Malaria Policy Advisory Committee (MPAC) Meeting

22-24 March 2017
Kofi Anan Room, UNAIDS bldg., World Health Organization, Geneva, Switzerland

PROVISIONAL PROGRAMME*

Wednesday, 22 March 2017			
	Session 1	**Open**	**for information**
09:00 – 09:30	Welcome for Chair, MPAC	Dr Kevin Marsh	
09:30 – 10:30	Report from the Director, GMP	Dr Pedro Alonso	
10:30 – 11:00	*Coffee break*		
	Session 2	**Open**	**for information**
11:00 – 11:30	Update on RTS,S malaria vaccine implementation programme	Dr David Schellenberg Dr Mary Hamel	
11:30 – 12:30	Report back from the ERG on the cardiotoxicity of antimalarials/Presentation	Prof Josep Brugada	**For decision**
12:30 – 13:30	*Lunch*		
	Session 3	**Open**	**for guidance**
13:30 – 14:30	*Surveillance, monitoring and evaluation. An operational manual* (Draft 2) -- Presentation	Dr Abdisalan Noor	
14:30 – 15:00	Development of a Guideline for malaria vector control	Dr Peter Olumese Dr Martha Quinones	
15:00 – 15:30	*Coffee break*		
	Session 4	**Open**	**for information**
15:30 – 16:00	Outcomes from the ERG on *Plasmodium knowlesi*	Dr Rabindra Abeyasinghe	
16:00 – 16:30	Update on the *Global Vector Control Response 2017-2030*	Dr Jan Kolaczinski	
16:30 – 17:00	Online mapping tool	Dr Tessa Knox	**for guidance**
17:00	*End of day*		
18:30	MPAC Dinner	Closed	
Thursday, 23 March 2017			
	Session 5	**Open**	**for information**
09:00 – 10:00	Strategic Advisory Group (SAG) on malaria eradication	Dr Marcel Tanner	

