pharma PK/PD data	Completed	WHO to request pharma companies to present their data	Yes

ANNEX 1 - List of studies on cardiotoxicity antimalarials with timelines

	Actions	Responsible group (contact person)	Objectives	Status	Timeline	WHO ERG presentation (Oct 2016)
6	OZ439+piperaquine	MMV	To evaluate the effect of OZ439+piperaquine on QTc intervals 1. In healthy volunteers 2. Phase IIb study 3. Comparison between healthy volunteers and malaria patients	Completed (Darpo *et al.)* Ongoing Not started		Yes Yes TBC
7	Electrophysiology cardiotoxicity study	Xin Hui Chan	To evaluate alternative approaches to assessing cardiotoxicity	Ongoing	Preliminary result end of September	Yes
8	START-IPT	Eva Maria, Sarah Staedke	To evaluate the safety of IPT with DHA-piperaquine in school children in Uganda	Ongoing	End of September	Yes
9	STOPMIP	Feiko ter Kuile	To evaluate the safety of IST or IPT with DHA- piperaquine in pregnant women in Indonesia	Ongoing (EMH doing the PK/PD safety analysis)	End Q1 2017	No
10	Pooled DP PK/PD analysis	Anja / Joel / Cheryl & Piperaquine safety study group	To assess the relationships between antimalarial exposure and ECG / cardiac safety, adjusting for the effects of confounders (including malaria disease severity, age, dose intake), using pooled PK/PD data from healthy volunteers, those given preventive treatment, and uncomplicated malaria patients, with an initial focus on 1. Cardiac safety of DP; 2. ARV-ACT drug interactions; and 3. Other adverse events associated with antimalarials, if resources are available	Ongoing Invitations sent	Preliminary analysis by March 2017	Yes, only summary of data invited / contributed & statistical analysis plan
11	Other analyses	Cardiabase	To assess through pooled data analysis the relationships between antimalarial exposure and QTc prolongation in relation to multiple covariates for studies available to Cardiabase, pending the agreement of sponsors/PI of individual studies	Ongoing Request to sponsors/PI sent	End of September	Yes

WHO plans for reviewing the cardiotoxicity of antimalarial medicines

Malaria Policy Advisory
Committee (MPAC) Meeting
14 - 16 September 2016
Salle A, World Health Organization, Geneva, Switzerland

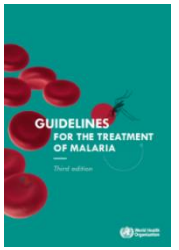
Global **Malaria** Programme

World Health Organization

Presentation Outline

- New indications of antimalarial medicines, e.g. SMC and MDA
- QT prolongation and risk of life-threatening arrhythmias
- The cardiotoxicity of antimalarial medicines
- WHO plans to review of the cardiotoxicity of antimalarials
- List of studies included in the review
- Panel members, participants, observers & secretariat
- Outline Agenda

Mass Drug Administration for malaria



- The objective of MDA in the context of transmission reduction to provide therapeutic concentrations of antimalarial drugs to as large a proportion of the population as possible in order to cure asymptomatic infections, to prevent re-infection during the period of post-treatment prophylaxis and, in some circumstances, to interrupt transmission.
- To impact on transmission, MDA requires high coverage of the target population which, in turn, demands a high level of community participation.
- Mass drug administration rapidly reduces the prevalence and incidence of malaria in the short term. However, if transmission is not interrupted or importation not prevented, transmission eventually returns to pre-intervention levels, unless the vectorial capacity is reduced and maintained to a very low level.

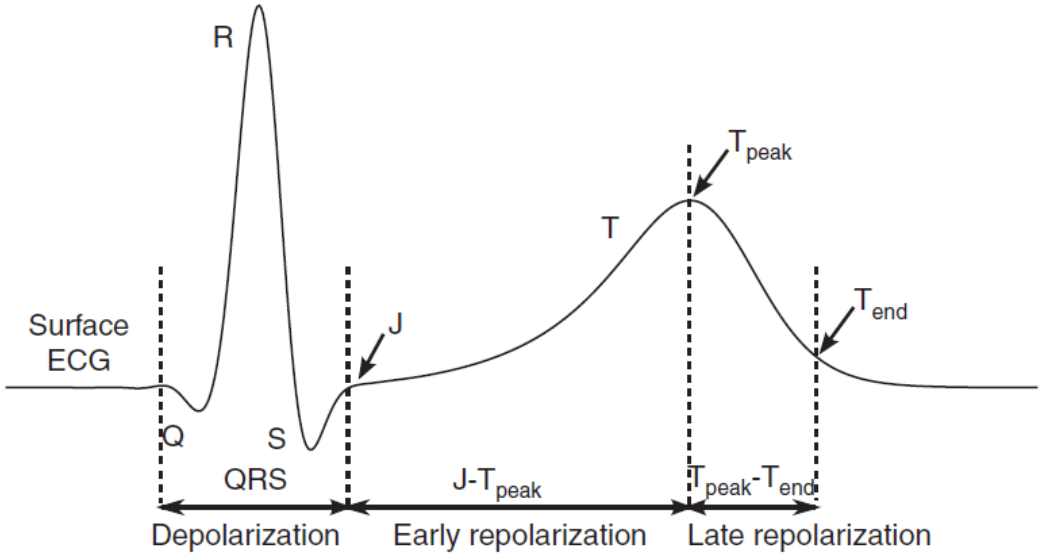
New WHO recommendations on MDA

Based on a recent evidence review, the WHO Malaria Policy Advisory Committee made the following recommendations on the role of MDA:

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.

2. 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, as well as in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.

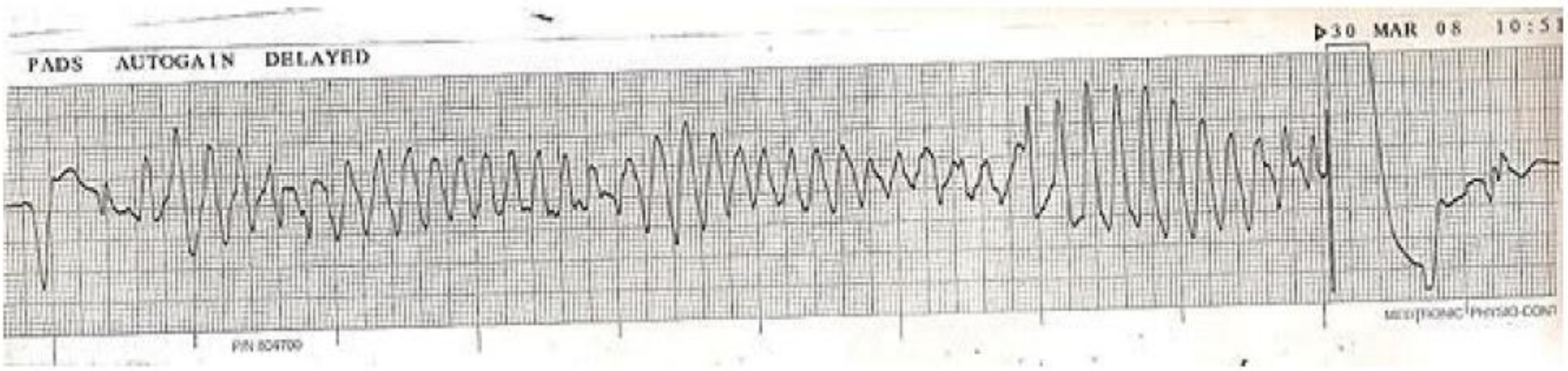
QT prolongation and cardiotoxicity



The QT interval represents electrical depolarization and repolarization of the ventricles. QT prolongation increases vulnerability to premature action potentials during the late phase of depolarization which may trigger ventricular tachyarrhythmias.

- A lengthened QT interval is a biomarker of drug-induced hERG potassium channel block and risk of torsade de pointes (TdP) which can lead to sudden death. The risk is not specific and the relation between QTc prolongation and TdP is not entirely clear. Only some drugs which lengthen the QT interval are associated with life-threatening ventricular tachyarrhythmias and only a small proportion of patients with prolonged QT interval develop them.

Torsade de Pointes (TdP)



- The ECG in torsade de pointes (TdP) shows a *polymorphic ventricular tachycardia* giving the illusion that the QRS complex twists around the isoelectric baseline. It is haemodynamically unstable causing a sudden drop in arterial blood pressure, leading to dizziness and fainting. Most episodes of TdP revert to normal sinus rhythm within a few seconds, but may also persist and degenerate into ventricular fibrillation, which will lead to sudden death in the absence of prompt medical intervention.

Drug induced QTc prolongation and TdP

- TdP as a drug side effect has been a major reason for withdrawal of medications from the market, in spite of the unclear relations between drug-induced prolongation of the QTc interval and predictors of life-threatening ventricular tachyarrhythmias.
- The US-FDA is investing in a research programme to identify better predictors of drug-induced torsade de pointes, with the aim of superseding the current Thorough QT (TQT) study requirements for registration. This programme is expected to be completed over the next two years, and involves *in vitro* studies, use of detailed ECG recordings in clinical studies with exposure–response analysis, and ECG studies of multichannel block by multiple drugs to identify combined hERG potassium channel and inward calcium or late sodium current block, which may lower TdP risk .

Antimalarials and QTc prolongation

- Several quinoline antimalarial medicines are associated with prolongation of the QT interval, namely chloroquine, quinine, mefloquine and piperaquine (in fixed-dose combination association with dihydroartemisinin), all recommended by WHO for malaria treatment. Quinidine is associated with significant cardiotoxicity and is no longer in use for malaria treatment. Halofantrine induces marked increase in QT prolongation, has been associated with over 30 reports of sudden cardiac death and has never been recommended by WHO for treatment of malaria.
- Studies on the effects of antimalarials on QT interval prolongation may lead to systematic overestimation of drug-induced effects in malaria patients as anxiety, fever and fasting shorten the QT interval – which normalises with recovery. The QT should be corrected for the heart rate, preferably using the Fridericia correction (QTcF), to improve the detection of patients at increased risk of ventricular arrhythmia.

Plans for WHO review of cardiotoxicity

- On advice from WHO/EMP, EMA and US-FDA, the WHO Global Malaria Programme consulted a small group of expert cardiologists and QTologists on a plan a review of the cardiotoxicity of antimalarials.
- The experts recommended that WHO analyse large individual patient data series for documentation of sudden unexplained death following drug exposure. The documentation of torsade de pointes in ECG recordings even in a single death should be taken as strong indicator of the mechanisms of drug-induced death. The analysis should include not only the quinoline antimalarial medicines, but also possible exposure to concomitant medicines which prolong the QTc interval. There was general consensus that search and analysis of drug associated "syncope" was unnecessary as it will be influenced by too many confounders.

Review of cardiotoxicity of antimalarials

Objectives

- Inform the risk assessment for antimalarial cardiotoxicity
- Evaluate the risk of sudden unexplained death following exposure to quinoline antimalarials (Vigibase, WWARN, Pharma)
- Evaluate the dose-response effect and risk factors of QTc prolongation from PK/PD studies of the main ACTs
- Evaluate PK/PD relationships for piperaquine in healthy volunteers compared to malaria patients from comparative clinical trials of dihydroartemisinin-piperaquine and artefenomel-piperaquine
- Identify evidence sources and gaps, and provide recommendations for additional studies to inform risk assessments

List of studies considered for review

Vigibase: analysis of ADR reports of sudden deaths and torsade de pointes with halofantrine	INESS PK/PD analysis of multicenter trial data to assess piperaquine – QTc relationship
Vigibase: analysis of ADR reports of DHA-PQP	Cardiabase pooled analysis: WANECAM, OZ439-PQP, DP, ASAQ
Vigibase: analysis of unexplained sudden death for antimalarials	Healthy volunteer study in Thailand (PK/PD analysis)
Meta-analysis of sudden deaths in ongoing DP MDA studies	DP IPT in infants, schoolchildren and pregnant women in Africa and Asia (UCSF, LSHTM and LSTM)
Safety meta-analysis of repeated DP dosing (LSTM and CDC)	Review of cardiotox safety data for individual antimalarials (research, PDP and Pharma)
WWARN pooled analysis of sudden death among infected patients	Evaluation of QTc effect of Oz439+piperaquine in healthy volunteers and infected patients

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- Xin Hui CHAN (Rapp)
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- GSK
- Novartis
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- Pedro Alonso
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Outline agenda

DAY 1 – Plenary sessions

- Review of Principles of Electrophysiology and Methods for Assessing Cardiotoxicity
- Literature Review of Antimalarial Cardiotoxicity
- Sudden Death in Antimalarial Therapy
  - WHO ICSR database, MDA operations, IPTp-DP, literature review
- Studies on Antimalarial effects on the ECG
  - Halofantrine, Artemether-lumefantrine, Artesunate-amodiaquine, OZ439/Ferroquine, Dihydroartemisinin-piperaquine, artesunate-pyronaridine, artemisinin naphtoquine (?) and arterolane-piperaquine (?)

Outline agenda (continued)

DAY 2 – Plenary session

- PK/PD Analyses of Antimalarial Effects on the ECG
  - Pooled data from Cardiabase
  - Pooled data from studies shared with ERG
  - DHA-PQP intermittent preventive therapy
  - INESS / MORU healthy volunteer studies
- Planned next studies and reviews
  - WWARN piperaquine pooled data analysis plan

DAY 2 – Closed session for ERG Panel and WHO

- Development of draft recommendations

Discussion

Malaria Policy Advisory Committee Meeting
14–16 September 2016, Geneva, Switzerland
Background document for Session 7

World Health Organization

P. falciparum hrp2/3 gene deletions

Conclusions and recommendations of
a Technical Consultation
Geneva, Switzerland, 7-8 July 2016

Summary of conclusions and recommendations

Rapid diagnostic tests (RDTs) are a critical tool for malaria diagnosis in most endemic areas. The most common RDT target for the detection of *Plasmodium falciparum* is the antigen histidine-rich protein 2 (HRP2). The vast majority of RDTs manufactured, procured and used around the world are designed to detect HRP2 alone or in combination with other antigen/s. Monoclonal antibodies in RDTs target epitopes that are abundant in HRP2, as well as in HRP3, a structurally similar parasite protein.

Although the functions of HRP2 and HRP3 remain undefined, it is clear that they are not essential for parasite growth and transmission. Indeed, parasites can delete the genes encoding these proteins and continue to transmit in communities. Parasites with such gene deletions can cause false-negative results when HRP2-detecting RDTs are used. The first published clinical reports of infections with confirmed *P. falciparum hrp2/3* gene-deleted parasites came from Peru in 2010. Additional reports from neighbouring countries in South America led WHO to recommend alternative diagnostic methods for affected areas; however, in recent years, *pfhrp2/3* gene deletions have emerged in multiple endemic countries in Africa and Asia, causing concerns over malaria case management and control.

Although non-HRP2-based RDTs are commercially available, a rapid shift away from HRP2-based tests could pose serious supply security issues and disrupt the marketplace. In addition, there are few non-HRP2-based RDT options, as alternative detection systems are frequently less sensitive and are frequently more susceptible to heat and humidity.

In May 2016, the WHO Global Malaria Programme (GMP) published an information note for manufacturers, procurers and users of HRP2-based RDTs with interim guidance on how to investigate suspected false-negative RDT results, including those resulting from *pfhrp2* gene deletions, and on alternative non-HRP2-based RDT options (http://www.who.int/malaria/publications/atoz/information-note-hrp2-based-rdt/en/). In parallel, a technical consultation on *P. falciparum hrp2/3* gene deletions was held in Geneva on 7–8 July 2016. The consultation set out seven objectives. The final conclusions and recommendations related to these meeting objectives are proposed in bold text for the Malaria Policy Advisory Committee's consideration.

1. Review the currently available data, and define the scope and scale of *pfhrp2/3*-deleted parasite populations based on published or in-press reports and recent unpublished investigations.

In 2014–2015, published reports of *pfhrp2/3* deletions came from several countries in South America (Colombia, Brazil, Suriname and Bolivia), the China-Myanmar border and Ghana. Furthermore, unpublished data from studies investigating *pfhrp2/3* gene deletions in Eritrea, India, Mozambique, Democratic Republic of Congo, Western Kenya, Western Indonesia, Uganda and Tanzania were reviewed

WHO/HTM/GMP/MPAC/2016.12

during the meeting. In addition, preliminary results were reviewed from the Pf3k project, which is analysing the whole genome sequence of approximately 3000 geographically diverse *P. falciparum* isolates for *pfhrp2/3* deletions. Studies have varied in size; their inclusion of symptomatic versus asymptomatic patients; their use of prospective versus retrospective design; the availability of paired RDT and microscopy and/or PCR results; and the prevalence of single versus double *pfhrp2/3* deletions (from 0% in Mozambique and Western Kenya to 80% double deletions in Eritrea).

Based on the data reviewed, it can be concluded that *P. falciparum* parasites populations lacking one or both of the *pfhrp2/3* genes are now present outside of South America in both high and low transmission areas and with varying prevalence across narrow geographic ranges. **In South America**, **deletions were observed in parasite samples collected before HRP2-based RDTs were introduced and have spread with human migration; however, there is no strong evidence for the selection of *pfhrp2*-deleted genetic alleles.** Nevertheless, strong selection for *pfhrp2*-deleted parasites may occur in areas where RDTs are used as the predominant diagnostic tool. A stochastic simulation model has found that theoretically, the use of HRP2-detecting only RDTs for the diagnosis and treatment of *P. falciparum* malaria is sufficient to select for *pfhrp2/3* double-deleted parasites**.** Given the public health implications of the continued use of HRP2-based RDTs where *pfhrp2/3* deletions occur, **WHO should promote a harmonized approach to investigating, surveying and reporting *pfhrp2/3* gene deletions through the provision of standard protocols (including sample size calculations) and operating procedures. Furthermore, WHO should provide a list of reference laboratories** that can provide full or partial support for PCR required to confirm (or exclude) *pfhrp2/3* gene deletions, as well as laboratories that can perform complementary serological assays and targeted or whole genome sequencing. **A harmonized approach will accelerate learning and future policy development.**

2. Discuss options for the expanded mapping of *pfhrp2/3* deletions

Generally, ***pfhrp2/3* surveys and surveillance activities** should **first target countries where deletions or concerns have been identified and in the neighbouring countries.** Once deletions have been confirmed above a defined threshold (see below), continued surveillance and detailed mapping is not likely to be required because the action to be taken is dichotomous: to use or not use HRP2-only RDTs in the country.

Deletions identified and confirmed by a reference laboratory, referred through a range of scenarios, i.e. via complaint-reporting of suspected false-negative RDT results, or the retrospective analysis of discordant samples (HRP2-RDT negative and microscopy/PCR positive) from population surveys or small exploratory studies, **should trigger prospective investigations such as i) community-based surveys around the index case(s); ii) geographically targeted hospital/health centre surveys of malaria suspects; iii) nationwide sentinel site surveillance of malaria suspects.** All approaches should **target symptomatic patients in all transmission settings; screen with either two RDTs (HRP2-based and non-HRP2-based, recommended by WHO) or an HRP2-based RDT and quality-assured microscopy. Blood for PCR confirmation of *P. falciparum* infection and *pfhrp2/3* gene analysis should be collected only from patients with discordant results** (i.e., HRP2-RDT negative/non-HRP2-based RDT positive or *P. falciparum* microscopy positive).

Where **deletions have not been reported** locally or in neighbouring countries, **and** when there is **no evidence**[1] **to suggest they are present**, **new initiatives** to identify these gene deletions should **not be prioritized**. However, **it is recommended that complaint-reporting mechanisms be strengthened and supervisors and NMCP staff be educated about *pfhrp2/3* gene deletions**. If **resources** are **available**, **the recommended approach to screen for *pfhrp2* gene deletions** is to establish **periodic sentinel site**

[1] Rates of discordance between RDT and microscopy results are systematically ≥ 10–15%, with higher positivity rates with microscopy, where routine quality control is done by crosschecking or both are performed on the same individuals (e.g. during surveys); multiple formal complaints or anecdotal evidence of RDTs returning false negative results for *P.falciparum*.

surveillance of symptomatic patients in all transmission areas where possible building on existing sentinel sites (e.g. for drug efficacy monitoring).

WHO should integrate *pfhrp2/3* gene deletions into the global mapping database currently under development.

3. Review and update current recommended procedures for investigating and reporting *pfhrp2/3* gene deletions

The published recommended procedures for investigating and accurately reporting *pfhrp2/3* deletions consist of three steps: **establishing initial evidence, confirmatory evidence, and prevalence** (Cheng Q et al., *Malaria Journal* 2014 13:283). Procedures should be **revised to indicate the roles and responsibilities of stakeholders at each level of the health system,** i.e., end-users, supervisors, national malaria control programme managers/MOH, reference laboratories, WHO.

In establishing the initial evidence, it was agreed that, given current workloads and capacities, front-line health workers can be asked to report, but *not* to investigate their own suspected false-negative RDTs. Health workers should report suspicious test results to their supervisors as part of routine reporting; if an explanation is not found, the supervisors should report the results to the NMCP. It is the **NMCP** that **coordinates the investigation and** subsequent **response that generates the *initial and confirmatory evidence***. **The national health authorities should *avoid*** promulgating a message that all **RDT-negative results are suspicious and/or that RDT results need to be confirmed with microscopy.**

It is recommended that **confirmatory evidence include PCR for *pfhrp3*, in addition to PCR for *pfhrp2*,** as HRP3 proteins can show cross reactivity in HRP2-based RDTs**; however, the analysis of flanking genes for *pfhrp2* (and *pfhrp3*) and the serological confirmation of the absent HRP2 antigen (by ELISA or a second brand of RDT) are optional.**

4. Develop a plan for technical support for countries conducting investigations into suspected pfhrp2*/3* gene deletions

***Pfhrp2/3* gene deletions are challenging to confirm and represent an urgent public health threat**. Failure to recognize *pfhrp2/3* deletions raises the risks of false-negative *P. falciparum* infections going untreated or mistreated; of increased malaria transmission (due to failure to diagnose and treat infections); and of increased malaria morbidity and mortality. Unsubstantiated reports risk decreasing confidence in RDTs, and triggering unnecessary and costly changes to diagnostic strategy. Therefore, in order to promptly and effectively respond to this threat, **WHO should establish a consortium** made up of RDT procurers, NMCPs and their implementing partners, surveillance experts, malaria reference laboratories and research institutes to **provide technical support for the investigation of suspected false-negative RDTs due to *pfhrp2/3* deletions, to establish appropriate surveillance systems, and to elaborate the factors influencing the emergence and spread of *pfhrp2/3* deletions.**

5. Propose alternative RDT-procurement and case-management strategies for areas affected by pfhrp2-deleted parasites.

A nationwide change to an RDT that detectsnon-HRP2 target antigens for *P. falciparum* is recommended when a prevalence threshold of patients carrying *pfhrp2*-deleted parasites meets or exceeds the lower 90% confidence interval for 5% prevalence[2]. If the prevalence is < 5%, the recommendation is to plan for change over a longer time frame, as it is anticipated that *pfhrp2/3*-deleted parasites will persist and spread. Acquiring additional surveillance data would help to prioritize the roll-out of non-HRP2-based RDTs.