Report from the Global Malaria Programme

Malaria Policy Advisory Committee

Geneva, Switzerland

Dr Pedro L. Alonso

22 March 2017

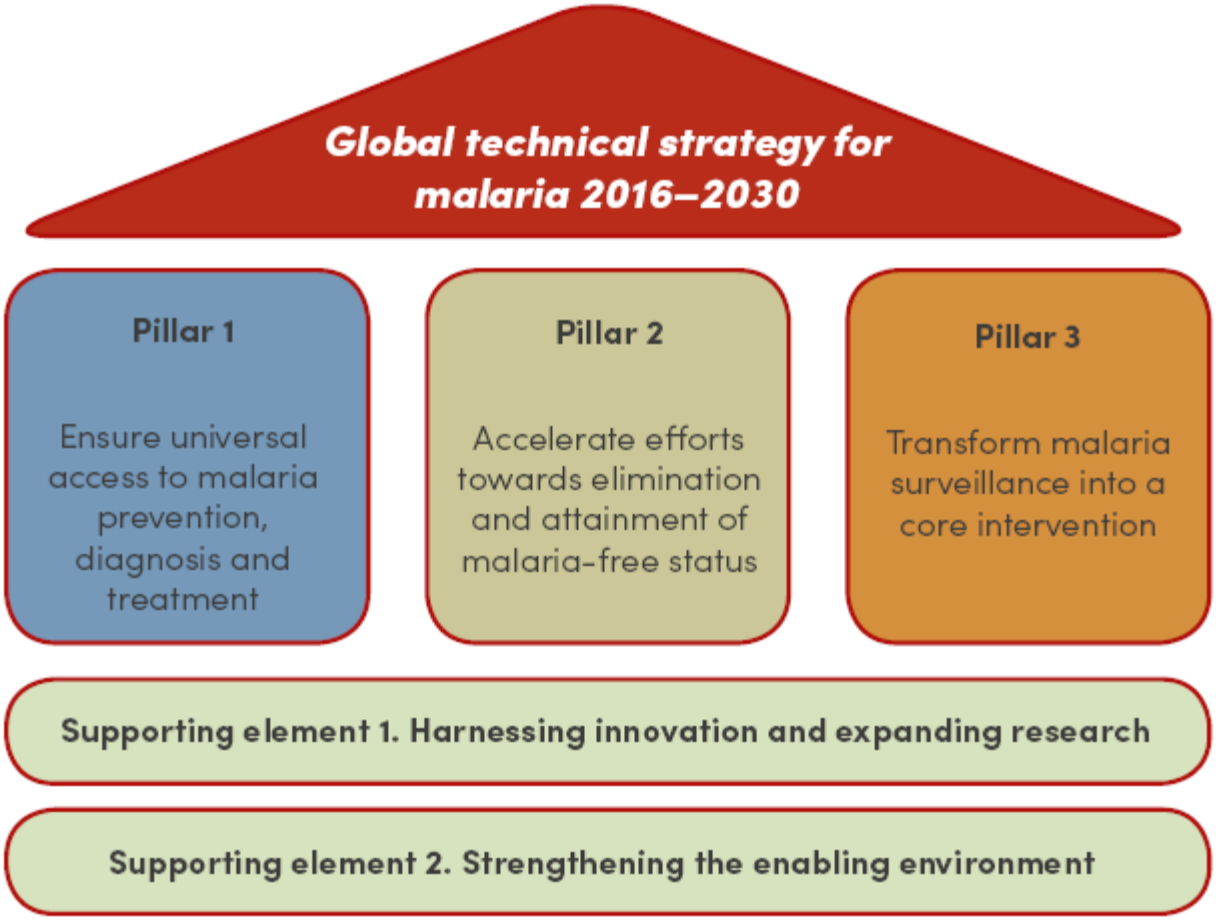
Global **Malaria** Programme

World Health Organization

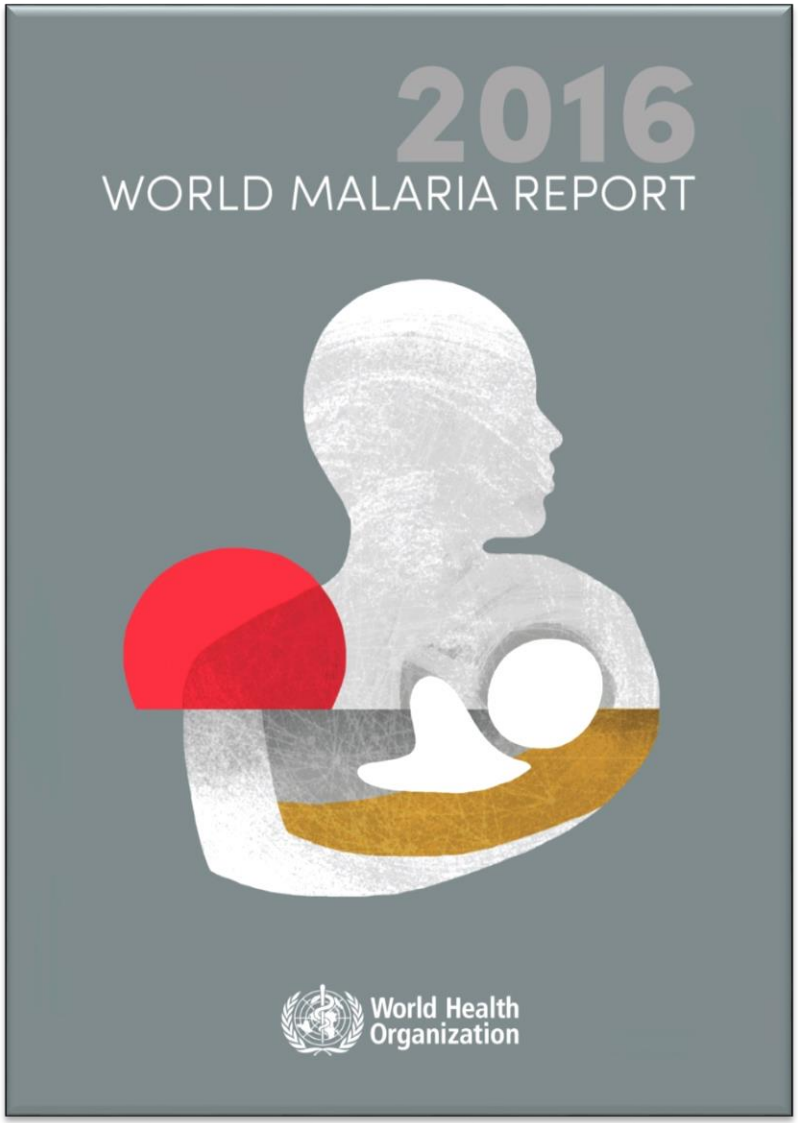
GTS global targets and milestones

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

FIG. 2.
GTS framework: pillars and supporting elements

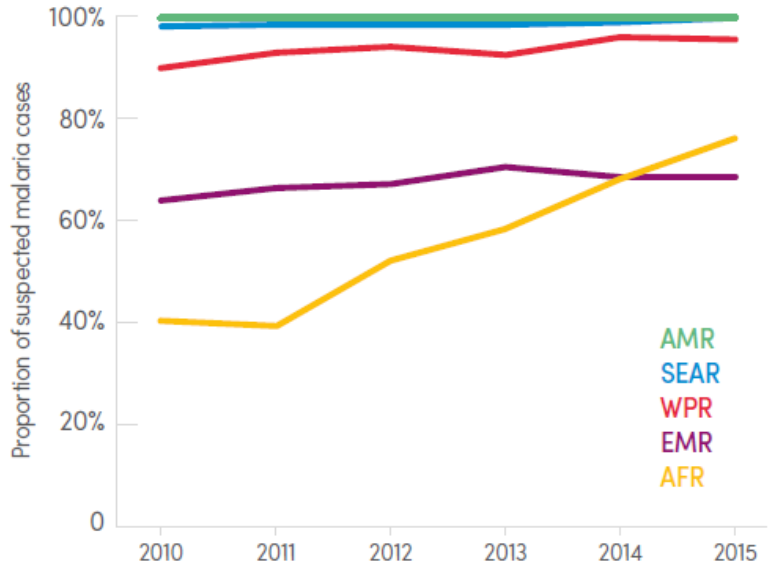


Overview



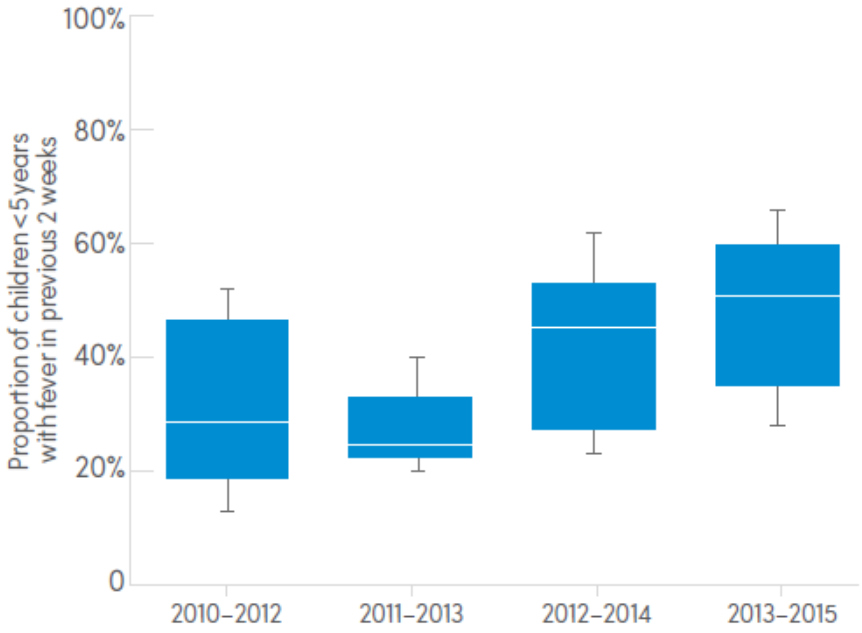
Pillar 1: universal access to core prevention, diagnostic and treatment strategies (diagnostic testing)

Reported by NMCPs



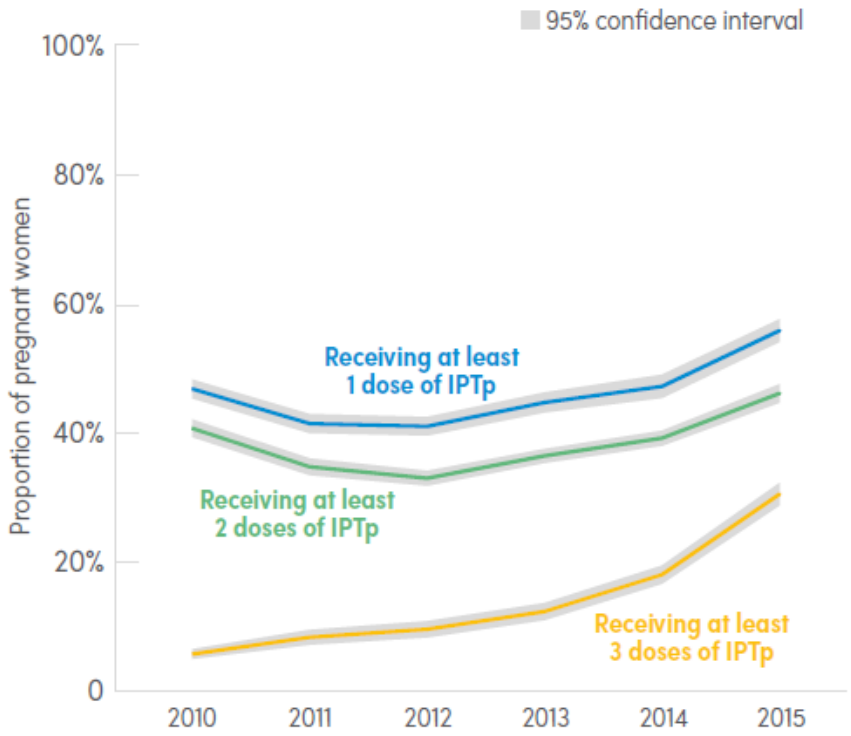
AFR, WHO African Region; AMR, WHO Region of the Americas; EMR, WHO Eastern Mediterranean Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region

Household surveys (children<5)



51% of febrile children <5 attending public health facilities received a malaria diagnostic test in 2013–2015 compared to 29% in 2010–2012, according to national surveys from 23 countries in sub-Saharan Africa

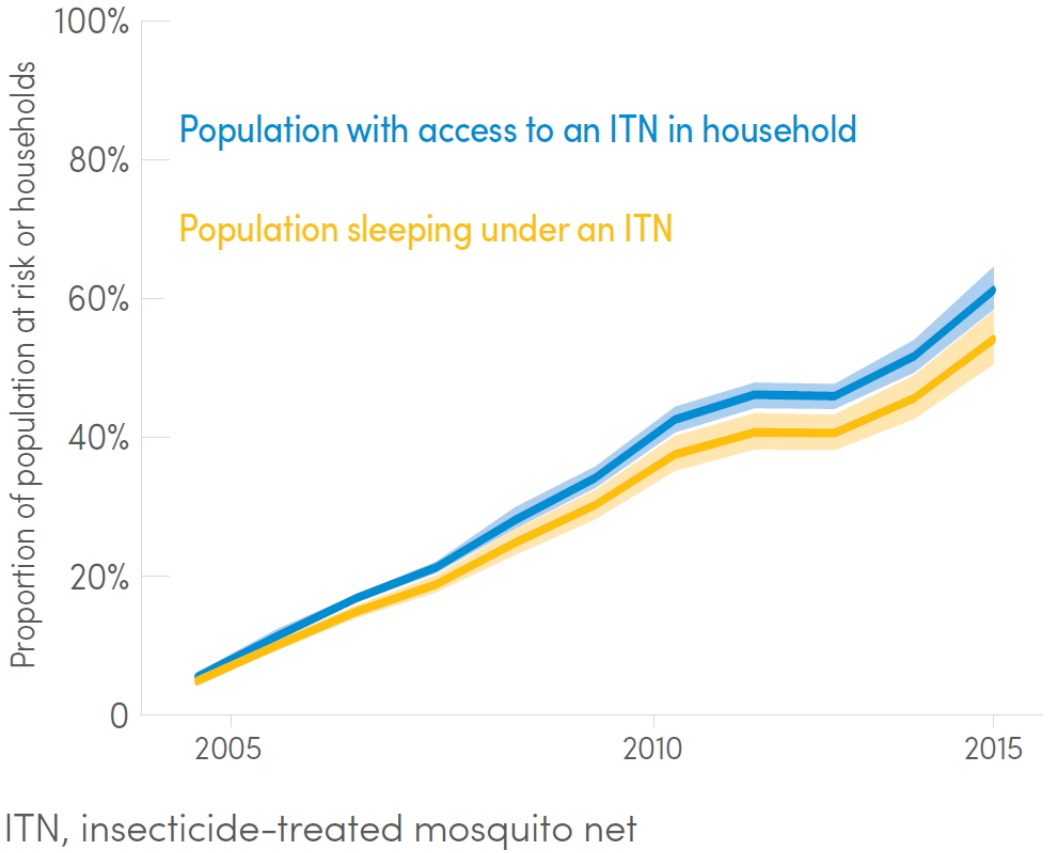
Pillar 1: universal access to core prevention, diagnostic and treatment strategies (IPTp in sub-Saharan Africa



ANC, antenatal care; IPT, intermittent preventive therapy

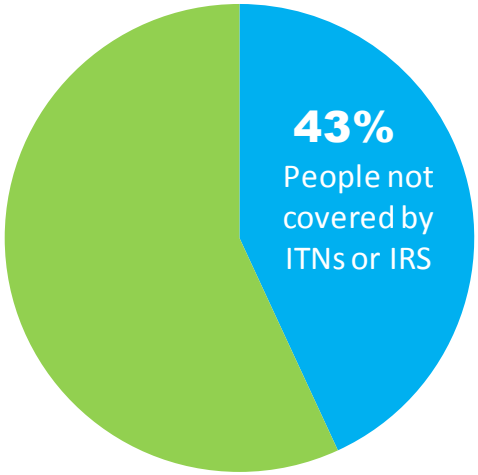
31% of eligible pregnant women received three or more doses of IPTp
a five-fold increase from 6% receiving three or more doses in 2010

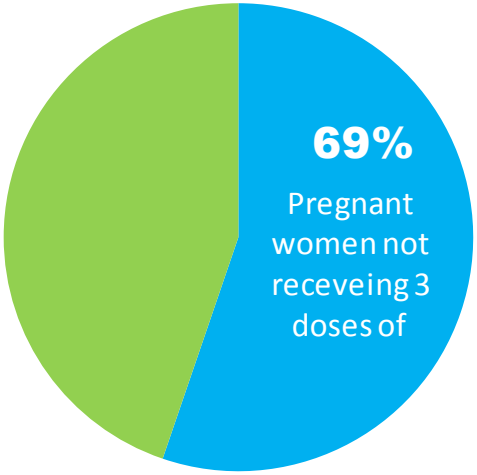
Pillar 1: universal access to core prevention, diagnostic and treatment strategies (ITNs in sub-Saharan Africa)

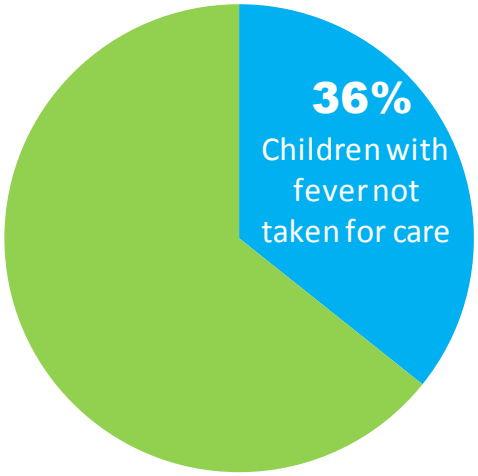


- 53% of the population at risk in sub-Saharan Africa, slept under an ITN in 2015 increasing from 30% in 2010
- This rise is driven by increased access to an ITN in households

Pillar 1: universal access to core prevention, diagnostic and treatment strategies: coverage gaps