[2] This is to allow for sampling variability

In all other cases, if *pfhrp2* deletions are confirmed in samples from any source, the suggested action is to establish prevalence through sentinel site surveillance or surveys.

A threshold of 5% was selected because it is around this point that the public health impact and proportion of cases missed by less sensitive non-HRP2-based tests is likely to be less than that associated with the continued use of HRP2-based tests.

Currently, the **choice of non-HRP2-based RDTs** that meet WHO's recommended procurement criteria or WHO Prequalification requirements is **very limited** due to the reduced sensitivity and heat stability of such tests compared to HRP2-based RDTs. **Tests with both HRP2 and pLDH antibodies on the same test line** should be **prioritized for assessment** by WHO prequalification; assessment should include a laboratory evaluation against *pfhrp2/3* single- and double-deleted parasites (culture and clinical samples) to determine whether they meet the recommended performance criteria. Programmes **should not replace Pf-only HRP2-based RDTs with current HRP2/pan-pLDH or aldolase combination tests for the purpose of detecting non-HRP2-expressing parasites**; only RDTs that specifically target pf-pLDH or pan-pLDH-only tests should be used.

6. Review the landscape of new tools for non-HRP2-based malaria diagnosis

Options for improving current pLDH-based RDTs exist, e.g., electronic readers, larger sample volume and related flow modifications; in addition, new nanoparticles, enzymatic labels, new or improved antibodies, and alternatives to HRP2-based RDT parasite detection are in development, e.g., cassette-based PCR, as well as field-adapted thermostable hydrogel PCR.

WHO should promote new test development and the improvement of existing tests, as well as the improvement of manufacturing processes. Furthermore, WHO should **work with procurers to ensure an adequate pricing structure** that will enable quality manufacture, and endeavour to **accelerate prequalification/regulatory processes** and field evaluations **of new tests and electronic readers for non-HRP2-based malaria diagnosis**.

7. Update WHO interim guidance on *pfhrp2* gene deletions

The WHO interim guidance on investigating suspected false-negative RDT results and the implications of new reports of *P. falciparum hrp*2/3 gene deletions should be revised to reflect the conclusions/recommendations of the technical consultation and MPAC recommendations.

Malaria Policy Advisory Committee Meeting
14–16 September 2016, Geneva, Switzerland
Background document for Session 8

Monitoring and Evaluation of the Global Technical Strategy for Malaria 2016–2030 and Action and Investment to defeat Malaria 2016–2030

August 2016, Geneva, Switzerland

Contents

1. Introduction

The WHO *Global Technical Strategy for Malaria 2016–2030* (GTS) and the Roll Back Malaria (RBM) Partnership's *Action and Investment to defeat Malaria 2016–2030* (AIM) provide a vision of how endemic countries can accelerate progress towards malaria elimination. These documents emphasize (i) the need for universal access to interventions for malaria prevention, diagnosis and treatment, (ii) that all countries should accelerate efforts towards malaria elimination, and (iii) that malaria surveillance should be a core intervention. The GTS and AIM share the same global targets for 2030 and milestones for 2020 and 2025,[1,2] as shown in Table 1:

Table 1.
Goals and milestones of the GTS and AIM

Vision – A world free of malaria

Goals	Milestones		Targets
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	≥40%	≥75%	≥90%
2. Reduce malaria case incidence globally compared with 2015	>40%	≥75%	≥90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

The purpose of this document is to describe how the GTS and AIM will be monitored and evaluated. It (i) contains a list of recommended indicators along the continuum from high transmission to elimination, (ii) suggests milestones for the development of information systems, (iii) describes how information from these systems should be used to influence decision-making and programme performance, and (iv) defines institutional responsibilities for the monitoring and evaluation of the GTS and AIM.

This document is intended for managers of national malaria programmes and health information systems who wish to set up or adapt surveillance, monitoring and evaluation systems to be aligned with the GTS. It is also relevant to other implementing partners and financiers of malaria programmes or information systems development.

[1] Countries will set their own national or subnational targets, which may differ from the global targets.
[2] The Sustainable Development Goals also include a target for malaria for 2030, namely, "to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases". Ending the epidemic for malaria is interpreted as securing a 90% reduction in malaria incidence and mortality rates and eliminating malaria from at least 35 countries.

2. The aims of monitoring and evaluation

Monitoring and evaluation[3] (M&E) are critical to achieving the objectives of the GTS and AIM, and central to malaria programme implementation in endemic countries. In such settings, it is important to assess the malaria situation of a country or area and establish plans that make the most effective use of resources – either to eliminate or reduce the public health impact of malaria. As plans are implemented, they need to be periodically reviewed to assess whether programme activities are on track and achieving the desired outcomes, or whether they need to be adjusted (see Section 7).

While high quality and timely information is critical for programme planning and implementation, it is not the sole preserve of malaria programme managers. Information can be used to lobby external stakeholders for the required resources. The performance of malaria programmes can also be enhanced by making information from programme planning and monitoring more widely accessible. Public disclosure of information enables politicians, patients and citizens to monitor the services they are financing, and encourages managers to be more responsive to their clients' needs. Accordingly, the AIM emphasizes a high degree of participation and consensus building in the development, implementation and monitoring of malaria plans.

The primary purpose of malaria programme data is to support decision making and action at the local level, but information generated at the country level is also used to inform progress at the international level through reports produced by WHO and the UN. Such data also inform international financiers of malaria programmes and are an important determinant of future funding flows.

Box 1.
Major uses of monitoring and evaluation

Monitoring and evaluation can accelerate progress towards malaria elimination if used:

- to advocate for investment in malaria programmes in line with the malaria disease burden in a country or subnational area;
- to allocate resources to populations most in need in order to achieve the greatest possible public health impact;
- to regularly assess whether plans are progressing as expected or whether adjustments in the scale or combination of interventions are required;
- to account for the funding received and to enable the public, their elected representatives and donors to determine if they are obtaining value for money;
- to evaluate whether programme objectives have been met and to learn what has worked and not worked, so that more efficient and effective programmes can be designed.

[3] Monitoring is a continuous process of gathering and using data on programme implementation (weekly, monthly, quarterly or annually), with the aim of ensuring that programmes are proceeding satisfactorily or, if necessary, making adjustments. The monitoring process often uses administrative data to track inputs, processes and outputs, although it can also consider programme outcomes and impacts. Evaluation is a more comprehensive assessment of a programme, normally undertaken at discrete points in time and focused on the longer term outcomes and impacts of programmes. The overall goal of M&E is to improve programme effectiveness, efficiency and equity.

3. The epidemiological transition to malaria elimination

Many countries and areas are undergoing reductions in malaria transmission[4] due to the increased implementation of malaria interventions and socio-economic change. As this transition occurs, the epidemiology of malaria is likely to change in the following ways:

- The numbers of severe cases and deaths will decrease;
- The number of uncomplicated malaria cases will decrease;
- Malaria transmission will become more focal;
- The age distribution of cases, severe cases and deaths becomes more evenly distributed across age groups and reflects degree of exposure;
- Populations will become less immune, and the risk of epidemics and associated mortality will increase;
- Imported cases may represent an increasing fraction of the overall incidence.

The goals and possibilities of surveillance, monitoring and evaluation also evolve throughout this transition (see Table 2), such that:

- In areas of high transmission, programme monitoring and evaluation is mostly based on aggregate numbers, and actions are undertaken at a population level to ensure that all populations have access to services and there are no adverse disease trends.
- In areas with low or moderate transmission, there is greater heterogeneity in the distribution of malaria. As a result, it is important to identify the population groups most affected by the disease and to target interventions appropriately. This will be facilitated by mapping of cases and foci and analysis of case distribution at community level. As transmission is reduced, the risk of epidemics also increases; thus more frequent analysis of cases at health facility level is needed to allow early detection of potential outbreaks.
- As progress is made towards elimination, prompt detection of, and response to new cases and foci, is critical. Individual cases of infection or clusters of cases, need to be investigated in order to understand risk factors, eliminate foci of transmission and maintain malaria-free status. Surveillance systems become more complex and resource-intensive, and additional skills, training and activities are required.

[4] The term 'high transmission' has usually been used to indicate hyper- and holoendemic malaria (parasite prevalence in children aged 2–9 years > 50%), 'moderate transmission' to indicate mesoendemic malaria (10–50% parasite prevalence) and 'low transmission' to indicate hypoendemic malaria (parasite prevalence < 10%). For consistency, the threshold of 10% is used to characterize low transmission in this document and to provide a general guide as to the types of malaria surveillance possible at different levels of malaria endemicity. The thresholds are not, however, fixed, and surveillance strategies for low-transmission settings might sometimes be more appropriate when parasite prevalence is < 5%, for example, rather than < 10%.

Table 2.
Changes in malaria epidemiology and surveillance systems in the transition to malaria elimination[5]

Transmission	High & moderate	Low	Very low
Parasite prevalence (2–9 yrs)	>10%	<10%	
Incidence	Cases and deaths common and concentrated in <5yrs Limited temporal variation Limited geographical variation	Cases and deaths less common and distributed according to exposure Variable within and between years Risk of epidemics Geographical heterogeneity Concentrated in marginal populations	Cases sporadic Relapses and imported cases a high proportion of the total Focal distribution
Fevers	Proportion of fevers due to malaria relatively large, often >30%	Proportion of fevers due to malaria small, <10%	Proportion of fevers due to malaria very small
Health facility attendance	High proportion due to malaria	Low proportion due to malaria	Very few due to malaria
Vectors	Efficient	Controlled efficient/ inefficient	Controlled efficient/ inefficient
Aims of programme	Mortality and case reduction	Case reduction	Transmission elimination
Resources	Low expenditures per head Low-quality and poorly accessible services	Widespread availability of diagnostics and treatment	High expenditures per case with resources to investigate each case
Data recording	Aggregate numbers	Aggregate numbers List of admissions → cases	Case details
Investigation	Inpatient cases	Inpatient cases → all cases	Individual cases

[5] Adapted from *Disease Sureveillance for Malaria Control : An operational manual*, World Health Organization, Geneva, 2012.

4. Recommended indicators along the continuum to elimination

The GTS highlights a minimum set of 14 outcome and impact indicators according to which progress in malaria control and elimination should be monitored. The AIM recommends five indicators covering financing and governance. This document builds on these recommended indicators to define the core set of indicators that will be used to track malaria programmes globally, as shown in Table 3. The indicators consider:

(i) the resources available for malaria control (programme financing, commodities);

(ii) levels of service provision (intervention coverage);

(iii) the populations affected by malaria and trends in disease;

(iv) the performance of systems for surveillance, monitoring and evaluation.

While the majority of indicators are relevant at global and national levels (and frequently sub-national level), some indicators are primarily intended for use at national level and will not be used to track global progress. These are highlighted with an asterisk.

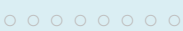
Eight indicators (numbered 18 to 25) concern the performance of systems for surveillance monitoring and evaluation. In addition to these indicators a set of bench-marks or milestones is presented in Section 6 of this document. The status of surveillance systems against these milestones will be assessed periodically (at least every 5 years) to provide additional insight into the development of effective systems for surveillance, monitoring and evaluation. One of the indicators specified in the AIM has been included in this category (country web-sites allowing access to geographically disaggregated data on malaria incidence or prevalence and interventions).

The indicators listed in Table 3 may not reflect the programmatic strategies used in all settings. For example, intermittent preventive therapy (IPTp) and seasonal malaria chemoprevention (SMC) are only used in certain high-transmission areas, whereas case investigation is generally only carried out as a programme approaches elimination.

Notes: excludes SMC, malaria vaccines, mass drug administration (MDA) and larviciding. No specific indicators for treatment of severe malaria.

Table 3. Recommended indicators along the continuum to elimination. Indicators highlighted in the AIM are shaded green while those from the GTS are shaded blue. Indicators that are relevant for national level monitoring but will not be used for global monitoring are shown with an asterisk (*). The relative importance of an indicator in different settings is indicated by the intensity of the dots. Indicators obtained through household surveys have red dots, while indicators obtained through routine health information systems have grey dots. Detailed specifications of the indicators, a description of when they should be used, data collection methods, and issues related to their interpretation are provided in Annex 1.

	Indicator[1]	Applicability of indicator by transmission setting[2]		
		High transmission	Low transmission	Elimination/ prevention re-establishment
	Inputs			
1	Malaria expenditure per capita for malaria control and elimination	●●●●●●●●	●●●●●●●●	●●●●●●●●
2	Funding for malaria relevant research	●●●●●●●●	●●●●●●●●	●●●●●●●●
3	Number of top-10 registered corporations that invest in malaria*	●●●●●●●●	●●●●●●●●	○○○○○○○○
	Outcome			
4	Proportion of population at risk that slept under an insecticide-treated net (ITN) the previous night	●●●●●●●●	●●●●●●●●	○○○○○○○○
5	Proportion of population with access to an ITN within their household	●●●●●●●●	●●●●●●●●	○○○○○○○○
6	Proportion of households with at least one ITN for every two people	●●●●●●●●	●●●●●●●●	○○○○○○○○
7	Proportion of households with at least one ITN	●●●●●●●●	●●●●●●●●	○○○○○○○○
8	Proportion of existing ITNs used the previous night	●●●●●●●●	●●●●●●●●	○○○○○○○○
9	Proportion of population at risk potentially covered by ITNs distributed*	●●●●●●●●	●●●●●●●●	○○○○○○○○
10	Proportion of targeted risk group receiving ITNs	●●●●●●●●	●●●●●●●●	●●●●●●●●
11	Proportion of population at risk protected by indoor residual spraying (IRS) in the previous 12 months	●●●●●●●●	●●●●●●●●	○○○○○○○○
12	Proportion of targeted risk group receiving IRS*	●●●●●●●●	●●●●●●●●	●●●●●●●●
13	Proportion of households with at least one ITN for every two people and/or sprayed by IRS in the previous 12 months	●●●●●●●●	●●●●●●●●	○○○○○○○○
14	Proportion of pregnant women who received ≥3 doses of intermittent preventive therapy (IPTp)	●●●●●●●●	○○○○○○○○	○○○○○○○○
15	Proportion of pregnant women who received 2 doses of IPTp	●●●●●●●●	○○○○○○○○	○○○○○○○○
16	Proportion of pregnant women who received 1 dose of IPTp	●●●●●●●●	○○○○○○○○	○○○○○○○○
17	Proportion of pregnant women who attended antenatal care (ANC) at least once	●●●●●●●●	○○○○○○○○	○○○○○○○○
18	Proportion of malaria cases detected by surveillance systems	●●●●●●●●	●●●●●●●●	●●●●●●●●

19	Proportion of children under 5 with fever in the previous 2 weeks for whom advice or treatment was sought			
20	Proportion of detected cases contacting health services within 48 hours of developing symptoms			
21	Proportion of cases investigated and classified (programmes engaged in elimination)*			
22	Proportion of foci investigated and classified (programmes engaged in elimination)*			
23	Proportion of expected health facility reports received at the national level			
24	Annual blood examination rate*			
25	Percentage of case reports received <24 hours after detection*			
26	Proportion of patients with suspected malaria who received a parasitological test			
27	Proportion of children under 5 with fever in the previous 2 weeks who had a finger or heel stick			
28	Proportion of patients with *P. vivax* or *P. ovale* malaria who received a test for G6PD deficiency			
29	Proportion of health facilities without stockouts of key commodities for diagnostic testing*			
30	Proportion of patients with confirmed malaria who received first-line antimalarial treatment according to national policy			
31	Proportion of *P. vivax* and *P. ovale* patients who received radical cure treatment			
32	Proportion of children under 5 with fever in the previous 2 weeks for whom advice or treatment was sought			
33	Proportion of treatments with ACTs (or other appropriate treatment according to national policy) among febrile children <5			
34	Proportion of health facility months without stockouts of first-line treatments*			
	Impact			
35	Parasite prevalence: proportion of population with evidence of infection with malaria parasites			
36	Malaria case incidence: number of confirmed malaria cases per 1000 persons per year			
37	Malaria test positivity rate*			
38	Number of foci by classification*			
39	Malaria mortality rate: number of malaria deaths per 100 000 persons per year			
40	Proportion of inpatient deaths due to malaria*			
41	Number of countries that have newly eliminated malaria since 2015			
42	Number of countries that were malaria-free in 2015 in which malaria has been re-established			

5. Role of routine systems and surveys

Multiple data sources are used in malaria monitoring and evaluation, including routine information systems, household and health facility surveys, sentinel sites and other special data collection efforts as needed (Box 2). The role and relative importance of these data sources change as programmes proceed from high transmission to malaria elimination.

Routine systems: In high-transmission settings, malaria accounts for a large proportion of health service attendance, and malaria information systems are necessarily embedded within integrated health management information systems. Simple and efficient recording and reporting systems are also needed to track vector control activities, notably ITN distribution and IRS coverage. Systems are also required to track resistance to insecticides and antimalarial drugs. In lower transmission settings, malaria-specific reporting systems are needed to satisfy the additional information demands for targeting and monitoring interventions among particular risk groups and foci.

Surveys: Information obtained from routine information systems is complemented by data from health facility and household surveys. Surveys can provide data on some indicators that cannot be measured with programmatic data, particularly indicators that require population level denominators such as coverage of interventions and parasite prevalence. Surveys can also enhance the interpretation of information gathered from routine information systems. For example, surveys may help to ascertain the percentage of patients with a febrile illness who attend public sector health facilities, thus providing information on the coverage of surveillance systems. Surveys may also be used to validate the data collected from routine systems.

The design of surveys changes with the intensity of malaria transmission. In high-transmission settings, nationally representative surveys enable the assessment of programme coverage and parasite prevalence across a country. In lower transmission settings, nationally representative surveys may be less useful and surveys better targeted at those populations most at risk.

The relevance of indicators and the feasibility of obtaining particular information through a survey also change with malaria transmission intensity. For example, parasite prevalence among children under 5 years of age is a relevant indicator in high-transmission settings because these children have a high risk of acquiring malaria, while prevalence in adults is generally low. It is also practical to obtain information from children under 5, as they are more likely to be at home during a household survey and available for a malaria test. In low-transmission settings, measuring parasite prevalence in children under 5 may not be very informative, as, in general, these children do not represent a high-risk group. It may therefore be preferable to examine prevalence among all age groups in such settings (although it may be more difficult to obtain a representative sample of school children and working adults, as they may not be at home when a survey is done). When transmission is low, however, a much larger sample size is required to measure prevalence and attention is, in any case, more often directed to measuring the incidence of symptomatic cases through routine health information systems.

The decision as to whether or not to measure parasite prevalence – and which age groups to cover – rests on weighing the potential benefits of obtaining the information (including the ability to more precisely identify the population groups most affected by malaria) against the costs of undertaking the survey (i.e., the increased sample size necessary, the diagnostic tools available and the potential to reach particular population groups), and considering the alternative uses to which such resources could be allocated.

Box 2.
Key information captured from routine health information systems, health facility surveys and household surveys

Routine health information systems

- Information on health facility resources
- Information on the use of health services and disease trends
- Information on patients treated by community health workers

Health facility surveys

- Information on the availability of staff, equipment and consumables to deliver services
- Verification of health facility service statistics (proportion of patients tested and treated with appropriate antimalarial medicines)

Household surveys

- Information on population coverage of services
- Information on patients not using government health services
- Information on population infection or anaemia rates

Sentinel sites and special studies

- Treatment efficacy studies
- Entomological surveillance
- Demographic surveillance sites

6. Milestones for development of systems

6.1 Case reporting

The initial phases of building an effective malaria information system will focus on ensuring good-quality data. This involves making sure that all patients with suspected malaria receive a diagnostic test, that cases are correctly classified according to the test result, that there is a quality management system for both microscopy and rapid diagnostic tests (RDTs), and that registration of and reporting from health facilities are complete and consistent. The quality of surveillance systems must be monitored continuously by maintaining an up-to-date list of operational health facilities, keeping track of which facilities have submitted the required reports, following up on missing reports, reviewing the data submitted, following up on incomplete or erroneous data, and providing positive feedback to health facilities that submit timely, complete and accurate data. In many settings community based case management and case reporting is an increasingly important component of service delivery and surveillance and it will be important to ensure the quality of diagnosis and reporting from community agents through training and supportive supervision from a linked health facility. Attention should be placed on ensuring improvement, and ultimately attainment of 100%, in two indicators, namely: the percentage of suspected cases that receive a diagnostic test and completeness of reporting. If data are incomplete, analyses of malaria morbidity and mortality may initially have to be confined to those health facilities that report data consistently, until reliable data can be obtained from all facilities.

As malaria becomes more focal and concentrated in particular population groups, analysis of indicators by health facility or population group is needed to target resources more precisely. Since malaria may be concentrated in marginalized populations, such as those living in remote border areas, migrant workers and tribal populations, programmes may need to find innovative ways to obtain information on these groups in order to design locally relevant programmes.

In low-transmission settings, data must also be reviewed more frequently at the health facility level in order to detect outbreaks as soon as possible. Epidemics may be more likely in areas where malaria has been successfully controlled but where efficient vectors remain than in areas with low levels of transmission due to environmental factors or inefficient vectors. Managers should be alert to malaria outbreaks and be ready to intensify control measures in some locations in order to prevent or contain outbreaks. As programmes approach elimination they identify and aim to clear remaining foci of malaria.

6.2 Case investigation

In the initial phase of control, it is recommended that each severe malaria case and death be investigated at the health facility level with the support of district staff, in order to identify and address programme weaknesses (such as poor ITN coverage, delays in seeking treatment and stockouts of antimalarial medicines). As transmission is reduced and the number of severe cases decreases, the opportunities for intensifying the investigation into severe cases and deaths increase. It becomes possible to establish a district-wide register of all severe cases, with which to investigate and eliminate future cases, and address programme weaknesses.

As transmission decreases even further, malaria programmes at the district level can begin to establish registers of all confirmed malaria cases reported in the district. These registers can contain information on the background characteristics of each case (e.g., location, age, sex, occupational group). Analysis of such registers can help to identify which population groups are most affected, to better target interventions and further accelerate malaria control. As programmes approach elimination case investigation helps to distinguish between locally acquired and imported cases and therefore whether there is ongoing local malaria transmission.