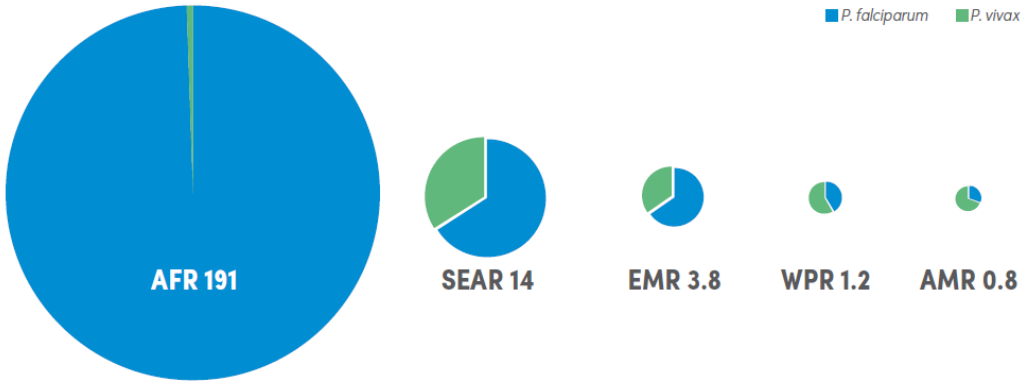




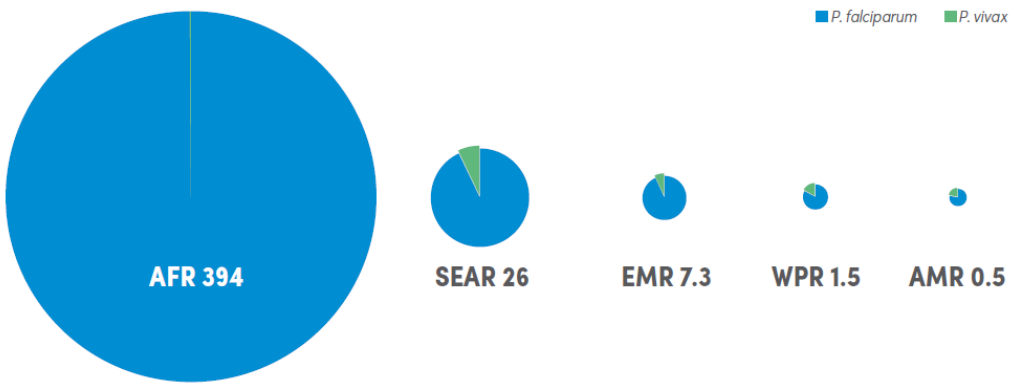
In many countries with a high malaria burden, health systems remain under-resourced

Goal 1 & 2 of the GTS: malaria burden

212 million cases



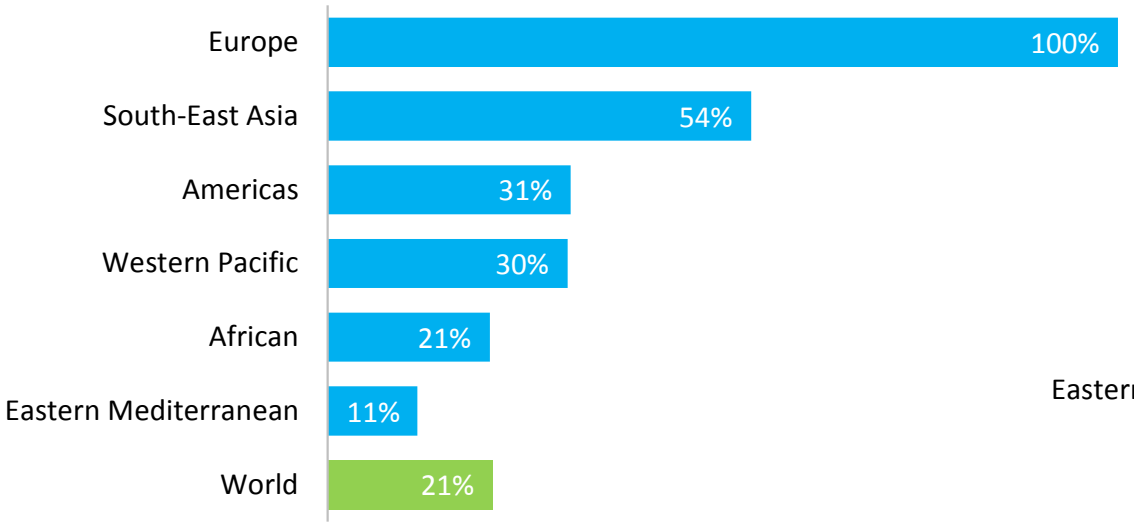
429 000 deaths



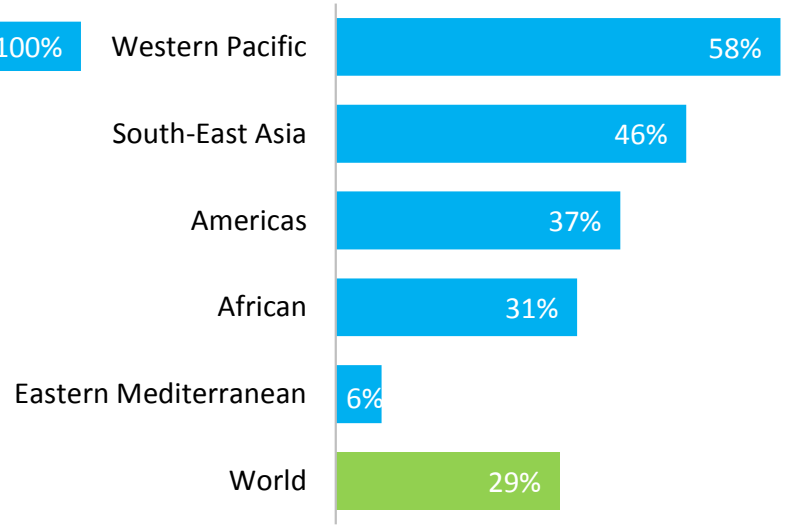
70% of deaths are in children under 5
– a child dies from malaria every 2 minutes –