6.3 Heterogeneity in programme implementation

Malaria control may progress more rapidly in some parts of a country than in others; the strategies for surveillance may therefore vary. For example, some districts may rely exclusively on reporting aggregate cases, while others may supplement this with details of individual cases. Indeed, some parts of a country may be pursuing elimination. Therefore, they must identify the origin of each case in order to intensify control measures in specific localities and ensure that transmission is halted at the earliest possibly opportunity.

Table 4 provides milestones for systems development for different epidemiological settings; these milestones are considered to be achievable by 2020. The attainment of these milestones is a particular focus in the monitoring and evaluation of Pillar 3 of the GTS: the strengthening of surveillance systems.

Table 4: Milestones for disease surveillance systems development

		High transmission	Low transmission	Elimination/ Prevention of re-establishment
Data generation	Diagnostic testing	Documented criteria for which patients should get a test		
		All suspected cases get tested in public sector, private sector engaged	All suspected malaria cases get tested	All suspected malaria cases get tested
	Data recording	Health facilities have registers as recommended (with age, sex, type of test, species, village etc.)		Case investigation form
		Health facilities have current guidelines for the diagnosis, treatment and reporting of malaria cases		
	Case investigation	All deaths	All severe cases	All cases - including reactive case detection
	Master list of health facilities/ reporting units	Public sector list updated within 2 years	Public & private facility list updated within 1 year	Public & private facilities current
	Catchment/ target populations	Catchment/ target populations up to date		Populations of foci known
	Household surveys	Care-seeking behaviour measured every 3 years	Care-seeking behaviour measured every 5 years	
	Parasite prevalence	Parasite prevalence measured every 3 years	Prevalence every 3 years - in high-risk groups	
	Resistance monitoring	Therapeutic efficacy testing of all antimalarial medicines undertaken every 2 years		
		Insecticide resistance monitoring undertaken every year		
Reporting	Information reported	Monthly numbers of tests performed by test type		
		Monthly numbers of cases by age group, test type, species	Monthly/ weekly numbers of cases	Immediate notification of cases
				Reporting of cases by classification
				National case register in place
	Reporting rates	Reporting rates systematically tracked		
		Null values reported when nil cases or health facility closed		
		Reporting rates 80%+ from public health facilities	Reporting rates 100% from public health facilities	Reporting rates 100% from public health facilities
			80% of reports within 1 week of due date	100% of reports submitted within 24 hours of case detected

		High transmission	Low transmission	Elimination/ Prevention of re-establishment
		Household survey to estimate % cases in private sector	Reporting 80%+ from formal private health facilities	Reporting rates 100% from private health facilities
Information use	Analysis	5 core charts used at district & higher levels		Tracking of individual cases and foci
		Geographic display of indicators by district	Display of indicators by sub-district/ village	Geographic display of indicators by household
		Annual progress report of all indicators		
	Disaggregation	Data available by health facility	Data available by village/ risk group	Data available by focus/ household/ individual
	Dissemination and feedback	Quarterly feedback of key indicators from HQ using scorecard		Real-time feedback of key indicators from HQ
		Publically accessible country web-site allowing access to disaggregated data on programme coverage and malaria incidence or prevalence		
Other	Coding systems	Common or linkable codes across systems	Common or linkable codes across systems	Common or linkable codes across systems
	Quality assurance	Lot quality assurance undertaken for RDTs		
		Health facilities undertaking microscopy participate in QA review by reference laboratory		All +ve slides & 10% of -ve slides rexamined
	Legislation		Malaria a notificable disease	Malaria a notificable disease
	Staffing	Health facility and community health workers participate in continuing education/on the job training in malaria case management and notification every two years		

7. Use of information

It is essential that information collected is used in ways that improve programme impact. To that end, two major uses for this information include programme planning, and programme monitoring and evaluation.

7.1 For programme planning

A principal use of information is to develop a Malaria Strategic Plan (MSP) which defines the goals and objectives of a malaria programme, how they will be achieved and the resources required. The MSP should describe the roles of different stakeholders in the implementation of the plan, and set targets for monitoring progress and ensuring accountability.

The MSP should allocate available resources to the most effective interventions and to populations most in need, in order for reductions in malaria incidence and mortality to be maximized and wastage of resources minimized. A key approach to optimizing malaria responses within a country or territory is stratification, whereby a country or area is divided into smaller units in which where different combinations of interventions are delivered.

An MSP typically covers a period of 5 years. Its establishment is usually preceded by a review of the malaria situation in the country (the "malaria programme review"), which takes into account:

- The population groups most affected by malaria, in order to understand where malaria case incidence and mortality are highest and whether certain population groups are particularly affected. Information on the geographical distribution of malaria can be obtained from an analysis of reported case incidence and mortality rates, and presented in tables or maps. When interpreting geographical variation in reported malaria incidence or mortality rates, it is important to take into account variation in the proportion of the population that uses public health facilities, the extent of diagnostic testing and health facility reporting rates. Hence, it can be useful to tabulate or map general patient attendance, annual blood examination and health facility reporting rates alongside tables or maps of disease incidence. It may also be useful to examine geographical variation in test positivity rates or proportional malaria attendance, since these may be less distorted by variation in general patient attendance, diagnostic testing or health facility reporting rates. If available, data from household surveys can provide information on (i) if and where patients seek care for fever and thus the extent to which routine surveillance systems capture all malaria cases, and (ii) parasite prevalence, in order to help identify the populations most affected by malaria. It is also important to note particular risk factors associated with areas of higher incidence or mortality, including predominant vector and parasite species and population behaviours.

Figure 1. Timing of Malaria Strategic Plan and malaria programme reviews

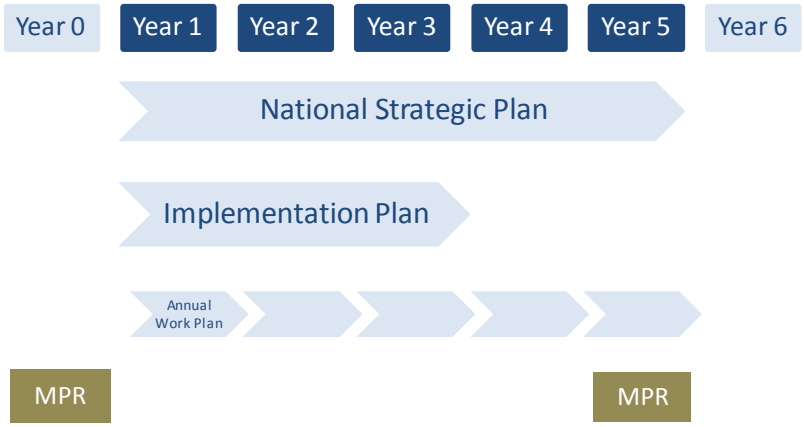
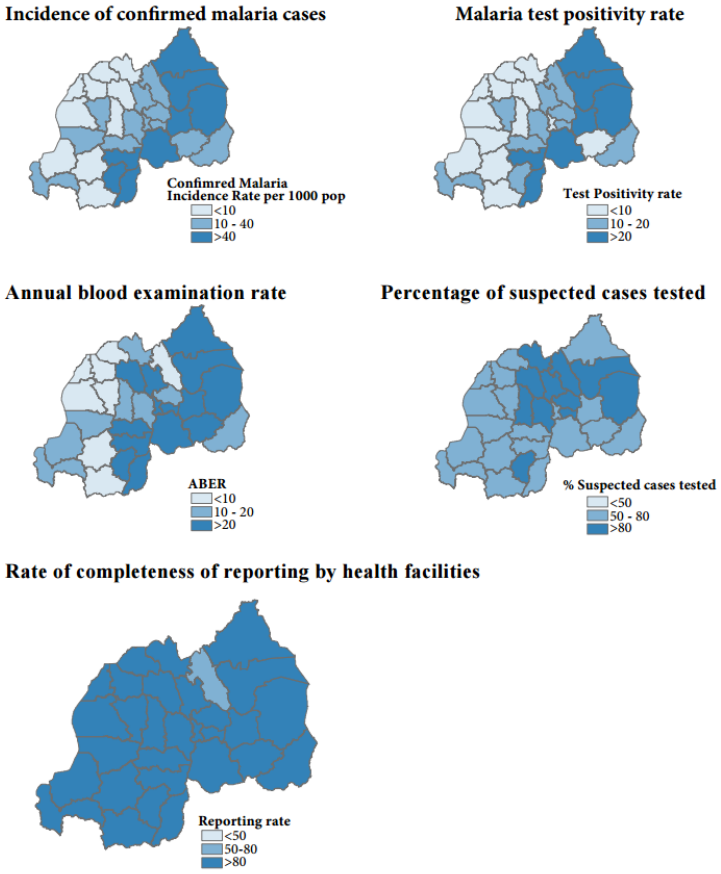


Figure 2. Examining the geographical distribution of malaria. Mapping of indicators allows programme managers to assess whether programme performance or malaria trends vary by geographical area and to determine whether malaria prevention, testing or treatment activities should be focused on particular geographical areas. Regional differences in the numbers of cases and deaths due to malaria might reflect the underlying epidemiology, the extent of malaria interventions, or diagnostic and case reporting practices. In the example below, higher case incidence rates are observed in eastern parts of the country, with higher annual blood examination rates and percentages of cases tested. Nonetheless, the same areas have a higher incidence rate as suggested by higher test positivity rates. Variation in the completeness of reporting may be due to communication delays or resource gaps in particular regions.

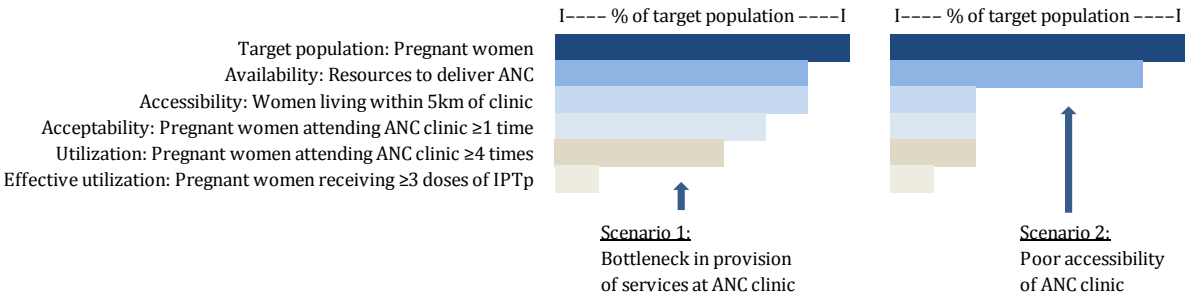


- Changes in disease incidence: Trends in the number of malaria cases, admissions and deaths reported may reflect change in malaria transmission and disease incidence in the population. However, they can also be influenced by changes in accessibility to health services, diagnostic testing practices and health facility reporting. Therefore, WHO recommends examining a set of six "control" charts that not only show changes in malaria incidence, but also factors that might influence observed trends (Figure 3). If there are too many gaps in routinely reported data to be able to assess malaria trends, it may be necessary to undertake a special study to retrospectively examine records of patient attendance in a sample of health facilities. If available, data drawn from 2 or more years of household surveys can provide information on changes in care-seeking behaviour and parasite prevalence.

Figure 3. Examining malaria trends. Trends in general patient attendance, annual blood examination rate and health facility reporting rates should be examined alongside trends in malaria disease incidence. It is useful to examine trends in test positivity rates or proportional malaria attendance, since these may be less distorted by changes in general patient attendance, diagnostic testing or health facility reporting rates. In the example below, there are fewer malaria cases, inpatients and deaths in the most recent months (graph 1). However, this trend could be due to less reporting and diagnostic effort in the same time period (graphs 4 and 5). Such a pattern is common and suggests that efforts are needed to improve the timeliness of reporting. There is also scope to increase the percentage of patients with suspected cases who receive a diagnostic test.

- Coverage of malaria interventions: It is useful to examine intervention coverage by geographical area or population risk group in order to assess whether or not interventions have been targeted appropriately. It is also useful to examine different stages in the delivery of interventions in order to identify the bottlenecks affecting service provision. In the two scenarios in Figure 4, the proportions of pregnant women receiving four or more doses of IPTp are the same – and low – but the reasons for the low coverage differ. In the first scenario on the left, while the utilization of ANC services is good, women do not receive multiple doses of IPTp, suggesting that the services on offer at antenatal clinics may need to be improved. In the second scenario, the utilization of antenatal clinics is poor, suggesting that more fixed or mobile antenatal clinics may be needed. Information on the coverage of malaria interventions can be obtained from (i) routine reporting systems, (ii) household surveys and (iii) health facility surveys.

Figure 4.
Identifying bottlenecks in malaria programmes



- Resources required and available for achieving programmatic targets: Information on programme financing should include both domestic and international financing. All malaria-specific expenditures should be included, e.g., commodities (ITNs, RDTs, ACTs etc), equipment (microscopes, vehicles), staffing (malaria managers, IRS sprayers) and activities (training, supervision). If expenditures that are shared with other programmes can be readily apportioned to malaria programmes, they can also be added to malria specific expenditures. If not, then a focus on malaria-specific expenditures is often sufficient for assessing trends in malaria investments and their impact on programme coverage. It is also useful to examine programme financing by geographical area or population risk group.

7.2 For programme monitoring and evaluation

The national malaria strategic plan should be monitored at regular intervals to assess whether programmes are proceeding according to plan or whether adjustments are required. Data for programme monitoring are usually obtained from routine health information systems, since programmes must be continuously monitored. Data from health facility and household surveys may, however, complement those from routine systems, e.g., in comparing the values of indicators obtained from routine systems and household surveys.

Managers at the national level should review indicators at least every quarter. Annual reviews should also be undertaken before budgets are prepared; mid-term reviews may be conducted to assess interim progress; and a final programme review should be undertaken before the next strategic plan is developed. The final malaria programme review (and mid-term review) would benefit from data from health facility surveys, household surveys and other special studies and these surveys and studies should be timed to contribute to the review(s).

In reviewing indicators, managers should ask specific questions regarding the progress of malaria programmes. The precise questions will depend on the local operational context, but are likely to include:

- Are programme coverage targets being met, or are particular interventions experiencing problems? For example, are targets for the percentage of suspected cases tested being met?
- Have there been important changes in the values of indicators over time? For example, has there been a decrease in the number of children receiving ITNs through immunization clinics? Of particular interest is whether the numbers of cases and deaths are being reduced or whether problems are being experienced in some locations, necessitating the modification of the programme. Managers should also be alert to potential epidemics.
- Are there particular bottlenecks in the delivery of services? For example, is there a large difference in the number of pregnant women receiving 1st and 3rd doses of IPTp?
- Are particular health facilities or geographical areas experiencing problems or doing well?

These questions can be answered easily if data are presented in such a way that indicators can be compared (i) with targets, (ii) across time, (iii) with other indicators, and (iv) between geographical areas. Other comparisons may also be informative, e.g., between different types of facilities or providers of services.

Managers at the health facility and district level need to review indicators on a monthly basis or even more frequently. Feedback on the status of selected key indicators should be communicated to districts and health facilities on a monthly or quarterly basis and include private health facilities where possible. It can be useful for district teams to be engaged in data analysis, presentation, and interpretation to improve buy-in and performance, and to enhance program capacity. It is important for data to be summarized in ways that enable staff in health facilities and districts to readily assess facilities' performance. Data may be presented through a dashboard, the ranking of districts or facilities, or colour coding of indicators according to their values.

Programme monitoring and surveillance should not be confined to malaria programme managers and implementers. Other government departments, elected leaders, community members and donors have a stake in ensuring the high quality of malaria programmes and need to be able to assess the operations they are supporting. If involved in the review process, these stakeholders can help to ensure that malaria programmes are responsive to populations' needs, and that malaria control and elimination are promoted as a development priority.

Figure 5. Comparison of districts
To be designed

8. Roles and responsibilities

8.1 International monitoring

Global progress in the reduction of mortality and morbidity and the eventual elimination of malaria will be tracked using countries' systems for surveillance, monitoring and evaluation. Progress will be monitored through the indicators outlined in this document (Table 3). Attention will also be given to the attainment of the milestones for systems development (Table 4).

Countries and partners are encouraged to ensure that data for these indicators are available at appropriate time points over the course of the GTS and AIM by ensuring adequate investments in routine information systems, and household and health facility surveys.

WHO and other partners will support endemic countries in strengthening their systems for surveillance, monitoring and evaluation, in line with the requirements of the GTS and AIM. This support will be aimed at improving the quality, availability and management of malaria data, and optimizing the use of such data for decision making and programmatic responses. Countries will also be supported in developing nationally appropriate targets and indicators to facilitate the subregional monitoring of progress.

WHO, in line with its core roles, will monitor regional and global malaria trends, and make these data available to countries and global malaria partners. WHO will monitor the implementation of the GTS and AIM, and regularly evaluate progress towards the milestones and goals set for 2020, 2025 and 2030 in an annual report and other periodic reports. It will support efforts to monitor the efficacy of medicines and vector control interventions, and – to this end – maintain global databases for the efficacy of medicines and insecticide resistance. It will regularly report to the regional and global governing bodies of the Organization, the United Nations General Assembly, and other United Nations bodies.

8.2 Development and review of guidance

WHO will set, communicate and disseminate normative and implementation guidance to support the development of effective systems for malaria surveillance, monitoring and evaluation. WHO's will convene a Technical Expert group (TEG) to provide advice to WHO on i) choice of indicators for monitoring the financing, coverage, quality and impact of malaria control interventions at the national and global level; ii) approaches for strengthening the capacity of member states to generate and use key information; and iii) strategies for obtaining, synthesizing and disseminating information on the indicators globally. It will ensure that guidance is responsive to the rapidly changing malaria context and regularly updated to incorporate innovative tools and strategies that are proven effective. The TEG will include representatives from country programmes and other major stakeholders.

The TEG will work closely with other partner groups from the RBM Partnership, whose primary responsibility is to support countries in the translation and implementation of WHO normative guidance. Partners will provide continuous input to the TEG on countries' priority SME needs and feed these back to the TEG for the revision/development of normative guidance.

By 2030, malaria morbidity and mortality are expected to be reduced dramatically compared to 2016, with the future eradication of malaria in sight. In this context, it will be increasingly necessary to establish a global monitoring system to systematically track and eliminate the remaining cases and foci of malaria. Regional efforts to monitor progress and share data, as exemplified by APLMA, ALMA, the Mekong and E8, have the potential to carve a path towards this goal.

9. Annexes

9.1 Reference list of indicators

Notes: The final document will have a more complete description of indicators, explaining the purpose of the indicator, and include more details on numerators and denominators. For now, the description is limited to numerators, denominators, data sources and breakdowns. Definitions have been made as consistent with previous guidance as possible.

	Indicator Name	Numerator	Denominator	Source	Breakdown	Comments
Input Indicators						
1	Malaria expenditure per capita	Malaria expenditure (domestic and international)	Population at risk of malaria	Routine administrative systems	Domestic (government, private sector, household) vs international, programme area, geographic area, time (year)	Direct malaria expenditures are sufficient if expenditures shared with other programmes cannot be readily apportioned to malaria.
Outcome Indicators						
2	Proportion of population that slept under an ITN[6] the previous night	Number of individuals who slept under an ITN the previous night	Total number of individuals who spent the previous night in surveyed households	Household survey	Geographic area, urban/rural, wealth index, educational status, gender, pregnancy status, age group (<5, 5–19, 20–45, 45+), household size	
3	Proportion of population with access to an ITN within their household	Total number of individuals who could sleep under an ITN if each ITN in the household is used by two people	Total number of individuals who spent the previous night in surveyed households	Household survey	Geographic area, urban/rural, wealth index, household size	
4	Proportion of households with at least one ITN for every two people	Number of households with at least one ITN for every two people	Total number of households surveyed	Household survey	Geographic area, urban/rural, wealth index, household size	
5	Proportion of households with at least one ITN	Number of households surveyed with at least one ITN	Total number of households surveyed	Household survey	Geographic area, urban/rural, wealth index, household size	
6	Proportion of existing ITNs used the previous night	Number of ITNs in surveyed households that were used by someone the previous night	Total number of ITNs in surveyed households	Household survey	Geographic area, urban/rural, wealth index, household size	

[6] An ITN is 1) a factory-treated net that does not require any treatment (an LLIN), or 2) a net that has been soaked with insecticide within the previous 12 months (see Reference Section 3.1 for explanation of revised definition).

	Indicator Name	Numerator	Denominator	Source	Breakdown	Comments
7	Proportion of population at risk potentially covered by ITNs distributed	Number of ITNs distributed in past 3 years * 1.8	Population at risk of malaria	NMCP records, census	Geographic area, time	
8	Proportion of targeted risk group receiving ITNs	Number of ITNs distributed to risk group	Number of people in risk group	NMCP records, census	Geographic area, risk group (e.g. antenatal clinic attenders, migrant populations)	
9	Proportion of population at risk protected by indoor residual spraying (IRS) within the previous 12 months	Number of people protected by IRS in the previous 12 months	Population at risk of malaria	NMCP records, census	Geographic area, time (year)	
10	Proportion of targeted risk group receiving IRS	Number of people in the targeted risk group protected by IRS in the past 12 months	Number of people in risk group	NMCP records, census	Geographic area, risk group (e.g. population in per-urban areas, those living in active focus)	
11	Proportion of households with at least one ITN for every two people and/or sprayed by IRS in the previous 12 months	Number of households with at least one ITN for every two people and/or sprayed by IRS in the previous 12 months	Total number of households surveyed	Household survey	Geographic area, urban/rural, wealth index, household size	
12	Proportion of pregnant women who received ≥3 doses of IPTp	Number of pregnant women who received ≥3 doses of IPTp	Number of expected pregnancies	Routine health information system, census	Geographic area, time (year and month)	
13	Proportion of pregnant women who received 2 doses of IPTp	Number of pregnant women who received 2 doses of IPTp	Number of expected pregnancies	Routine health information system, census	Geographic area, time (year and month)	
14	Proportion of pregnant women who received 1 dose of IPTp	Number of pregnant women who received 1 dose of IPTp	Number of expected pregnancies	Routine health information system, census	Geographic area, time (year and month)	
15	Proportion of pregnant women who attended antenatal care at least once	Number of first antenatal clinic visits	Expected number of pregnancies	Routine health information system, census	Geographic area, time (year and month)	

	Indicator Name	Numerator	Denominator	Source	Breakdown	Comments
16	Proportion of patients with suspected malaria who received a parasitological test	Number of suspected malaria cases receiving a parasitological test	Number of suspected cases of malaria	Routine health information system, health facility surveys	Geographic area, type of facility, time (year and month)	
17	Proportion of children under 5 with fever in previous 2 weeks who had a finger or heel stick	Number of children under 5 with fever in the previous 2 weeks who had a finger/heel stick	Total number of children under 5 who had a fever in the previous two weeks	Household survey	Geographic area, urban/ rural, wealth index, educational status of mother, gender	
18	Proportion of patients with *P. vivax* or *P. ovale* malaria who received a test for G6PD deficiency	Number of patients with *P. vivax* or *P. ovale* malaria who received a test for G6PD deficiency	Number of patients diagnosed with *P. vivax* or *P. ovale*	Routine health information system, health facility surveys	Geographic area, type of facility, time (year and month)	
19	Proportion of health facility months without stockouts of key commodities for diagnostic testing	Number of health facility months without stockouts of key commodities for diagnostic testing	Number of health facility months	Routine health information system, health facility surveys	Geographic area, type of facility, time (year and month)	Includes stockouts of RDTs and/ or microscopy consumables that prevent patients from receiving a diagnostic test. A stockout is defined as 7 days or more (not necessarily consecutive) of stockout. This may depend on the strength of the supply system.
20	Proportion of patients with confirmed malaria who received first-line antimalarial treatment according to national policy	Number of patients with confirmed malaria who received first-line antimalarial treatment according to national policy	Total number of confirmed malaria cases, including both passive and active surveillance	Routine health information system, health facility surveys	Geographic area, type of facility, parasite species, time (year and month)	
21	Proportion of persons with *P. vivax* and *P. ovale* infections who received radical cure treatment	Total number of persons with a confirmed *P. vivax* or *P.ovale* infection who received radical cure treatment	Total number of persons with confirmed *P. vivax* or *P. ovale* infections	Routine health information system	Geographic area, type of facility, time (year and month)	See above

	Indicator Name	Numerator	Denominator	Source	Breakdown	Comments
22	Proportion of children under 5 with fever in the previous two weeks for whom advice or treatment was sought	Number of children under 5 with fever in the previous two weeks for whom advice or treatment was sought	Total number of children under 5 with fever in the previous two weeks	Household survey	Geographic area, urban/ rural, wealth index, educational status, gender	
23	Proportion of all malaria treatments that are with ACTs (or other appropriate treatment according to national policy) among febrile children <5	Number of children under 5 with fever in the previous two weeks who received an ACT (or other appropriate treatment according to national policy)	Total number of children under 5 with fever in the previous two weeks who received any antimalarial medicine	Household survey, health facility surveys	Geographic area, urban/ rural, wealth index, educational status, gender	
24	Proportion of health facility months without stockouts of first-line treatments	Number of health facility months without stockouts of first-line treatments	Number of health facility months	Routine health information system, health facility surveys	Geographic area, type of facility, time (year and month)	A stockout defined as 7 days or more (not necessarily consecutive) of stockout. This may depend on the strength of the supply system.
25	Completeness of health facility reporting	Number of reports received from health facilities	Number of reports expected from health facilities (number of health facilities multiplied by the number of reports expected per health facility over period)	Routine health information system	Geographic area, type of facility, time (year and month)	Some countries will include Community health worker - level reporting. Systems need to include zero reporting. A due date is implied by the indicator, e.g., by the 15th of the following month for reports from health facility to the district level.

	Indicator Name	Numerator	Denominator	Source	Breakdown	Comments
26	Annual blood examination rate	Number of patients receiving a parasitological test over a year	Mid-year number of persons at risk for malaria		Geographic area/foci, risk group, active vs. passive, time (year and month)	Some past guidance has suggested that the annual blood examination rate should be about 10% in order to provide reliable trends, but the empirical evidence supporting such a target is not strong. In high-transmission settings, the rate is likely to greatly exceed 10% due to passive case detection alone.
27	Proportion of detected cases contacting health services within 48 hours of developing symptoms	Number of cases contacting health services within 48 hours of developing symptoms	Total number of passively detected malaria cases		Geographic area/foci, risk group, time (year and month), type of facility	
28	Percentage of case reports received <24 hours after detection	Number of case reports received <24 hours after detection	Total number of malaria case reports		Geographic area/foci, risk group, time (year and month), type of facility	
29	Proportion of malaria cases detected by surveillance systems	Number of confirmed malaria cases identified through active and passive surveillance activities over a 1-year period x 1000	Estimated number of malaria cases over a 1-year period x 1000		Geographic area, time (year)	
30	Proportion of cases investigated and classified	Total number of malaria cases in the national case register with fully completed case investigation forms	Total number of malaria cases in the national case registry		Geographic area/foci, risk group, time (year and month), type of facility	

	Indicator Name	Numerator	Denominator	Source	Breakdown	Comments
31	Proportion of foci investigated and classified	Total number of new potential and active foci in the national foci register that have received full investigations within the previous year	Total number of foci in the national foci register		Geographic area/foci, time (year)	
Impact Indicators						
32	Parasite prevalence	Number of persons with malaria infection detected by rapid diagnostic test or microscopy	Total number of persons tested for malaria parasites by rapid diagnostic test or microscopy		Geographic area, urban/rural, wealth index, educational status, gender	In high-transmission settings, this indicator is usually only measured for children <5
33	Malaria case incidence (Annual Parasite Index)	Number of confirmed malaria cases identified through active and passive surveillance activities over a 1-year period x 1000	Mid-year number of persons at risk for malaria infection during reporting year		Geographic area/foci, risk group, active vs. passive, age, sex and species When approaching elimination: indigenous, introduced, imported by nationality, induced	May report numbers of cases when incidence is low
34	Malaria test positivity rate	Number of confirmed malaria cases	Number of patients receiving a parasitological test		Geographic area/foci, risk group, active vs. passive, age, sex and species	Test positivity of passive/active case detection and microscopy; RDTs should always be reported separately
35	Number of foci by classification (active, residual, cleared and pseudo)	Number and population of foci by classification (active, residual, cleared and pseudo)		Foci registry		
36	Malaria mortality rate: number of malaria deaths per 100 000 persons per year	Number of malaria-specific deaths reported in the previous year x 10 000	Mid-year number of persons at risk for malaria infection during the reporting year		Geographic area, age, sex, risk group and species	May report numbers of cases when mortality rate is low
37	Proportion of inpatient deaths due to malaria	Number of inpatient deaths due to malaria	Total number of inpatient deaths		Geographic area, age, sex	

	Indicator Name	Numerator	Denominator	Source	Breakdown	Comments
38	Number of countries that have newly eliminated malaria since 2015	Number of countries with malaria in 2015 that have subsequently reported zero indigenous cases for 3 consecutive years				
39	Number of countries that were malaria-free in 2015 in which malaria has been re-established	Number of countries that were malaria-free in 2015 that have subsequently reported epidemiologically linked indigenous cases for 3 consecutive years				

Recommendations from the Surveillance, Monitoring and Evaluation Task Force

Richard Cibulskis
Strategy Evidence and Economics
Global malaria Programme

Global **Malaria** Programme

World Health Organization

Outline

1. Background to formation and work of SME Task Force
2. Framework for M&E of GTS and AIM
   a) Indicators
   b) Milestones
   c) Use of information
   d) Roles and responsibilities
3. Role of SME TEG and MERG

GTS: Measuring Global Progress and Impact

1. Progress should be monitored through a minimal set of 14 outcome and impact indicators drawn from a larger set of indicators recommended by WHO and routinely tracked by malaria programmes.
2. Countries should ensure that a baseline for at least these 14 indicators is available for 2015.

Surveillance system should be monitored through metrics such as:

1. the percentage of health facilities submitting monthly reports,
2. the proportion of health facilities receiving quarterly feedback,
3. and, in the advanced phase of malaria elimination, the proportion of cases and deaths investigated.
4. Also timeliness, accuracy, representativeness and validity.

Impact indicators for GTS 2016-2030

Impact

- Parasite prevalence: proportion of the population with evidence of infection with malaria parasites
- Malaria case incidence: number of confirmed malaria cases per 1000 persons per year
- Malaria mortality rate: number of malaria deaths per 100 000 persons per year
- Number of countries that have newly eliminated malaria since 2015
- Number of countries that were malaria-free in 2015 in which malaria was re-established

Outcome indicators for GTS 2016-2030

Outcome
• Proportion of population at risk who slept under an insecticide-treated net the previous night
• Proportion of population at risk protected by indoor residual spraying within the past 12 months
• Proportion of pregnant women who received at least three or more doses of intermittent preventive treatment of malaria while attending antenatal care during their previous pregnancy (sub-Saharan Africa only)
• Proportion of patients with suspected malaria who receive a parasitological test
• Proportion of patients with confirmed malaria who receive first-line antimalarial treatment according to national policy
• Proportion of expected health facility reports received at national level
• Proportion of malaria cases detected by surveillance systems
• Proportion of cases investigated (programmes engaged in elimination)
• Proportion of foci investigated (programmes engaged in elimination)

Monitoring framework for action and investment to defeat malaria 2016-2030

Indicator	Operational definition	Illustrative data source(s)	Suggested level (s)
High-level commitment to control and elimination of malaria	Existence of high-level malaria advisory or governing body that includes representation from the non-health and private sectors, as well as civil society	Will require engagement of malaria leadership to review malaria bodies	Regional, national, and local levels, where possible
Resources committed to malaria control and elimination	Total funding and proportion of annual health funding (per capita) allocated to malaria in affected countries (by source, including national funding, donor, and out-of-pocket)	RBM Malaria Funding Data Platform, OECD/DAC, Country data and surveys	Global, regional, national and local levels, where possible
Accountability to citizens for progress in malaria control and elimination	Public (web-based) access to geographically disaggregated data regarding malaria incidence or prevalence and intervention (prevention, diagnosis and treatment)	Will require accessing of websites for each affected country	Global, regional, national and local levels, where possible
Engagement of the private sector in malaria control and elimination	Number of top-10 registered corporations in the national tax base that invest in malaria (programmatic or financial contribution to malaria prevention and control for the company's workforce or the broader community, or both)	Will require measurement by malaria leadership to interview top-10 corporations regarding these investments	National level
Investment in malaria research and innovation	Total funding and proportion of funding for malaria relevant research (including R&D and operations or implementation research)	GFINDER (Policy Cures), MMV, IVCC, MVI, Global Fund, WHO and national research agencies	Global and national levels, where possible

Rational for SME Task Force

Recommendation of meeting of WHO Regional Advisors, Jan 2015:

- There should be an overarching plan for surveillance, monitoring and evaluation of the *Global Technical Strategy 2016-2030*. Describing the indicators to be measured, roles of routine systems, household surveys and health facility surveys. To include in what circumstance household surveys should be done and how often, where parasite prevalence would be measured etc.

Recognition of overlap in roles of SME TEG (WHO) and MERG (RBM) that needed to be addressed.

Recommendation of SME TEG March 2015:

- A malaria SME task force should be convened to develop an overall blue print for monitoring and evaluating the GTS. This should include members of GMP, RBM and other key stakeholders in surveillance monitoring and evaluation of malaria. Should consider global architecture for harmonizing work around SME

Terms of Reference of SME Task Force

To develop a framework for monitoring and evaluation of the *Malaria Global Technical Strategy 2016-2030* and *Action and Investment to defeat Malaria 2016–2030*:

- Outline an overarching strategy for malaria surveillance, monitoring and evaluation for 2016-2030 in line with the *Malaria Global Technical Strategy 2016-2030* and *Action and Investment to defeat Malaria 2016–2030* (including recommended indicators & data collection strategies in different epidemiological settings)
- Review current status of systems and issues that need to be addressed
- Identify ways forward including costing of strategies,
- Consider global architecture for harmonizing work around SME (e.g. role of WHO, TEGs, MERG, progress reporting required for international community, specific donors, RBM board etc)

Task force composition

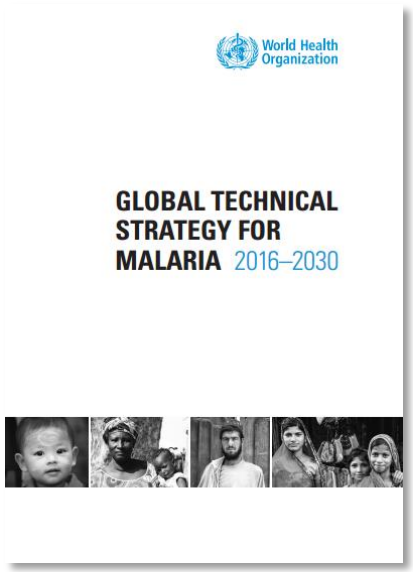
1. Agbessi Amouzou (UNICEF)
2. Richard Cibulskis (WHO)
3. Erin Eckert (USAID)
4. Scott Filler (Global Fund)
5. Kassoum Kayentao (Mali)
6. Abdisalan Noor (KEMRI)
7. Risintha Premaratne (Sri Lanka)
8. Arantxa Roca-Felterer (Malaria Consortium)
9. Anna Carolina Santeli (Brazil)
10. Larry Slutsker (CDC)

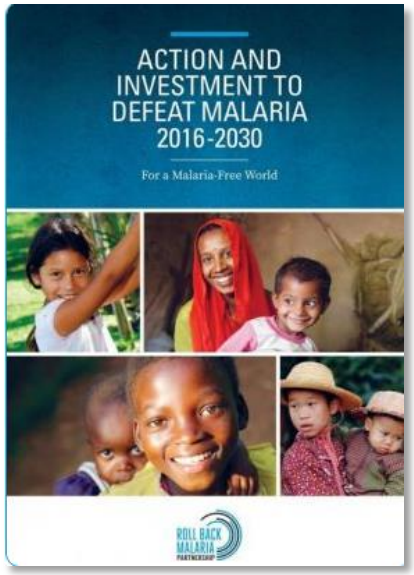
- Aimed to have representation from MERG, SME TEG, endemic countries and key international partners in malaria SME.
- Composition approved by RBM and WHO
- Meetings held December 2015 and June 2016

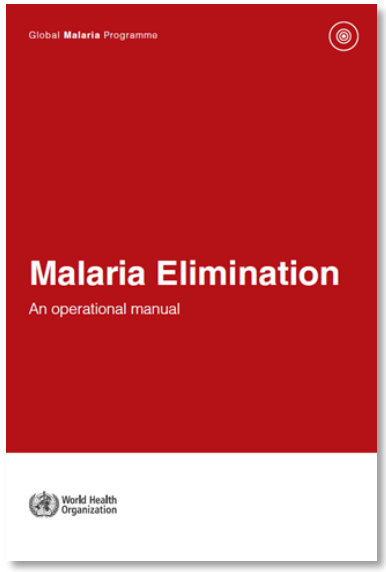
Contents of Monitoring and Evaluation Framework

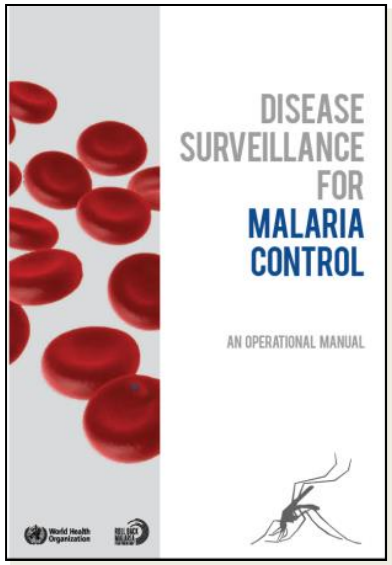
1. Introduction
2. The aims of monitoring and evaluation
3. The epidemiological transition to malaria elimination
4. Recommended indicators along continuum to elimination ✚
5. Role of routine systems and surveys
6. Milestones for development of systems ✚
7. Use of Information ✚
8. Roles and Responsibilities ✚
9. Annexes

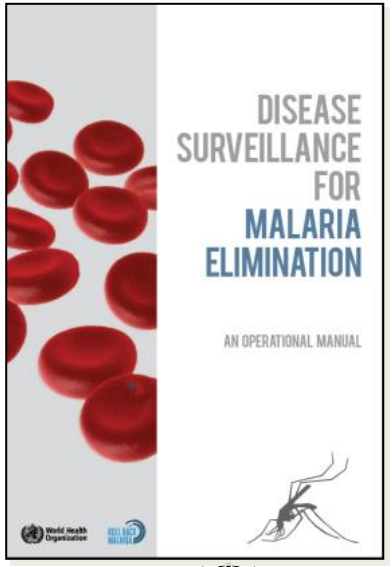
Recommended Indicators: Based on Existing Guidance











Global **Malaria** Programme

World Health Organization

Recommended Indicators: Financing and Vector Control

	Indicator[1]	Transmission: High	Low	Elim
Inputs				
1	Malaria expenditure per capita for malaria control and elimination	● ● ● ●	● ● ● ●	● ● ● ●
2	Funding for malaria relevant research	● ● ● ●	● ● ● ●	● ● ● ●
3	Number of top-10 registered corporations that invest in malaria*	● ● ● ●	● ● ● ●	○ ○ ○ ○
Outcome				
4	Proportion of population at risk that slept under an insecticide-treated net (ITN) the previous night	● ● ● ●	● ● ● ●	○ ○ ○ ○
5	Proportion of population with access to an ITN within their household	● ● ● ●	● ● ● ●	○ ○ ○ ○
6	Proportion of households with at least one ITN for every two people	● ● ● ●	● ● ● ●	○ ○ ○ ○
7	Proportion of households with at least one ITN	● ● ● ●	● ● ● ●	○ ○ ○ ○
8	Proportion of existing ITNs used the previous night	● ● ● ●	● ● ● ●	○ ○ ○ ○
9	Proportion of population at risk potentially covered by ITNs distributed*	● ● ● ●	● ● ● ●	○ ○ ○ ○
10	Proportion of targeted risk group receiving ITNs	● ● ● ●	● ● ● ●	● ● ● ●
11	Proportion of population at risk protected by indoor residual spraying (IRS) in the previous 12 months	● ● ● ●	● ● ● ●	○ ○ ○ ○
12	Proportion of targeted risk group receiving IRS*	● ● ● ●	● ● ● ●	● ● ● ●
13	Proportion of households with at least one ITN for every two people and/or sprayed by IRS in the previous 12 months	● ● ● ●	● ● ● ●	○ ○ ○ ○

Recommended Indicators: IPTp and Surveillance

	Indicator[1]	Transmission: High	Low	Elim
14	Proportion of pregnant women who received ≥3 doses of intermittent preventive therapy (IPTp)	● ● ● ●	○ ○ ○ ○	○ ○ ○ ○
15	Proportion of pregnant women who received 2 doses of IPTp	● ● ● ●	○ ○ ○ ○	○ ○ ○ ○
16	Proportion of pregnant women who received 1 dose of IPTp	● ● ● ●	○ ○ ○ ○	○ ○ ○ ○
17	Proportion of pregnant women who attended ANC at least once	● ● ● ●	○ ○ ○ ○	○ ○ ○ ○
18	Proportion of malaria cases detected by surveillance systems	● ● ● ●	● ● ● ●	● ● ● ●
19	Proportion of children under 5 with fever in the previous 2 weeks for whom advice or treatment was sought	● ● ● ●	● ● ● ●	○ ○ ○ ○
20	Proportion of detected cases contacting health services within 48 hours of developing symptoms	○ ○ ○ ○	○ ○ ○ ○	● ● ● ●
21	Proportion of cases investigated and classified*	○ ○ ○ ○	○ ○ ○ ○	● ● ● ●
22	Proportion of foci investigated and classified*	○ ○ ○ ○	○ ○ ○ ○	● ● ● ●
23	Proportion of expected health facility reports received at national level	● ● ● ●	● ● ● ●	● ● ● ●
24	Annual blood examination rate*	● ● ● ●	● ● ● ●	● ● ● ●
25	Percentage of case reports received <24 hours after detection*	○ ○ ○ ○	○ ○ ○ ○	● ● ● ●

Recommended Indicators: Case Management

	Indicator[1]	Transmission		
		High	Low	Elim
26	Proportion of patients with suspected malaria who received a parasitological test	● ● ● ● ○ ○ ○ ○ ○ ○ ○ ○		
27	Proportion of children under 5 with fever in the previous 2 weeks who had a finger or heel stick	● ● ● ● ○ ○ ○ ○ ○ ○ ○ ○		
28	Proportion of patients with *P. vivax* or *P. ovale* malaria who received a test for G6PD deficiency	● ● ● ● ● ● ● ● ● ● ● ●		
29	Proportion of health facilities without stockouts of key commodities for diagnostic testing*	● ● ● ● ● ● ● ● ○ ○ ○ ○		
30	Proportion of patients with confirmed malaria who received first-line antimalarial treatment according to national policy	● ● ● ● ● ● ● ● ● ● ● ●		
31	Proportion of *P. vivax* and *P. ovale* patients who received radical cure treatment	● ● ● ● ● ● ● ● ● ● ● ●		
32	Proportion of children under 5 with fever in the previous 2 weeks for whom advice or treatment was sought	● ● ● ● ● ● ● ● ○ ○ ○ ○		
33	Proportion of treatments with ACTs (or other appropriate treatment according to national policy) among febrile children <5	● ● ● ● ○ ○ ○ ○ ○ ○ ○ ○		
34	Proportion of health facility months without stockouts of first-line treatments*	● ● ● ● ● ● ● ● ○ ○ ○ ○		

Recommended Indicators: Impact

	Indicator[1]	Transmission: High	Low	Elim
	Impact			
35	Parasite prevalence: proportion of population with evidence of infection with malaria parasites	● ● ● ●	● ● ● ●	○ ○ ○ ○
36	Malaria case incidence: number of confirmed malaria cases per 1000 persons per year	● ● ● ●	● ● ● ●	● ● ● ●
37	Malaria test positivity rate*	● ● ● ●	● ● ● ●	○ ○ ○ ○
38	Number of foci by classification*	○ ○ ○ ○	○ ○ ○ ○	● ● ● ●
39	Malaria mortality rate: no. of malaria deaths per 100 000 persons per year	● ● ● ●	● ● ● ●	● ● ● ●
40	Proportion of inpatient deaths due to malaria*	● ● ● ●	● ● ● ●	● ● ● ●
41	Number of countries that have newly eliminated malaria since 2015	○ ○ ○ ○	○ ○ ○ ○	● ● ● ●
42	Number of countries that were malaria-free in 2015 in which malaria has been re-established	○ ○ ○ ○	○ ○ ○ ○	● ● ● ●

Indicator Summary

1. Based on existing guidance: GTS, AIM, Surveillance manuals …
2. Global Monitoring: Of 41 indicators, 29 indicators recommended for global monitoring, annually
   - 2 financing
   - 22 outcome
   - 5 impact

   May need to tweek 14 core indicators in GTS
3. Household Surveys: 12 indicators derived from household surveys, 29 from routine systems. Less reliance on surveys and more on routine systems as transition from high transmission to elimination
   - 12 of 34 in high transmission settings
   - 0 of 18 indicators in elimination settings