Goal 1 & 2 of the GTS: Progress to 2020 milestones

Case incidence rate reduction 2010–2015



Mortality rate reduction 2010–2015



40 of 91 countries on track

39 of 91 countries on track
10 already zero deaths

GTS global targets and milestones

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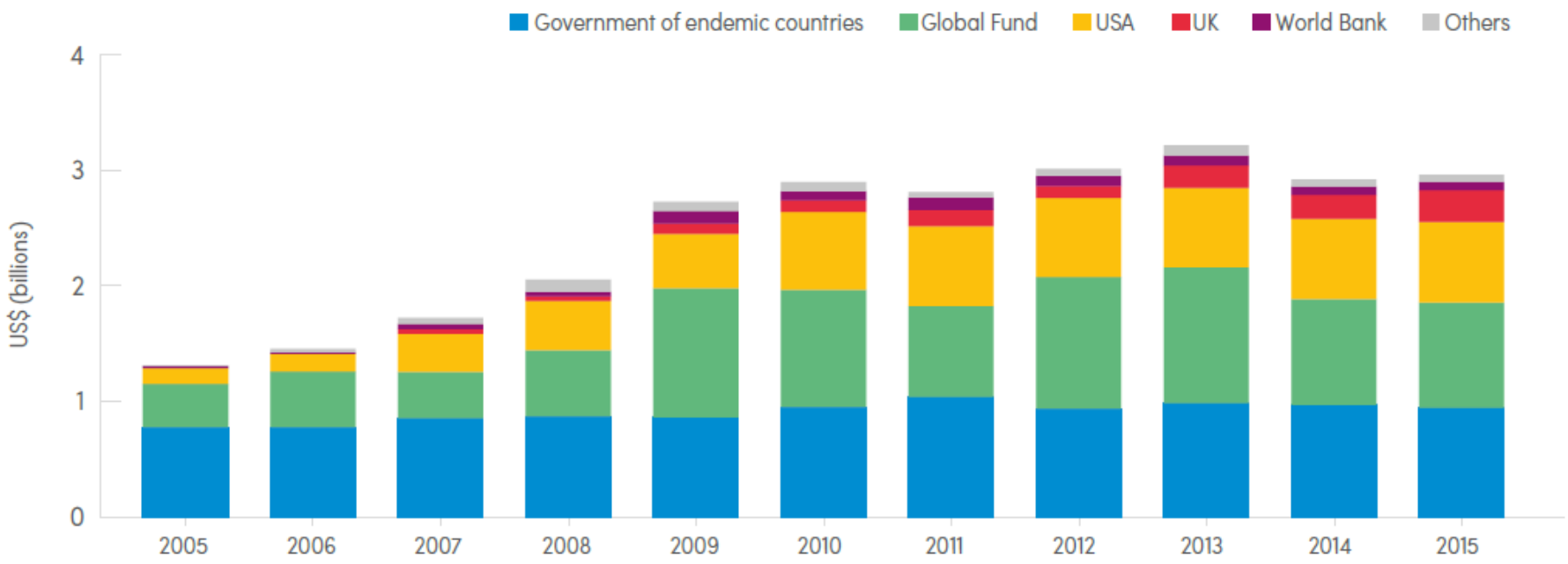
Goal 3 & 4 of the GTS: elimination and prevention of reintroduction

	Countries with zero indigenous cases for 3 years	Countries certified as free of malaria	
2000	Egypt	United Arab Emirates (2007)	
2001			
2002			
2003			
2004	Oman		
2005			
2006			
2007	Morocco (2010)	Syrian Arab Republic	
2008	Armenia (2011)		
2009	Turkmenistan (2010)		
2010			
2011	Iraq		
2012	Georgia	Turkey	
2013	Argentina	Kyrgyzstan (2016)	Uzbekistan
2014	Paraguay		
2015	Azerbaijan	Costa Rica	Sri Lanka (2016)

- 17 countries attained zero indigenous cases for ≥3 years 2000–2015, 10 since 2010
- 6 countries certified as free of malaria

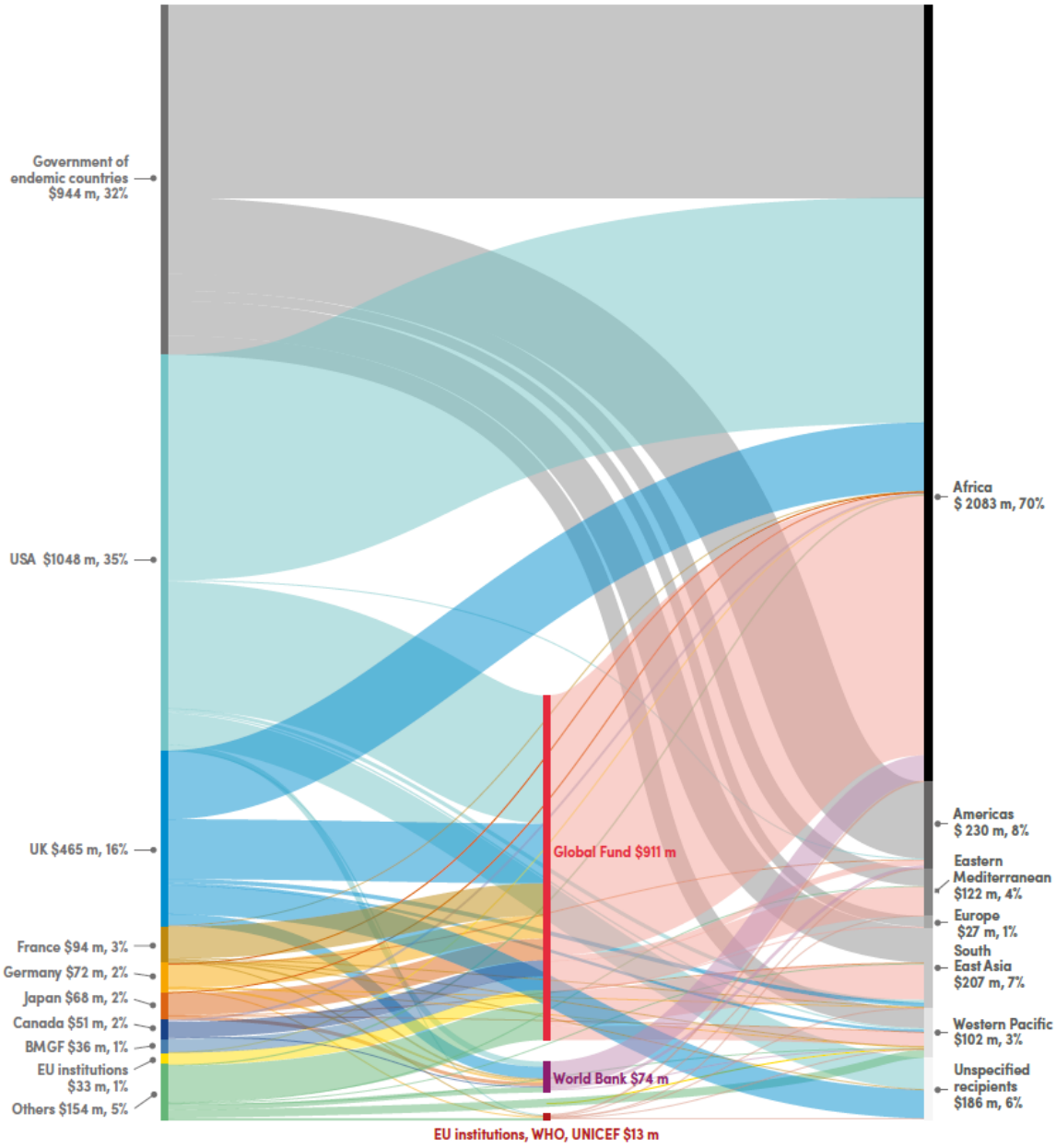
Malaria funding: trends



Global Fund, Global Fund to Fight AIDS, Tuberculosis and Malaria; UK, United Kingdom of Great Britain and Northern Ireland; USA, United States of America