Recommended Milestones:

		High transmission
Data generation	Diagnostic testing	Documented criteria for which patients should get a test
		All suspected cases get tested in public sector, private sector engaged
	Data recording	Health facilities have registers as recommended (with age, sex, type of test, species, village etc)
		Health facilities have current guidelines for the diagnosis, treatment and reporting of malaria cases
	Case investigation	All deaths
	Master list of health facilities/ reporting units	Public sector list updated within 2 years
	Catchment/ target populations	Catchment/ target populations up to date
	Household surveys	Care-seeking behaviour measured every 3 years
		Parasite prevalence measured every 3 years
	Resistance monitoring	Therapeutic efficacy testing of all antimalarial medicines undertaken every 2 years
		Insecticide resistance monitoring undertaken every year
Reporting	Information reported	Monthly numbers of tests performed by test type
		Monthly numbers of cases by age group, test type, species
	Reporting rates	Reporting rates systematically tracked
		Null values reported when nil cases or health facility closed
		Reporting rates 80%+ from public health facilities
		Household survey to estimate % cases in private sector

Recommended Milestones:

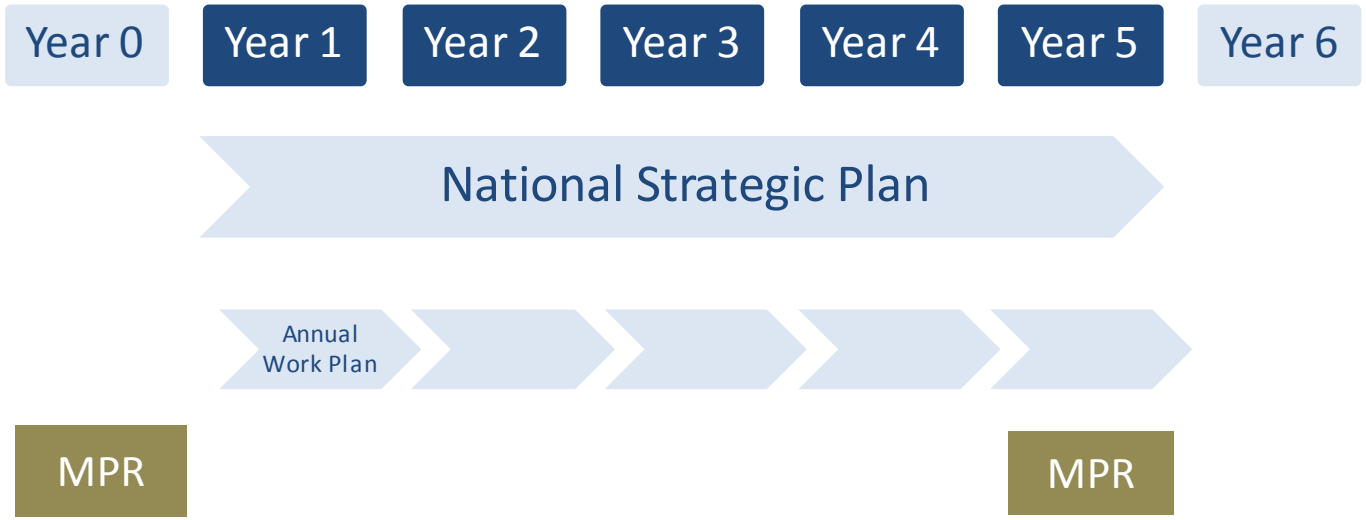
		Elimination/ Prevention of re-establishment
Data generation	Diagnostic testing	All suspected malaria cases get tested
	Data recording	Case investigation form
	Case investigation	All cases - including reactive case detection
	Master list of health facilities/ reporting units	Public & private facilities current
	Catchment/ target populations	Populations of foci known
Reporting	Information reported	Immediate notification of cases
		Reporting of cases by classification
		National case register in place
	Reporting rates	Reporting rates systematically tracked
		Null values for when nil cases/ HF closed
		Reporting rates 100% from public health facilities
		100% of reports submitted within 24 hours of case detected
		Reporting rates 100% from private health facilities

Milestones Summary:

1. Milestones represent
   - expected level of development of systems in transition from high transmission to elimination and
   - a target to be achieved by 2020 for countries in these stages
2. Initially focus on achieving high coverage of systems e.g. all suspected cases tested, inclusion of private sector providers, then increasingly emphasize granularity of data (from health facility to village to individual), timeliness and quality.
3. Progress towards milestones to be assessed at least every 5 years

Use of Information: principally at country level

(i)Planning – strategic plan annual work plans.



(i) For programme monitoring and evaluation - Use not confined to malaria programme managers and implementers. Other government departments, elected leaders, community members and donors have a stake. If involved, these stakeholders can help to ensure that malaria control and elimination is promoted as a development priority.

Roles and Responsibilities:

1. Countries and partners: To ensure that data for recommended indicators are available by investing in routine information systems, and household and health facility surveys.
2. WHO and other partners: To support endemic countries to strengthen their systems for surveillance, monitoring and evaluation. Such support to be coordinated.
3. WHO: To monitor the implementation of the GTS and AIM, through annual report and other periodic reports and make data available to countries and global malaria partners. To also regularly report to the regional and global governing bodies, the United Nations General Assembly, and other United Nations bodies.

By 2030, malaria morbidity and mortality should be dramatically reduced – increasing need for a global monitoring system to track and eliminate remaining cases and foci. Regional efforts to monitor progress (APLMA, ALMA, the Mekong and E8) are an important step to this goal.

Option 1: Two groups, the SME-TEG and a reconfigured and renamed MERG

- Two groups, MERG renamed as Monitoring and Evaluation Working Group (MEWG)
- SME-TEG will be responsible for setting normative guidance for malaria SME.
- Redefine the role of MEWG to harmonise it with functions of other working groups
- Major stakeholders will be represented in the SME TEG.
- A primary responsibility for MEWG will be to support countries in the translation and implementation of WHO normative guidance on SME
- MEWG will provide continuous inputs to SME-TEG on priority country SME needs

Preferred option - best aligned with current functioning of TEGs and WGs and allows inclusion of diverse cross-cutting constituents in both groups

Option 2: One group that combines the ToRs of TEG and MEWG

- Reconstitute the SME-TEG and allow for a wider stakeholder participation to support development of normative guidance and their implementation
- SME-TEG also takes up role of helping countries on the dissemination and implementation of normative guidance
- Use the ERG mechanism to undertake some of the roles of the MERG
- Have observers who can bring issues to the table that may require the development of normative guidance or their dissemination and implementation

Will minimise conflict but may lead to a large group that will be difficult to manage and may lead to inefficiencies

Questions for MPAC:

First stage in consultation – SMETEG, MERG, Others

<u>M&E Framework for GTS and AIM</u>

1. Appropriateness of indicators and milestones
2. Suggestions for improvement
    a) Additions
    b) Deletions
    c) Changes
3. Suggestions for next stages

<u>Role of SME TEG and MERG</u>

- Opinion on options

Plasmodium knowlesi current status and the request for review by an Evidence Review Group

Malaria Policy Advisory Committee
Geneva, Switzerland

Dr. Rabi Abeyasinghe

14 September 2016

Outline

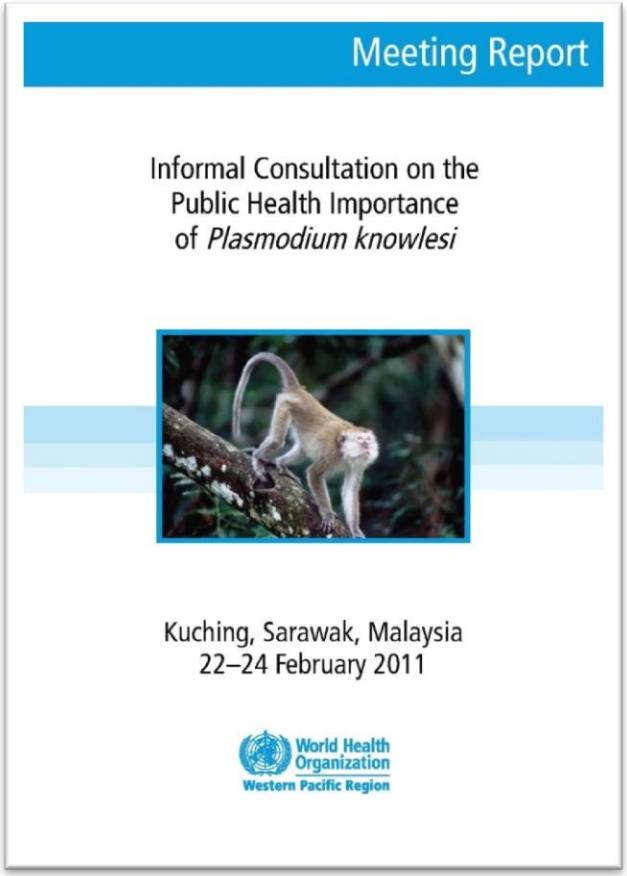
- What is *Plasmodium knowlesi*
- WHO Consultation on *P. knowlesi* (2011)
- Brief history and current situation
- Transmission, hosts and vectors
- Diagnosis, clinical and treatment
- Estimating risk of infection
- Gaps in knowledge and next steps

What is *Plasmodium knowlesi*?

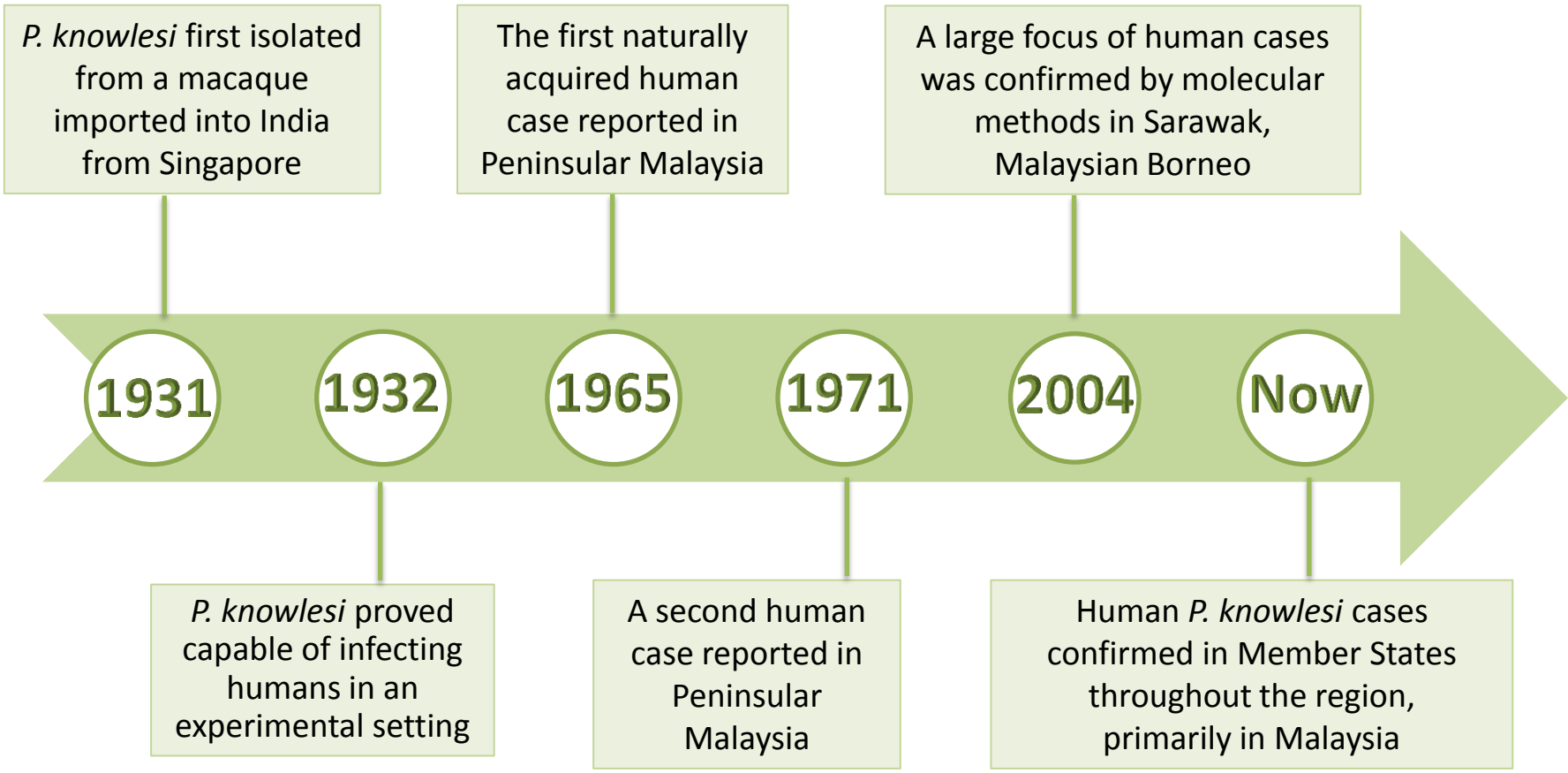
Plasmodium knowlesi (*P. knowlesi*) is a zoonotic malaria parasite, transmitted between non-human primate hosts by the *Anopheles (An.)* mosquitos, and causing spill-over infections in humans where the parasite, vector, host and human converge.

WHO Informal Consultation on the Public Health Importance of *P. knowlesi*

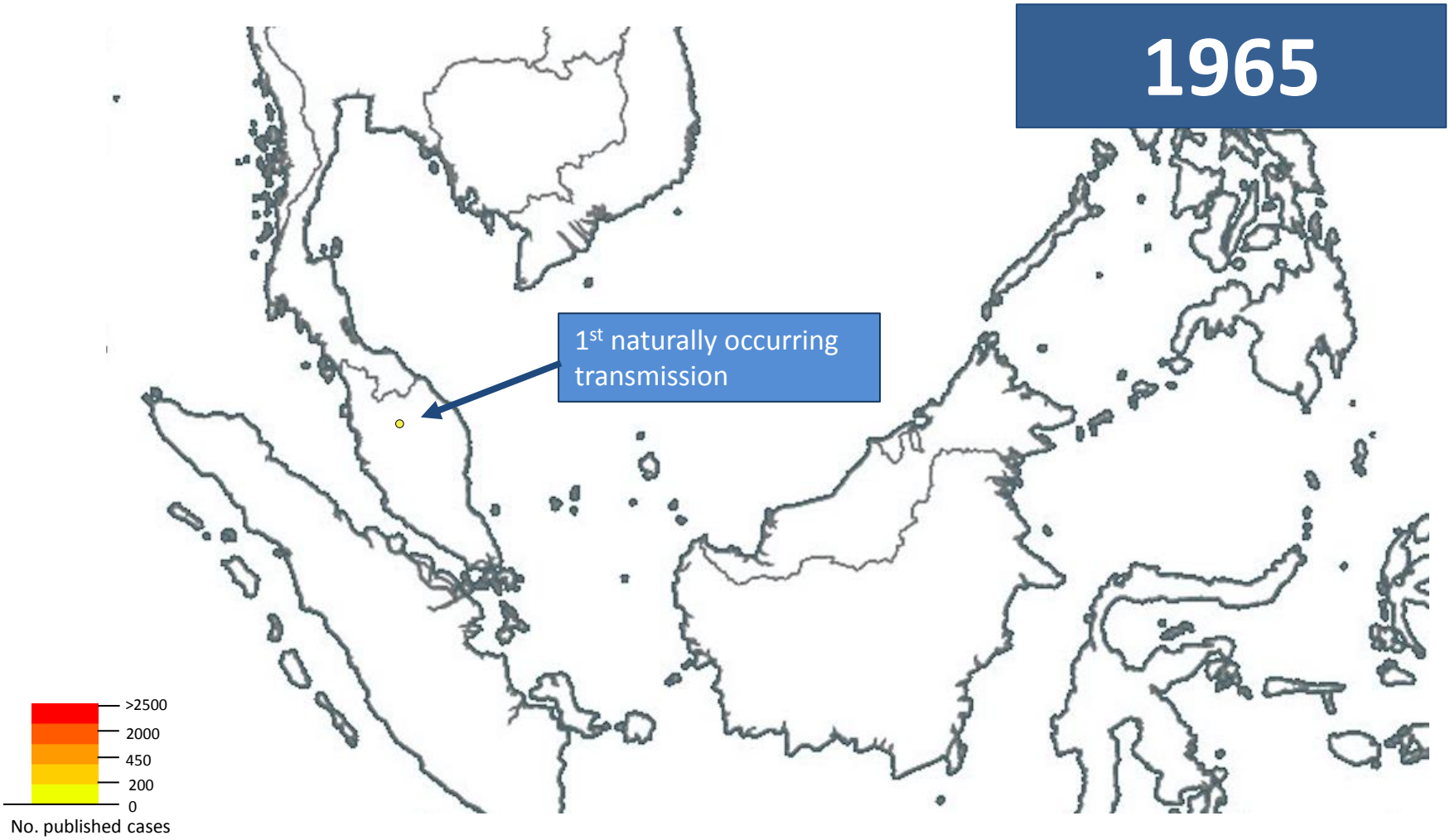
- Held in 2011 to review the *P. knowlesi* situation
- The Consultation provided 17 recommendations, many of which have contributed to our current understanding
- These included recommendations on diagnostics, determining vector and host distribution, protocols on diagnostic procedures and management among other areas



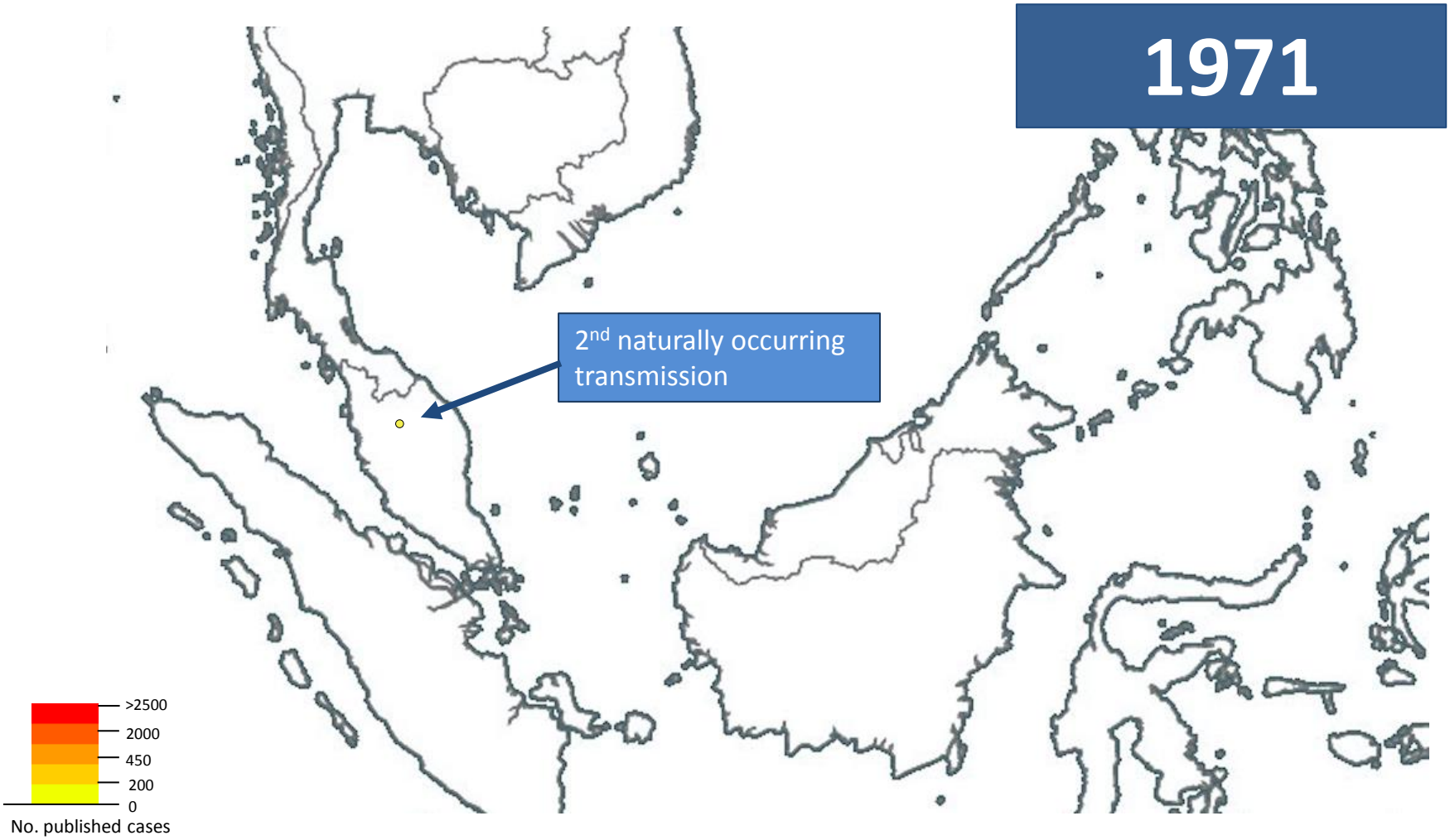
Brief history of *P. knowlesi*



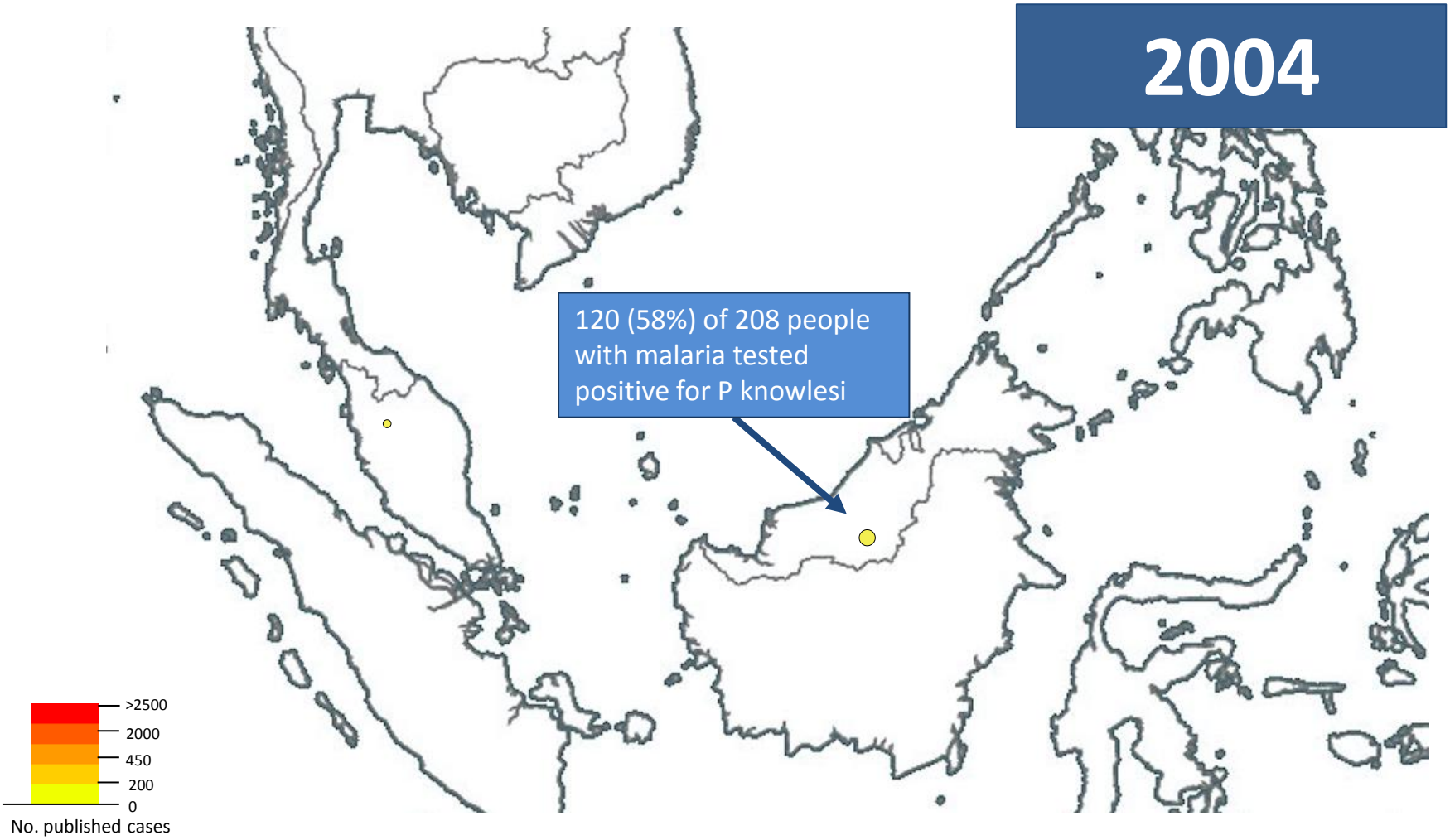
First *P. knowlesi* case reported in Peninsular Malaysia