Malaria funding totaled US$ 2.9 billion in 2015, just 45% of the GTS funding milestone for 2020, and increasing little since 2010

Malaria funding: flow



- Governments of endemic countries provided 32% of malaria funding in 2015
- The USA accounted for 35% of total funding in 2015, and the UK 16%
- 45% of international funds channeled through the Global Fund

World Health Organization

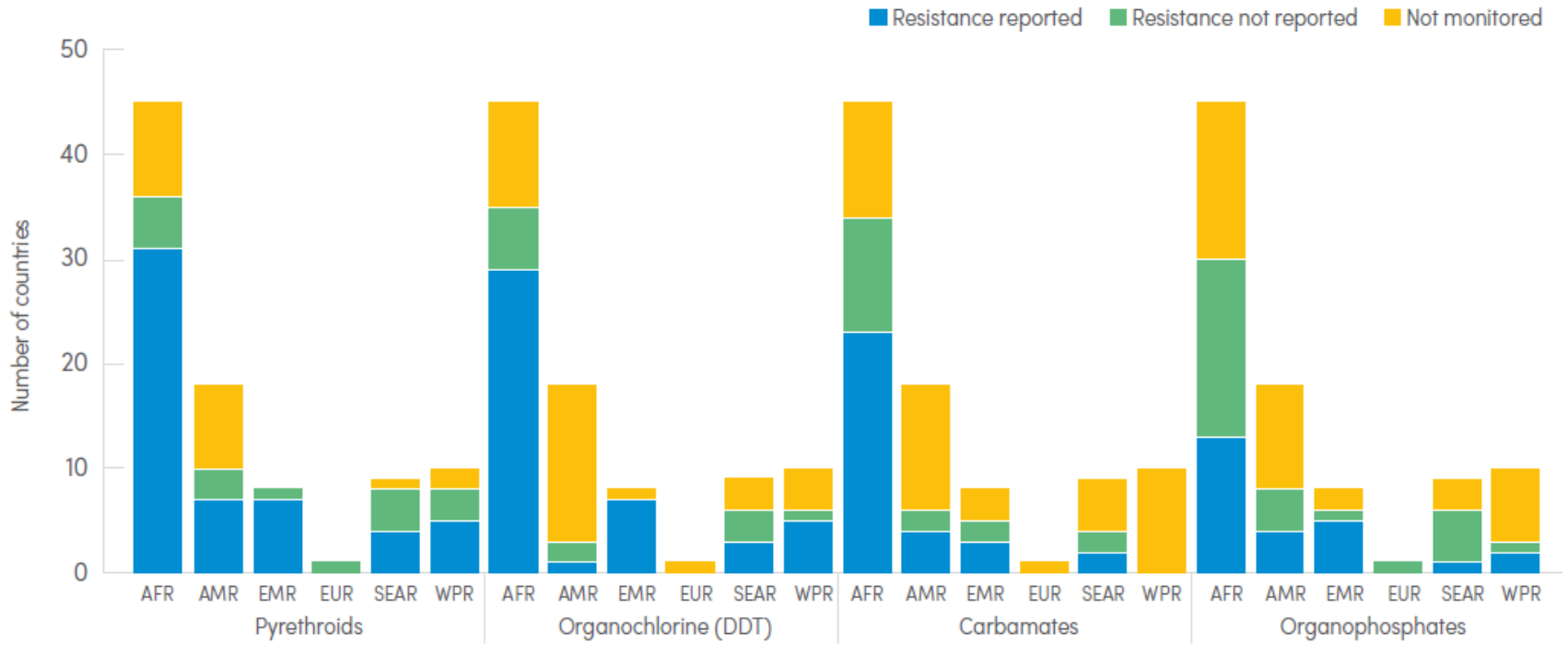
Key messages

1. Access to malaria interventions has expanded since 2010 especially in sub-Saharan Africa. However, coverage gaps imply large remaining burden.

2. Progress towards GTS 2020 milestones:
   - progress needs to be accelerated to achieve milestones of reducing case incidence and mortality rates by 40%
   - milestone of eliminating malaria from 10 or more counties looks attainable

3. Funding from both domestic and international sources must increase substantially if global targets are to be met

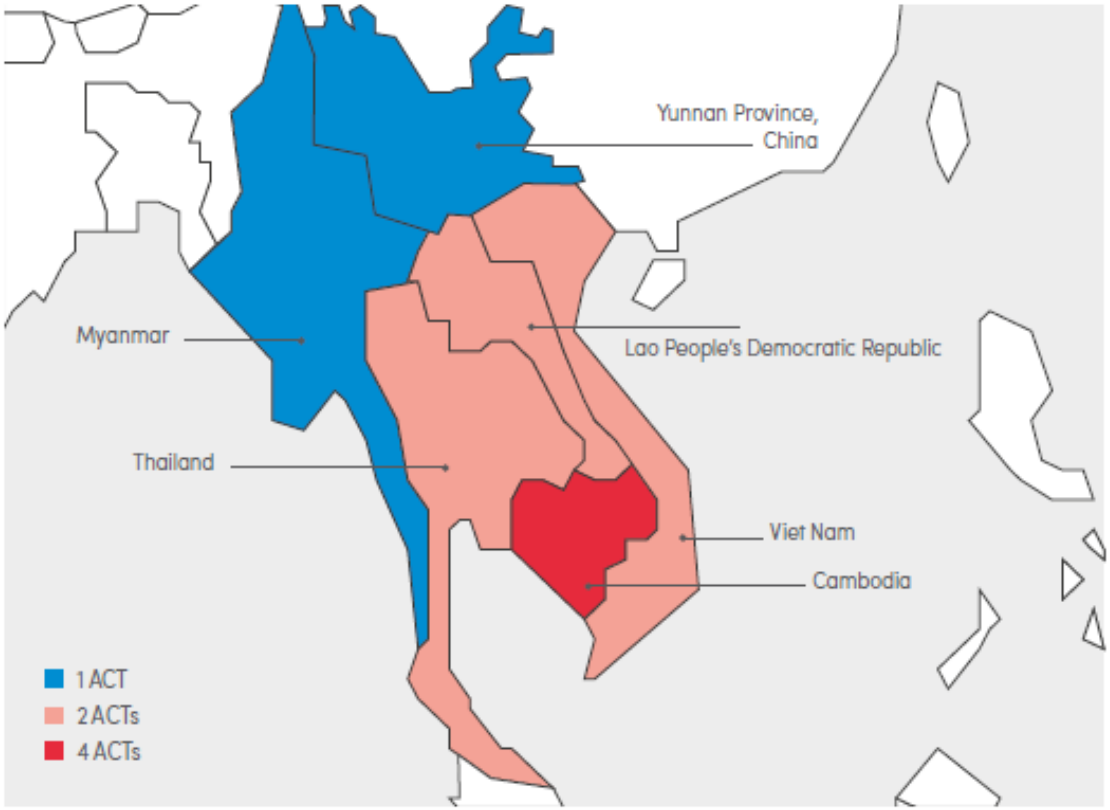
Biological challenges – insecticide resistance