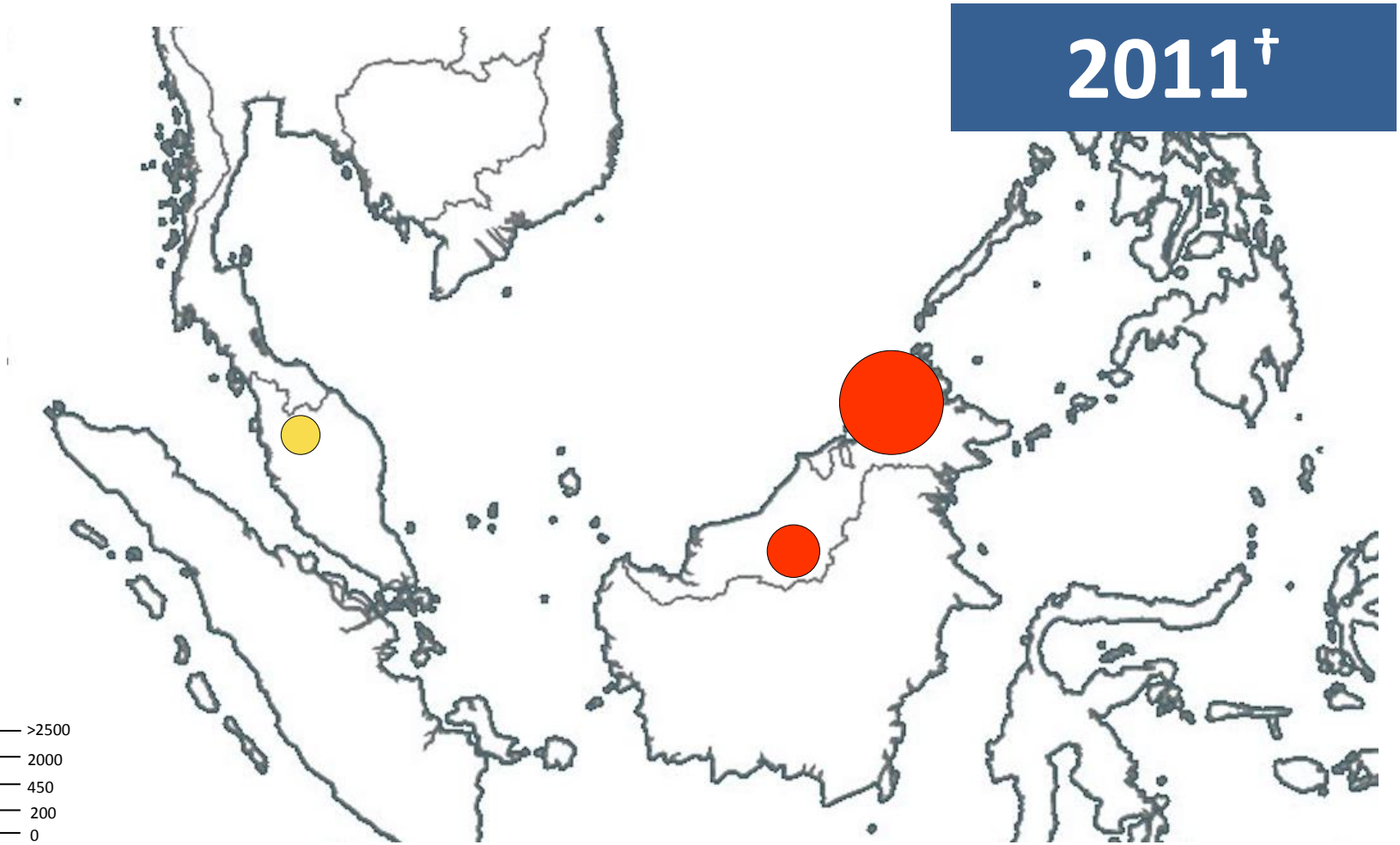
A second case reported in Peninsular Malaysia



A larger focus of naturally acquired *P. knowlesi* infections was confirmed in blood samples from 2002-2004



Cumulative account of confirmed *P. knowlesi* cases in Peninsular Malaysia, Sabah and Sarawak, Malaysian Borneo



†Cumulative cases confirmed by PCR and/or sequencing and reported in peer-reviewed published manuscripts

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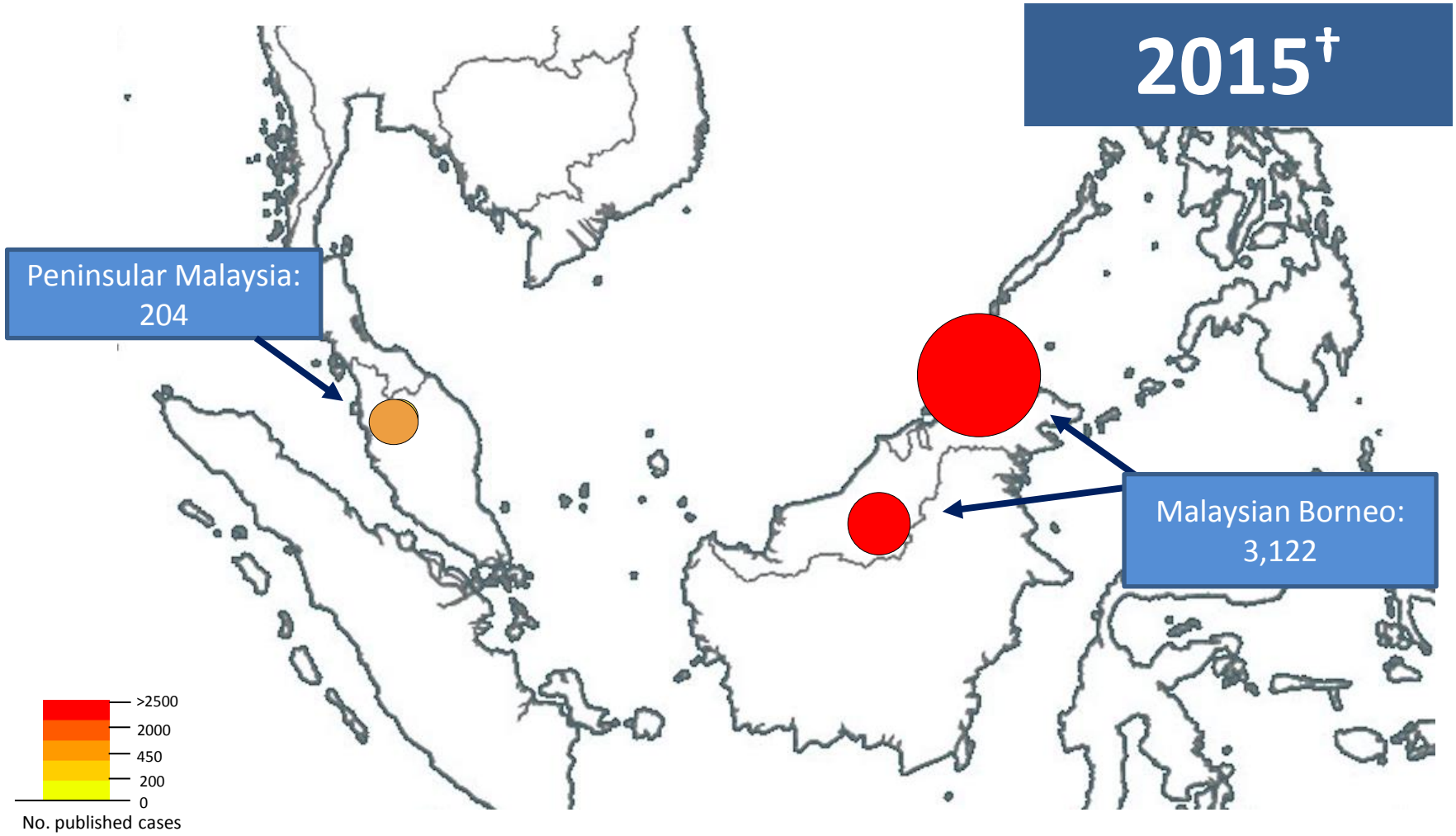
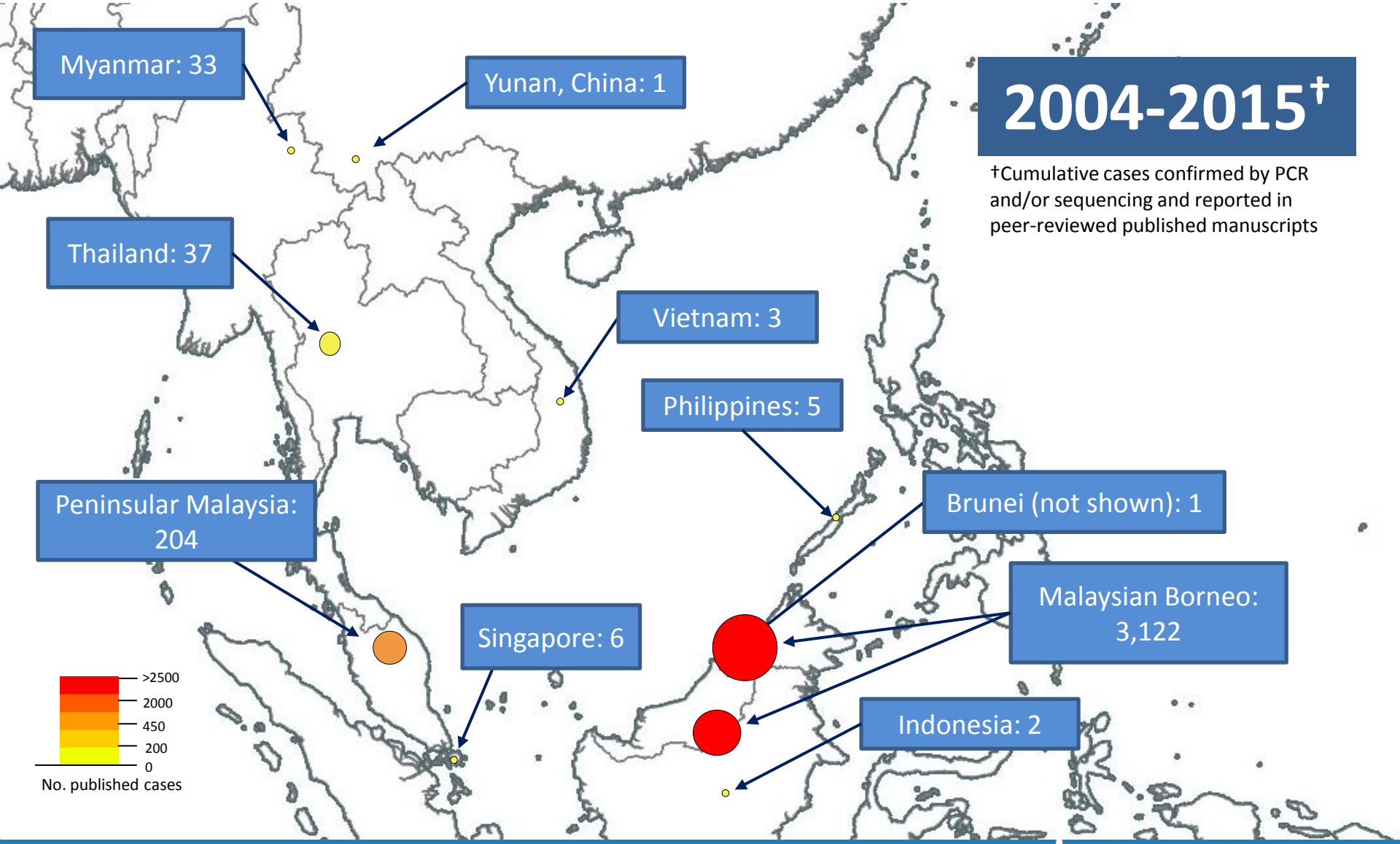
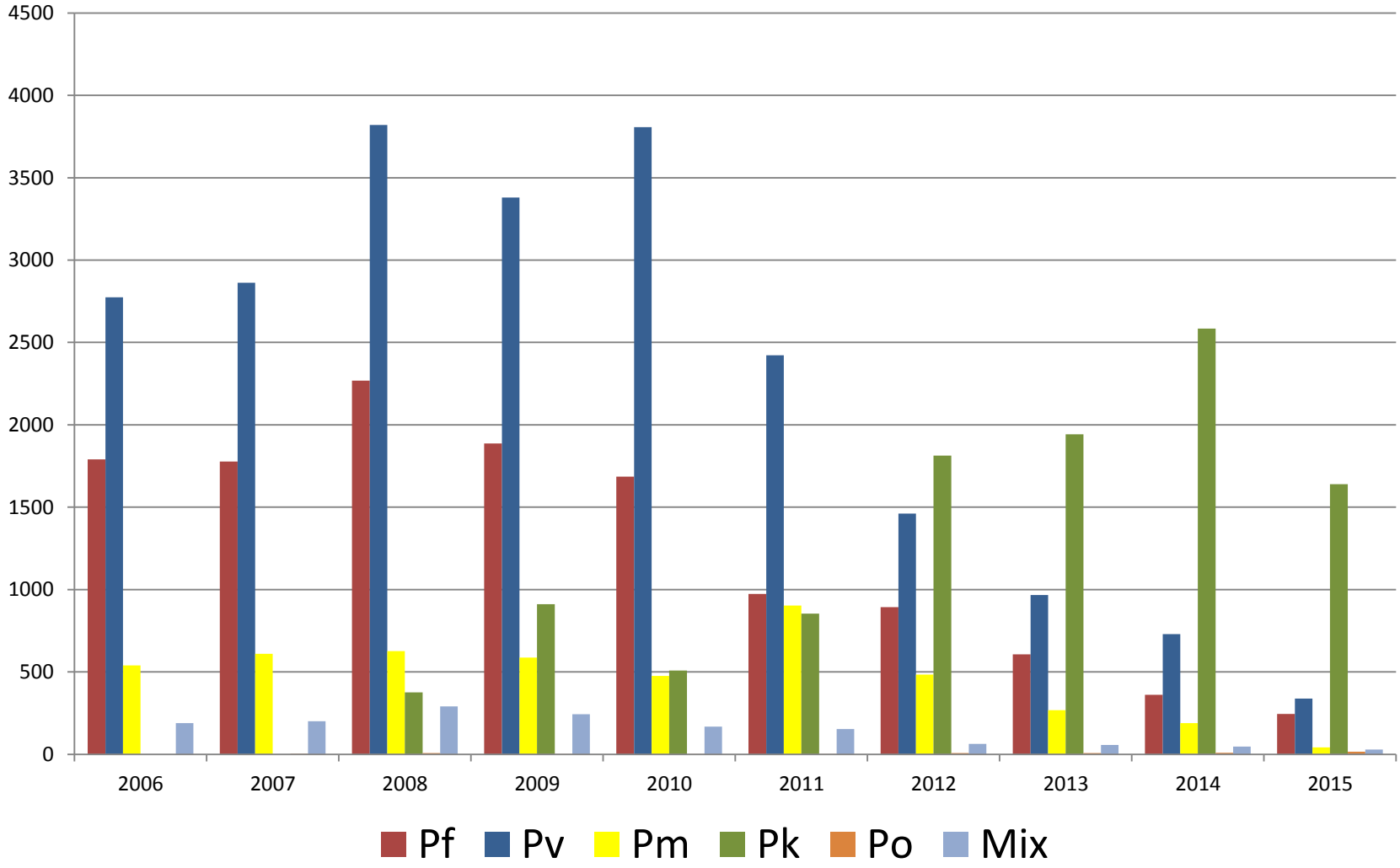


†Cumulative cases confirmed by PCR and/or sequencing and reported in peer-reviewed published manuscripts

Current situation and distribution

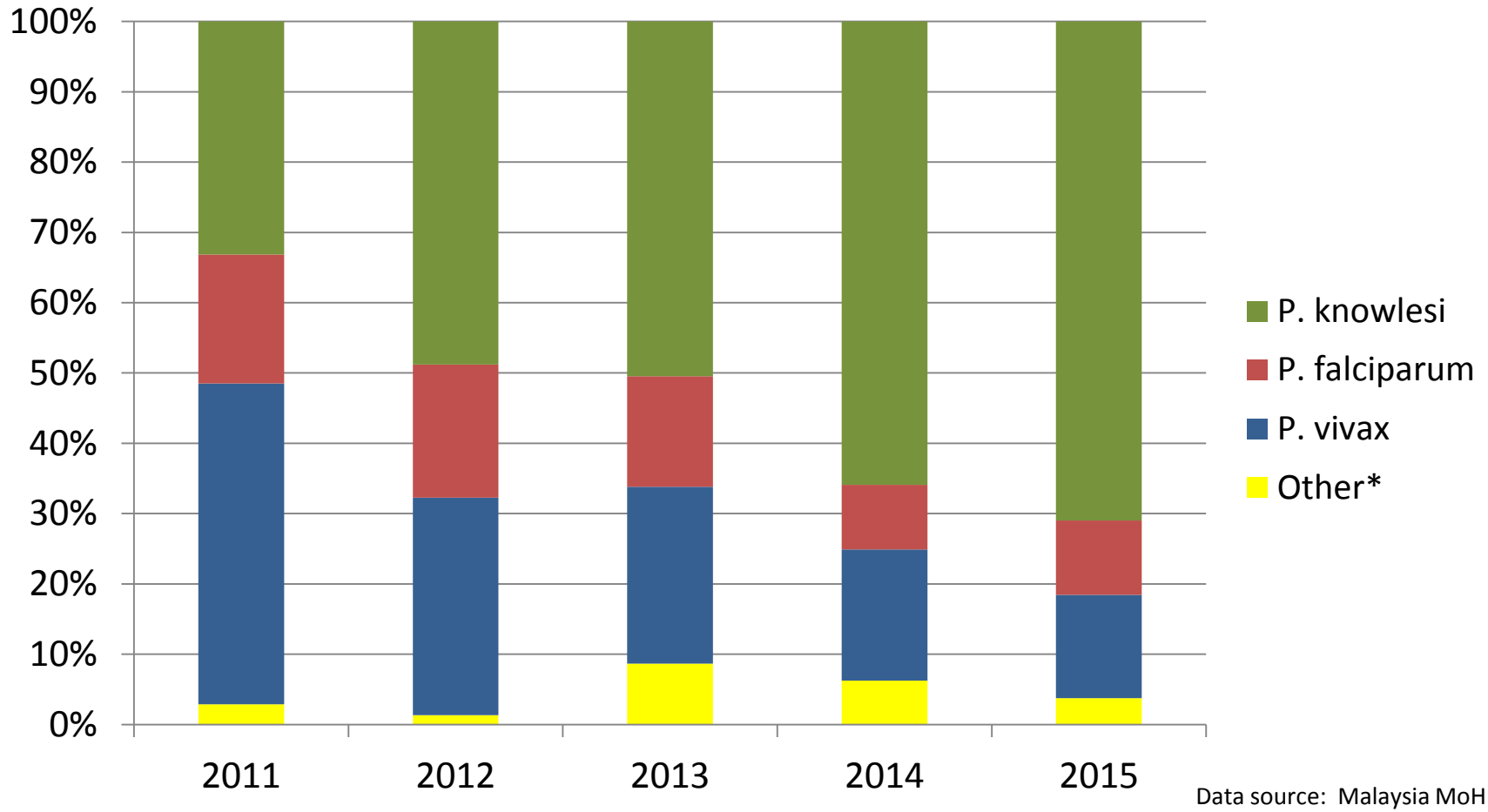


Parasite species distribution in Malaysia, 2006-2015



Source: Malaysia MoH

Proportion of parasite species from microscopy confirmed cases in Malaysia, 2011-2015



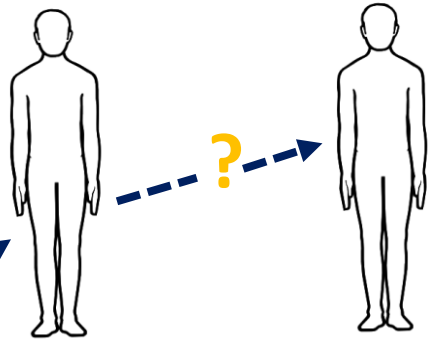
Data source: Malaysia MoH

Transmission and factors for zoonotic infections

HOST

Long-tailed macaque *(M. fascicularis)*
Pig-tailed macaque *(M. nemestrina)*
Banded leaf monkey *(P. melalophus)*

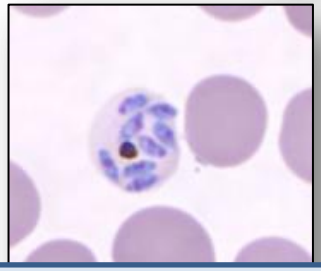
SOCIAL
Employment
Migration
Others



Humans:
Zoonotic infections

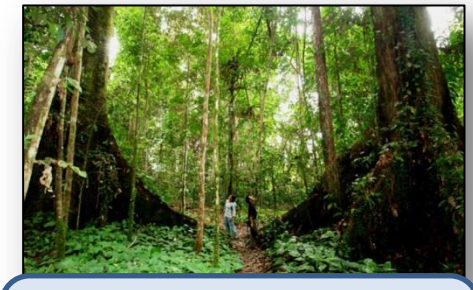
VECTOR

An. leucosphyrus mosquitoes:
An. latens (Sarawak)
An. balabacencis (Sabah)
An. cracens (Peninsular Malaysia)
An. dirus (Viet Nam)



MALARIA

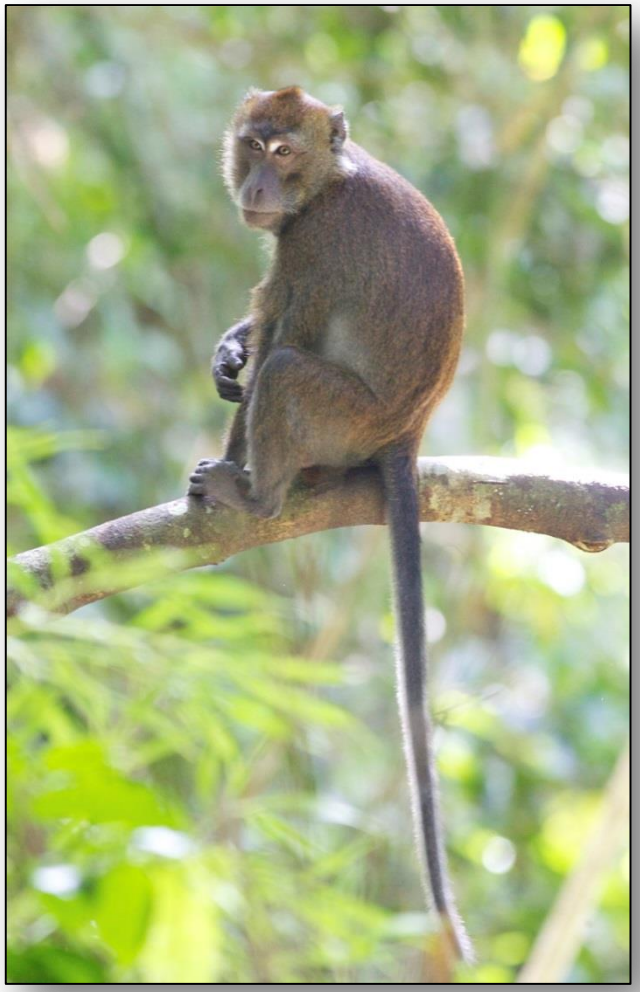
Plasmodium knowlesi



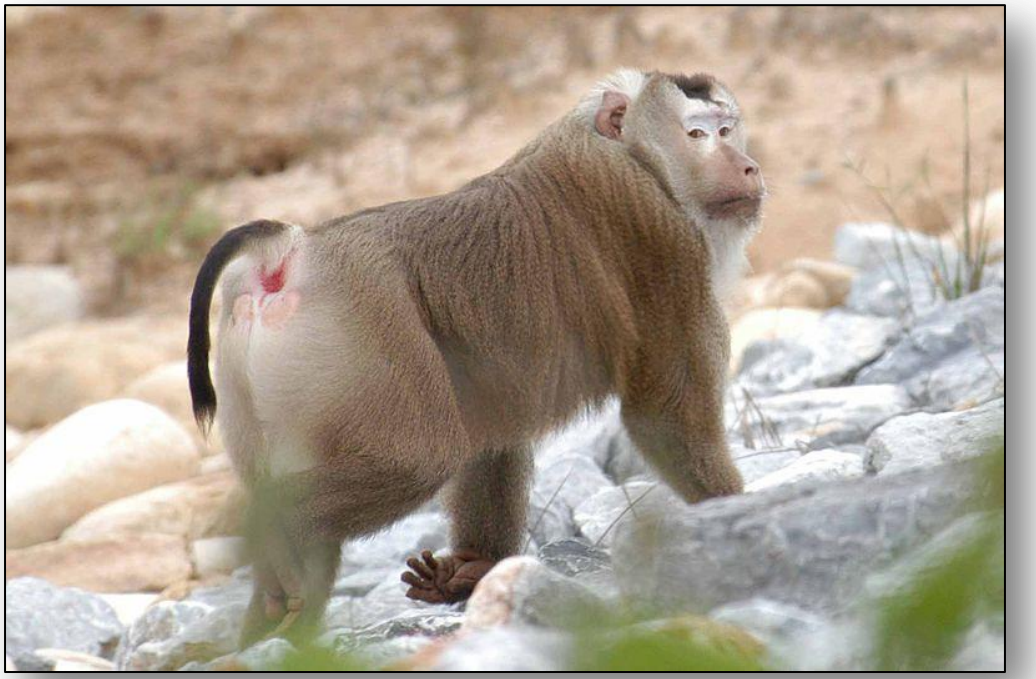
ENVIRONMENT

Dense jungle and forest fringe areas

Natural hosts in Sarawak, Malaysian Borneo



Macaca fascicularis
Long-tailed macaque

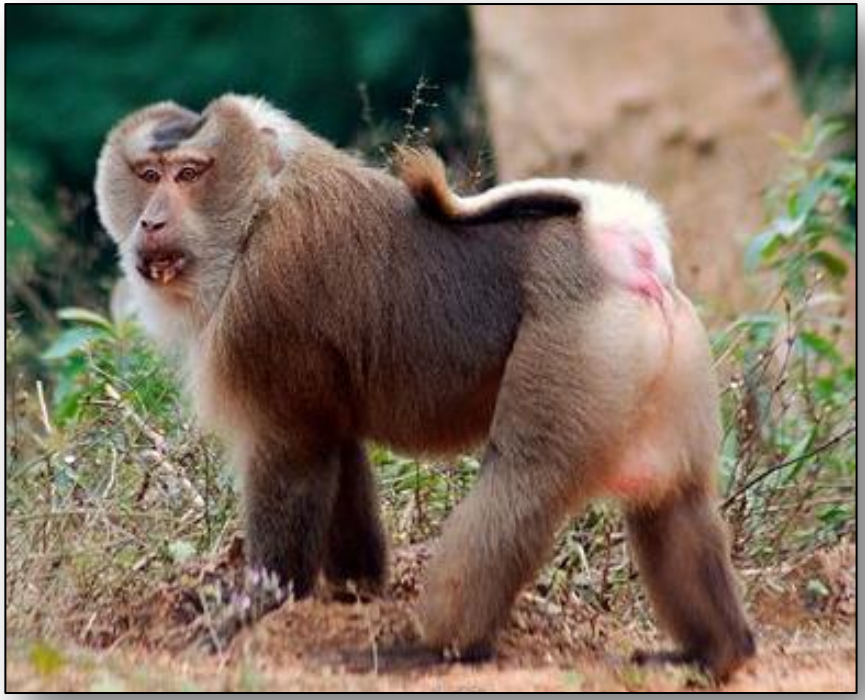


Macaca nemestrina
Pig-tailed macaque

Source: "Forest Ecology," 2014

Natural hosts in Peninsular Malaysia and Myanmar

Presbytis melalophus
Banded leaf monkey
Peninsular Malaysia



Macaca leonina
Northern pig-tailed macaque
Myanmar

Source: koushik/naturism.co.in

Factors contributing to increase of reported *P. knowlesi* infections

- Improved diagnostic capacity
- Reduction in human malaria cases and awareness of Pk
- Loss of relative immunity due to low rates of malaria
- Change in land use patterns creating increased opportunity for spill over of infections to humans – through closer associations with natural reservoir hosts or access to infected vectors

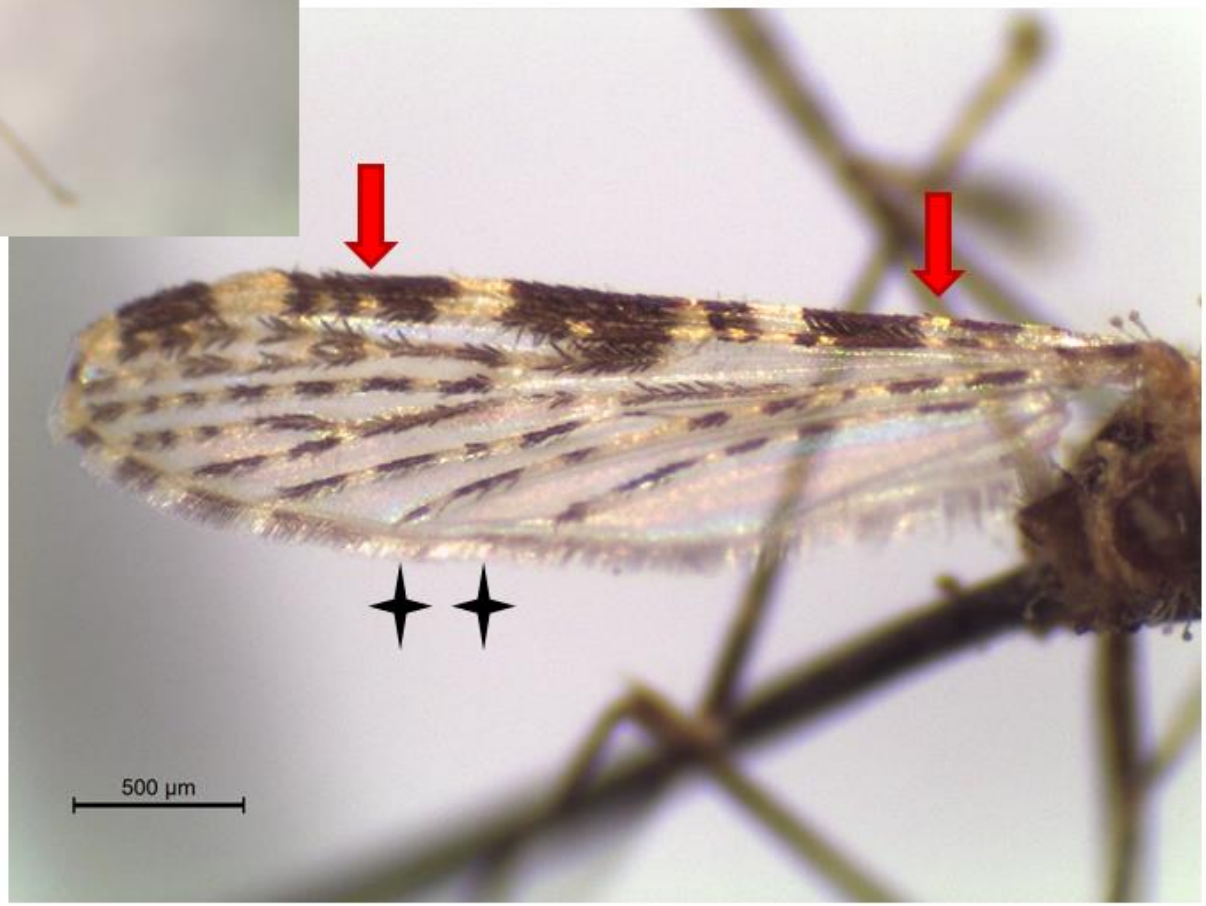
Host-parasite interactions

- Two distinct *P. knowlesi* populations identified in human patients from Malaysia have been linked to *M. nemestrina* and *M. fascicularis*, respectively
  - The strain associated with *M. fascicularis* is thought to be circulating and infecting humans in areas of continental Asia, where *M. nemestrina* is absent
  - This *M. fascicularis*-associated strain may have a distinct relationship with environmental and socioeconomic variables compared to the mixture of parasite infections in patients from Malaysia
- The presence of Leucosphyrus Complex vectors in Malaysia including Dirus Complex vectors in continental Asia further adds to the possibility of different relationships between disease risk and the environment in these two regions

Vectors

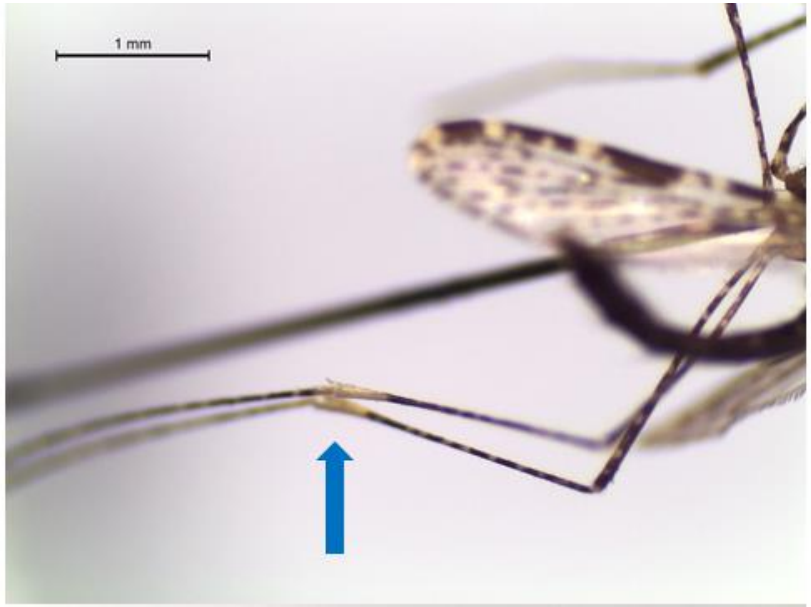
- *P. knowlesi* vectors are members of the An. leucosphyrus group
  - found throughout the region
  - associated with dense jungle and forest fringe
  - rest and feed outdoors (exophagic) typically after dusk
- In Sarawak the forest breeding *An. latens* was found to be the primary vector
  - *An. latens* has been found to harbor other simian malaria parasites: *P. inui*, *P. coatneyi*, and *P. fieldi*
- *An. balabacensis* implicated as vector in Sabah and it prefers to breed in ground pools formed in fruit orchard, rubber and palm oil plantations
- *An. cracens* is considered a major knowlesi malaria vector in peninsular Malaysia
- *An. dirus* appears to be the primary vector in Viet Nam and continental Asia

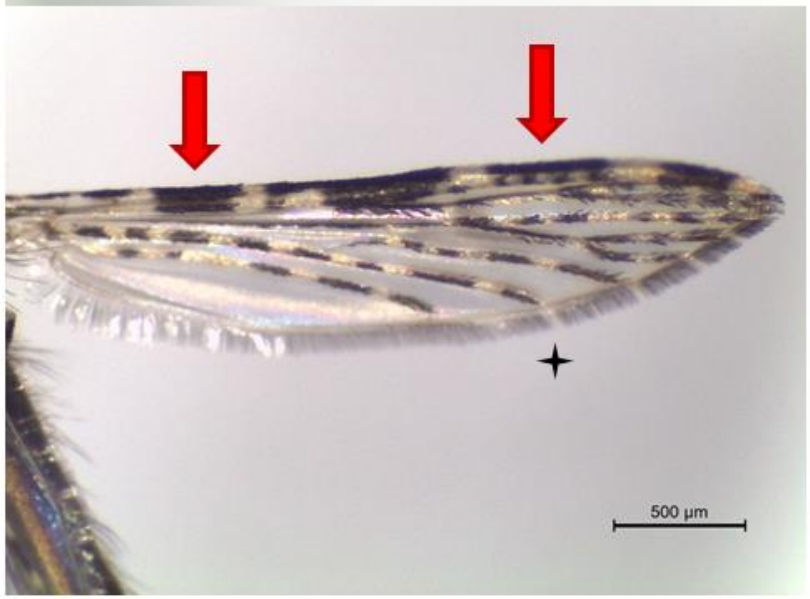
An. lantens



Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016

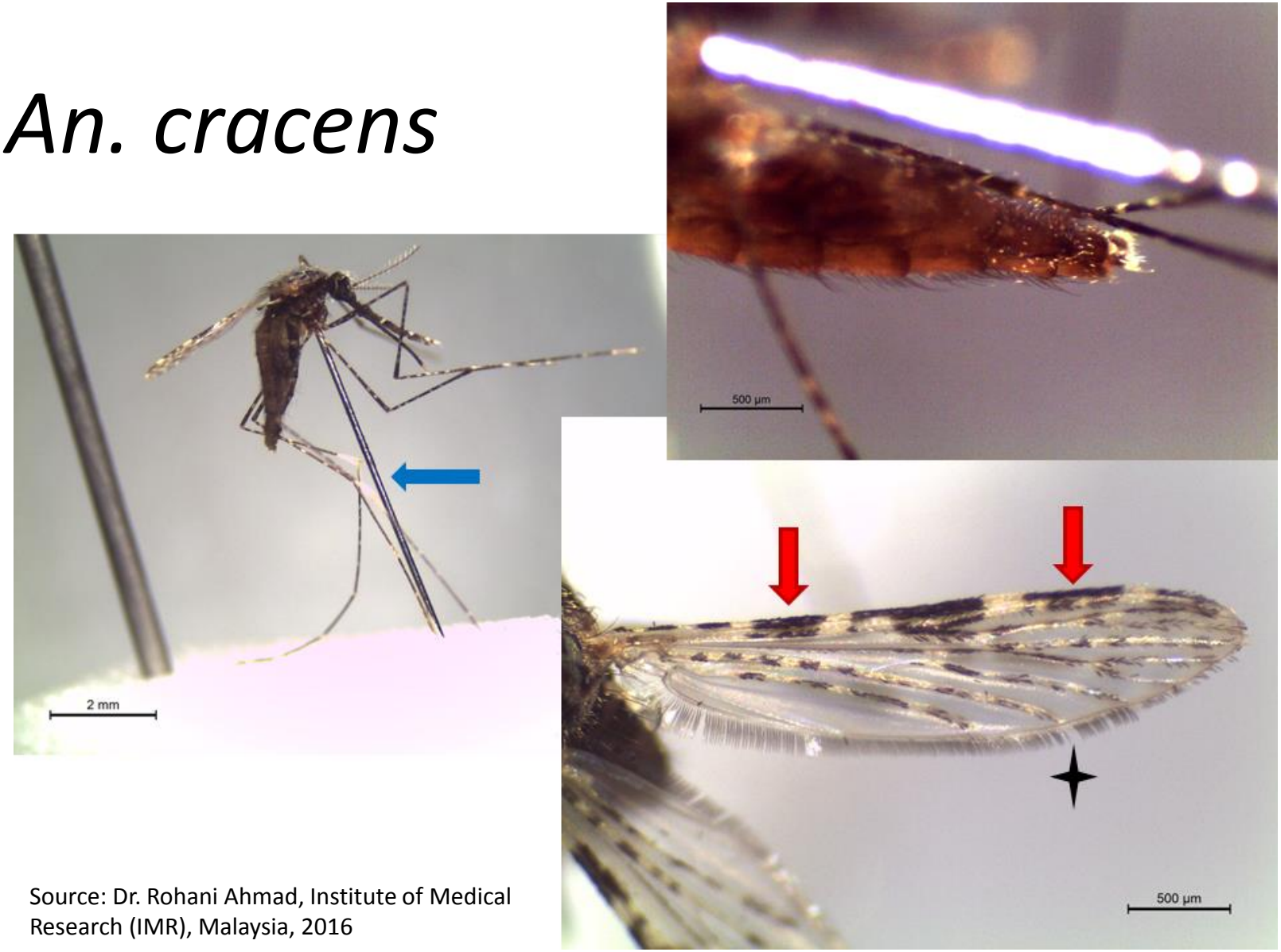
An. balabacensis





Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016

An. cracens



Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016

Vector habitat

Slow running streams

Animal foot paths

Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016

Vector habitat

Stagnant water

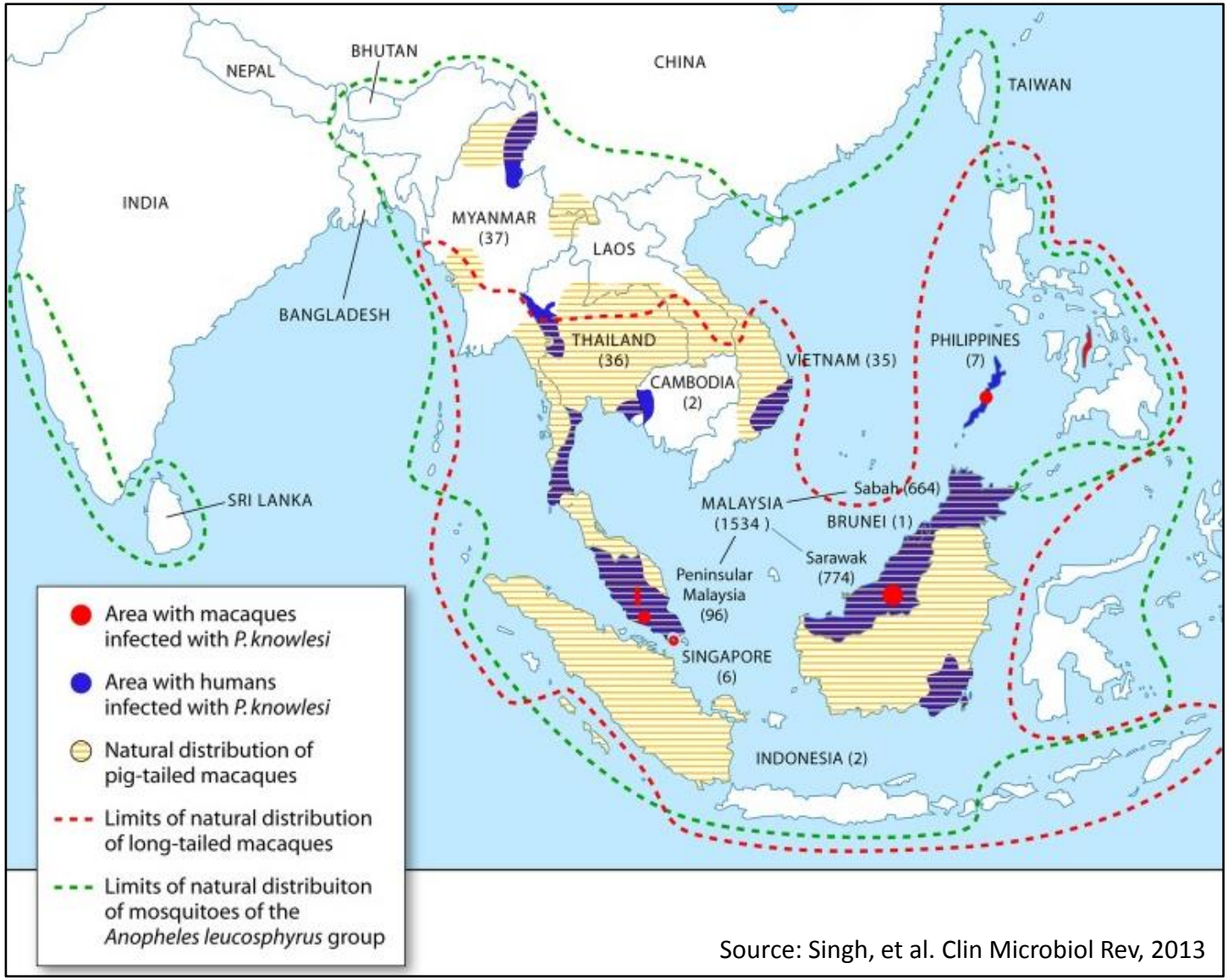
Ground pools

Sources: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, and EntoPest Unit of Sabah Health Department, Malaysia, 2016