AFR, WHO African Region; AMR, WHO Region of the Americas; DDT, dichloro-diphenyl-trichloroethane; EMR, WHO Eastern Mediterranean Region; EUR, European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region

- Mosquito resistance to at least one insecticide reported from 60 countries

Biological challenges – drug resistance



- Resistance to artemisinin has been detected in 5 countries in the Greater Mekong subregion
- In Cambodia, high failure rates after treatment with an ACT have been detected for 4 different ACTs

WHO key activities since last MPAC

- ERG on cardiotoxicity of antimalarials – Oct 2016
- Funding commitment for RTS,S pilot implementation – Nov 2016
- Findings from WHO LLIN study presented at ASTMH – Nov 2016
- ERG on new data on drug resistance in the GMS – Dec 2016
- WHO Executive Board requests resolution on Global Vector Control Response – Feb 2017
- Surveillance, Monitoring & Evaluation TEG – Feb 2017
- Strategic Advisory Group on malaria eradication 2nd meeting – Feb 2017
- Vector Control TEG – Mar 2017
- Getting to Zero by 2020 – Mar 2017

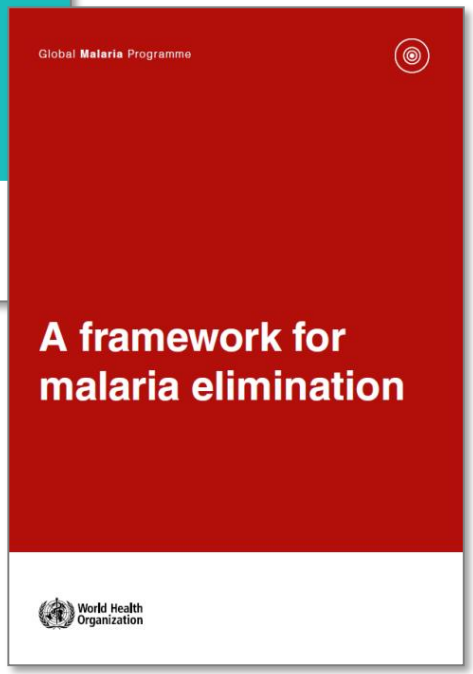
Key products

October 2016

January 2017

December 2016

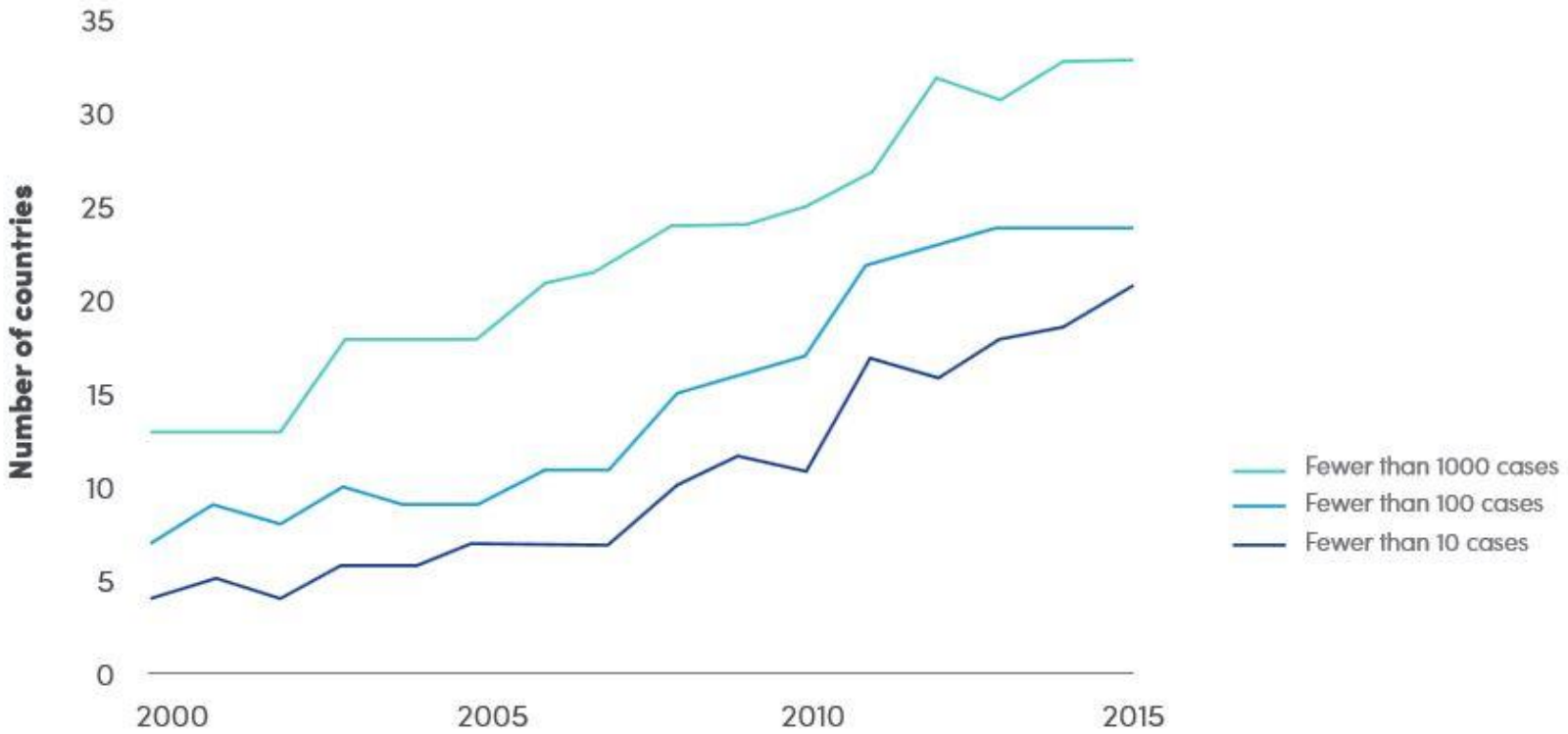
March 2017



Elimination and eradication

Country progress: 2000–2015

FIGURE 2.
Country progress towards malaria elimination, 2000–2015

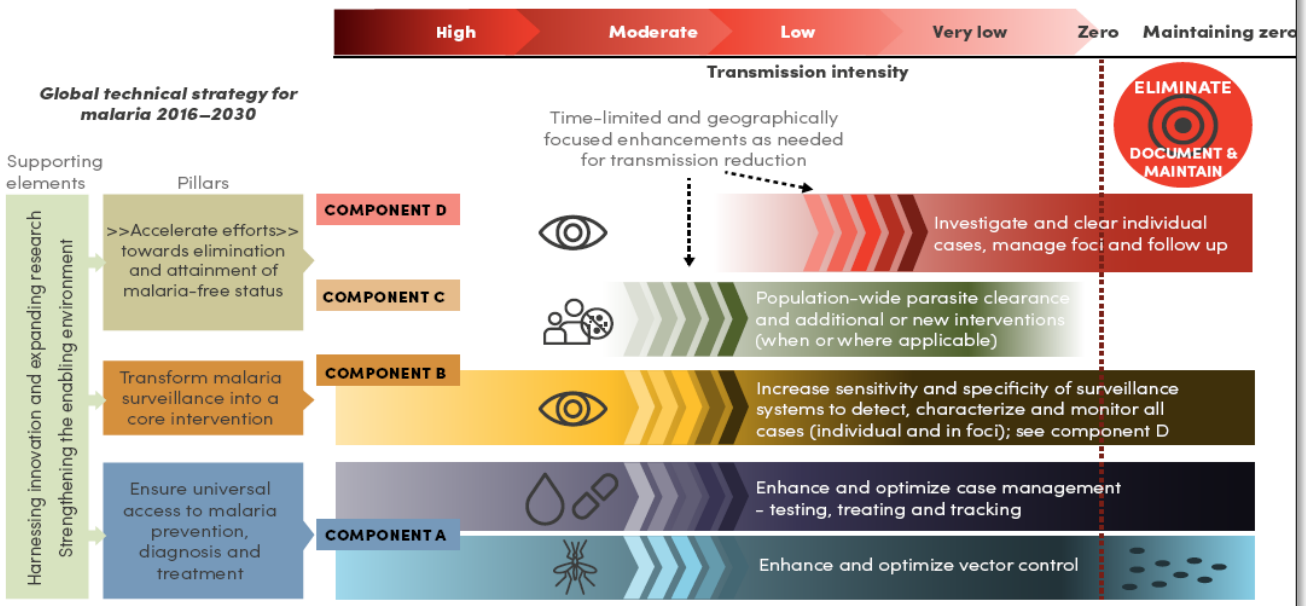


21 countries could achieve interruption of transmission by 2020

African Region	Algeria, Botswana, Cabo Verde, Comoros, South Africa, Swaziland