Larval sampling

Source: EntoPest Unit of Sabah Health Department, Malaysia, 2016

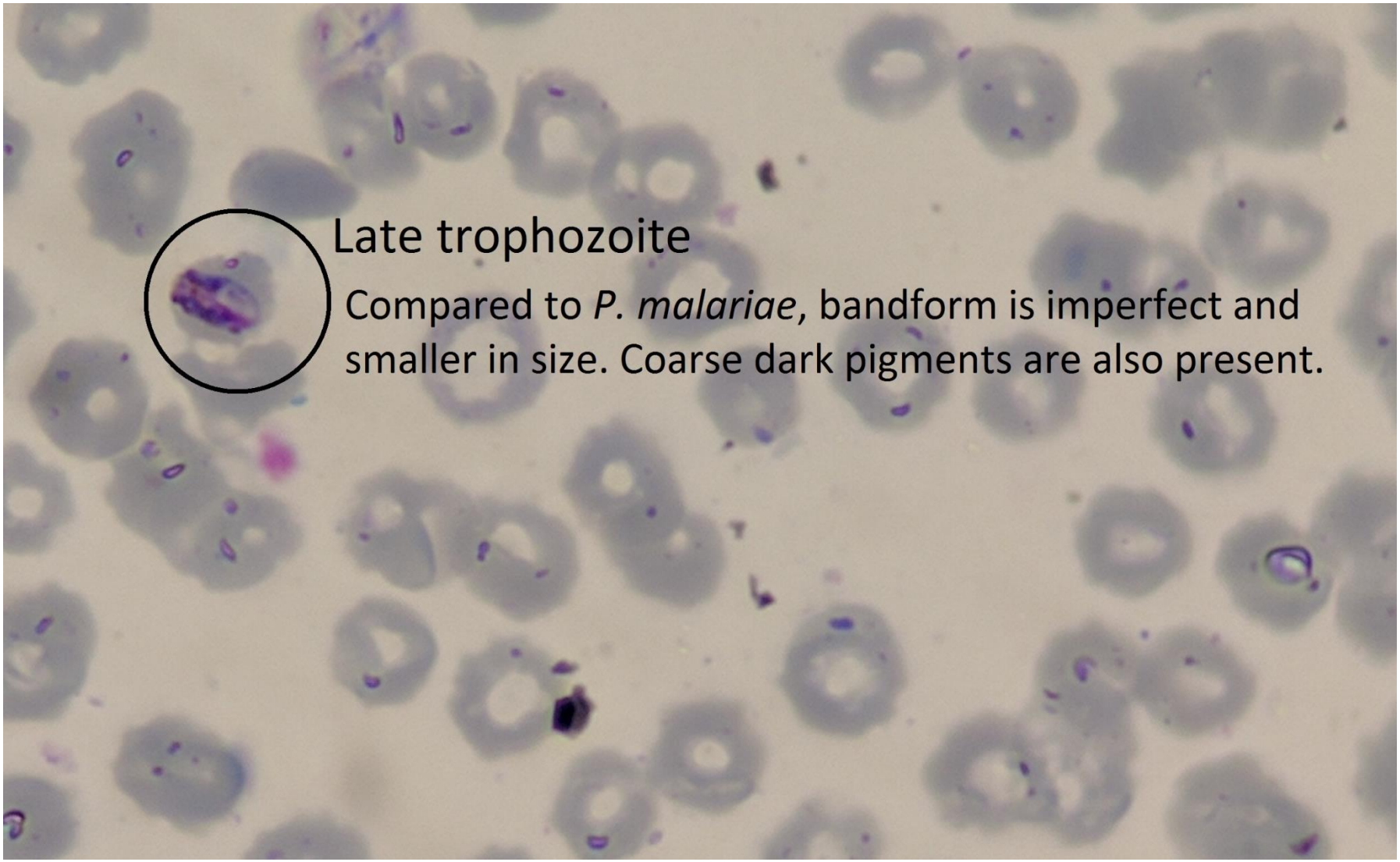
Host and vector range



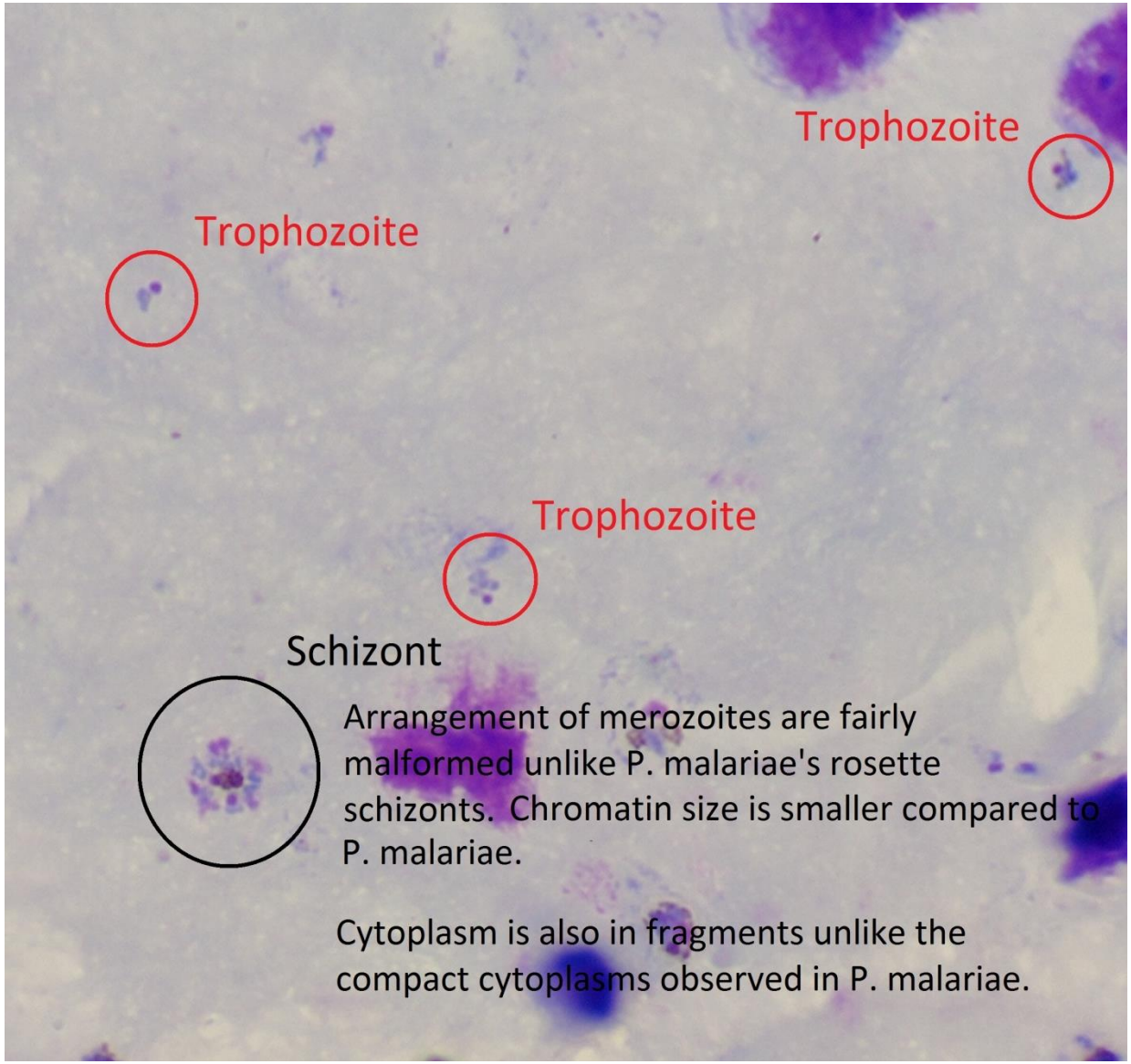
Source: Singh, et al. Clin Microbiol Rev, 2013

Diagnosis

- *P. malariae* and *P. knowlesi* may not be reliably distinguished by microscopy
  - PCR is the definitive diagnostic method
- pan-Plasmodium RDTs can be used for screening but not confirmation of *P. knowlesi*
- *P. knowlesi*-specific RDTs have demonstrated low sensitivity
  - Products are in the pipeline but performance to date is not yet optimal



Source: Malaysia National Public Helath Laboratory, MoH



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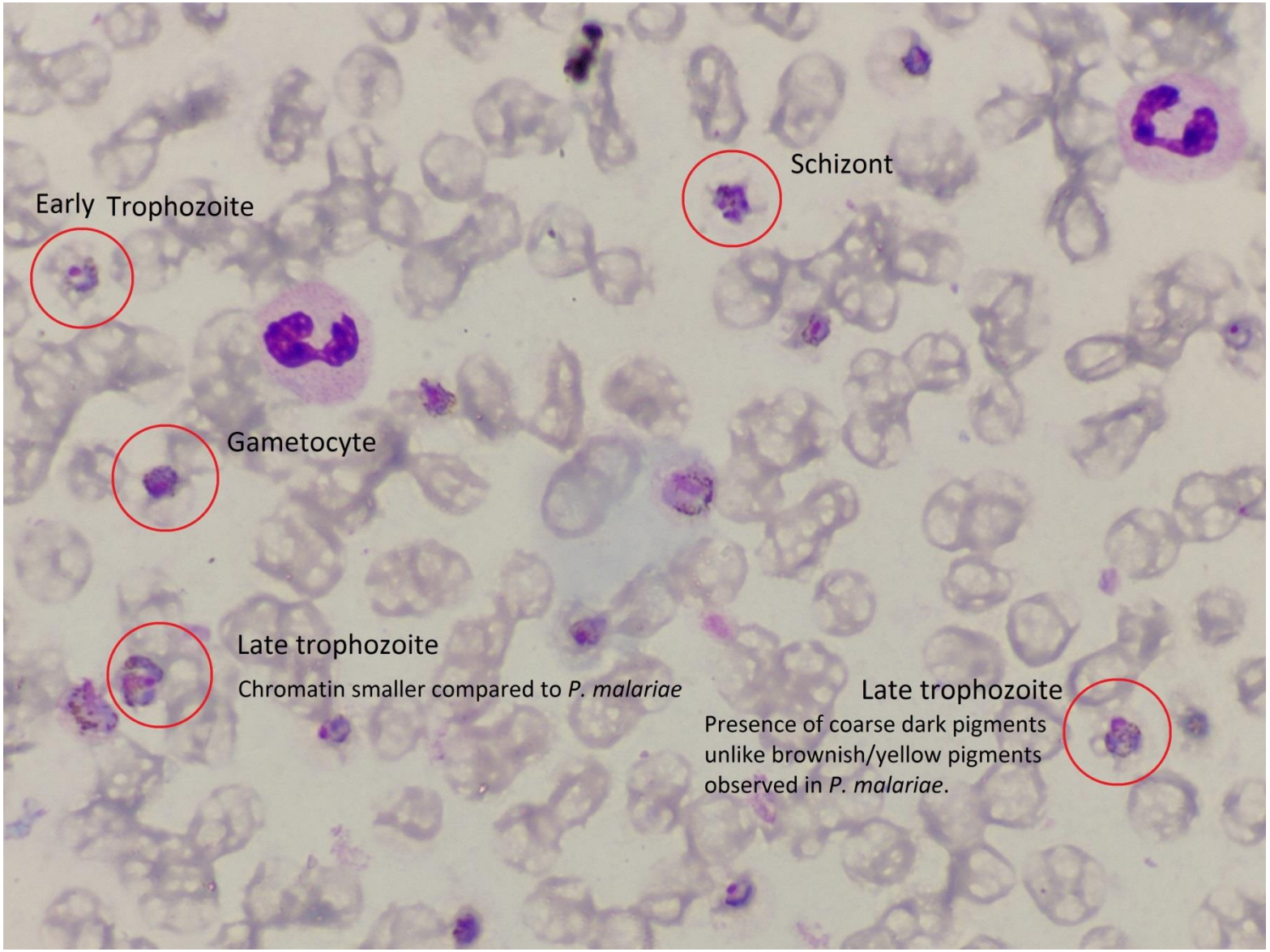


Source: Malaysia National Public Helath Laboratory, MoH

Clinical symptoms and parasitemia

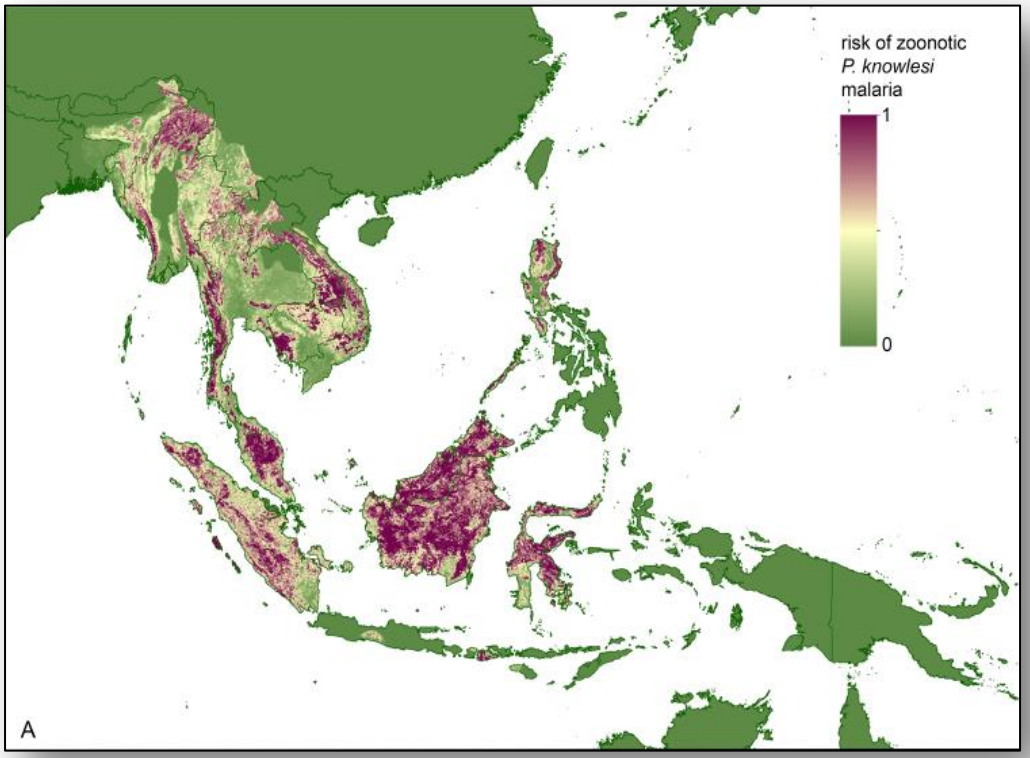
- Most human *P. knowlesi* cases are chronic and symptomatic but some can be severe leading to death
  - Clinical studies in Sarawak, Malaysian Borneo, indicated > 10% of patients with *P. knowlesi* malaria developed severe disease as classified by the WHO with approximately 1% CFR
- *P. knowlesi* has the shortest asexual replication cycle of all Plasmodium species leading to rapidly increased parasitemia levels
  - High parasitemia is associated with severe *P. knowlesi* malaria
  - Patients having parasitemia >50,000 parasites/ul should be treated urgently and closely monitored until parasitemia is controlled

Treatment

- *P. knowlesi* is highly sensitive to artemisinins; and variably and moderately sensitive to chloroquine and mefloquine
- ACT KNOW open-label, random controlled trial (2016) compared artesunate-mefloquine (A-M) and chloroquine (CQ) for the treatment of uncomplicated *P. knowlesi* malaria
  - A-M treated patients showed improved outcomes, demonstrating:
    - faster parasite clearance than CQ treated patients
    - lower risk of anaemia within 28 days
    - faster fever clearance
    - shorter duration of hospital bed occupancy

Estimating risk of infection

- A recent exercise to map the risk of *P. knowlesi* infection in the GMS resulted in suggesting surveillance priorities
- There is a need to better understand the distribution of *P. knowlesi*
- Efforts are required to increase surveillance of parasite, vector, and host in areas of Thailand, Myanmar, Indonesia, Vietnam and Cambodia as well as across Malaysia

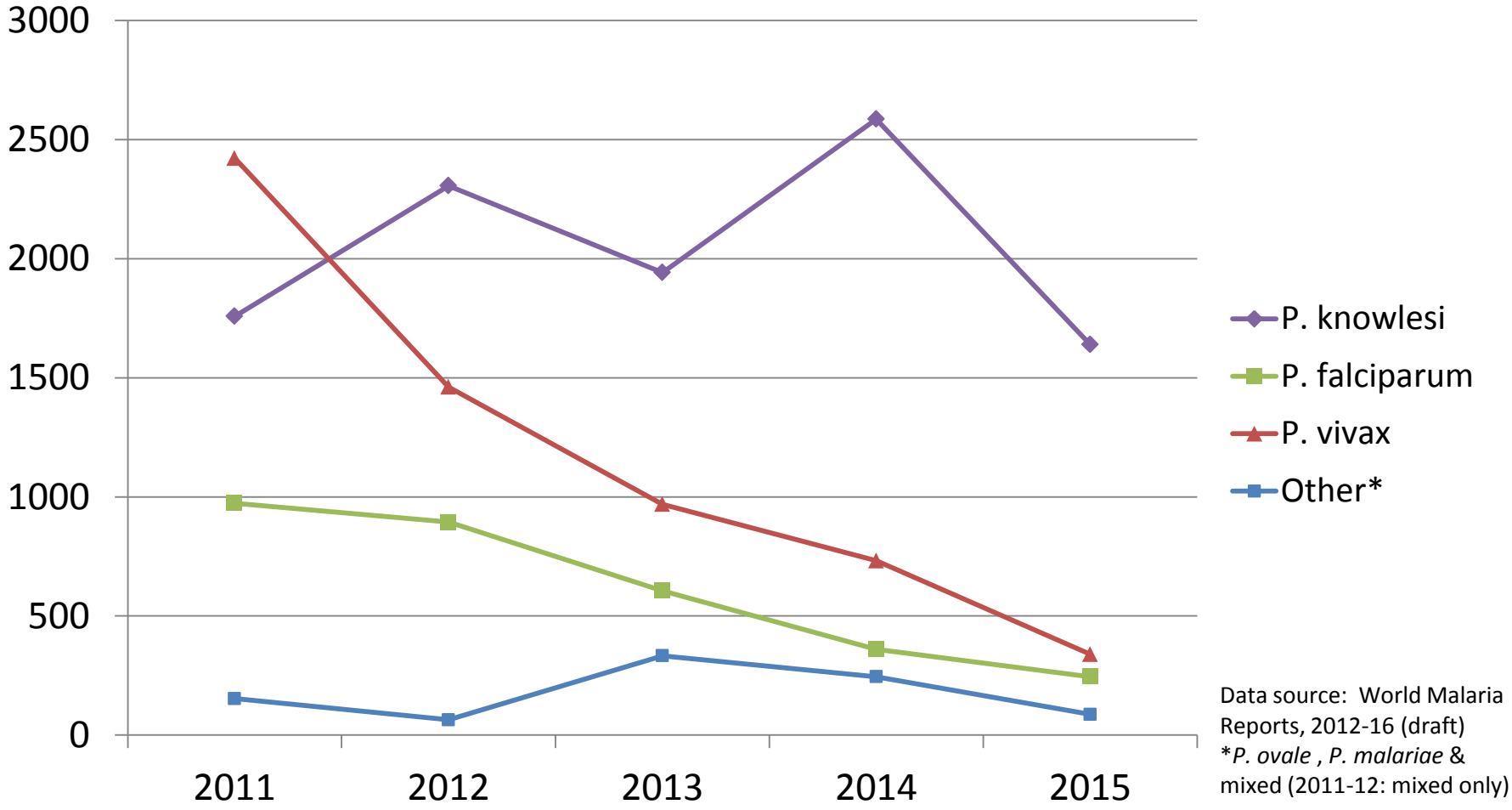


Map of estimated *P. knowlesi* malaria risk (Shearer, 2016)

Gaps in knowledge

- Determine if human-human transmission is occurring (experimental infections confirmed in the lab in 1960s, development of gametocytes in humans confirmed in 2009).
- Incidence of *P. knowlesi* infection in humans throughout its range and additional information on common clinical outcomes
- Range and distribution of primary hosts and vectors including their bionomics
- Sensitivity and suitability of available RDTs
- Most effective methods of control and prevention of Pk infections
- Likely impact on the success of malaria elimination campaigns

Number of microscopy confirmed cases in Malaysia by parasite species, 2011-2015



Data source: World Malaria Reports, 2012-16 (draft)
**P. ovale* , *P. malariae* & mixed (2011-12: mixed only)

Conclusions and next steps

- Modelling (Imai et al. 2014, Brock et al. 2016) suggest that human-vector-human transmission is plausible but is likely to be rare.
- There is a need to better understand the current and likely future changes that may influence this status and even levels of exposure to zoonotic *P. knowlesi*
- Unique enabling technologies may be needed to limit *P. knowlesi* transmission to humans - appropriate mitigating and preventive strategies should be sought
- A proposal for an ERG is requested to address gaps in knowledge and advise on a path towards elimination

Thank you.

Acknowledgements;
Dr James Kelley, STC, MVP WPRO
Ms Jamie Kim, Intern MVP WPRO

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EntoPest Unit of Sabah Health Department, Malaysia, 2016

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