Region of the Americas	Belize, Costa Rica, Ecuador, El Salvador, Mexico, Paraguay, Suriname
Eastern Mediterranean Region	Iran (Islamic Republic of), Saudi Arabia
South-East Asia Region	Bhutan, Nepal, Timor-Leste
Western Pacific Region	China, Malaysia, Republic of Korea

FIG. 3.
Illustrative intervention package

This package of intervention strategies can be adapted for different geographical areas in a country. The choice of interventions should be based on transmission intensity (from "high" to "very low" to zero and maintaining zero) and also on operational capacity and system readiness. The diagram should be seen as illustrative rather than prescriptive, as the onset and duration of interventions will depend on local circumstances. The shading in the boxes showing components indicates the enhancements and quality required as programmes progress towards elimination, with darker colours indicating more intense actions and shading from light to dark indicating enhancement of the quality and scale or focus of the work.

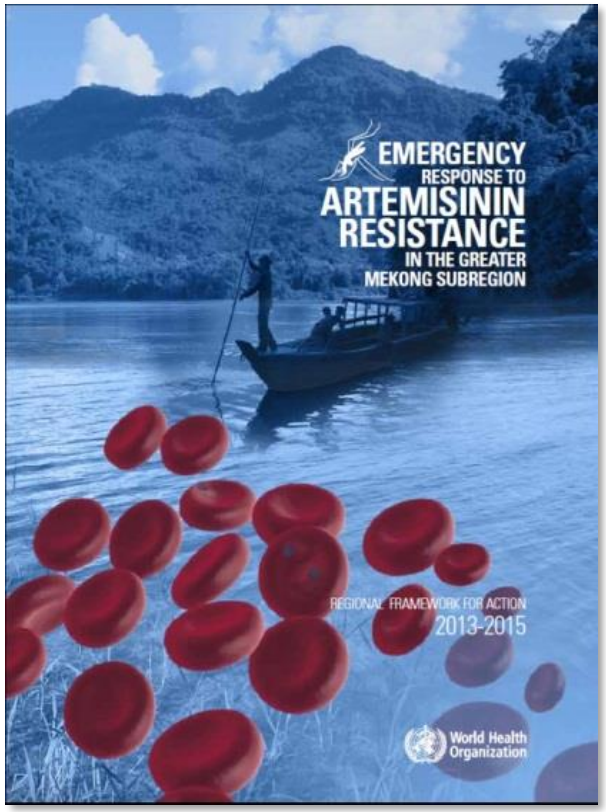


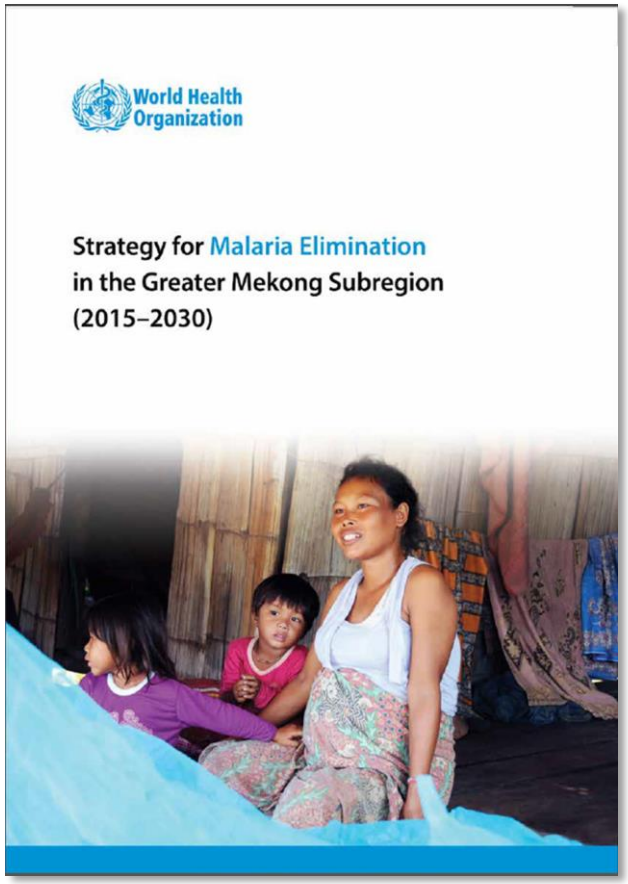
Acceleration – as represented by arrows here – relates to time-limited efforts made across all components in order to (1) achieve universal/optimal coverage in malaria prevention and case management (Component A**), and increase sensitivity and specificity of surveillance systems so they are able to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

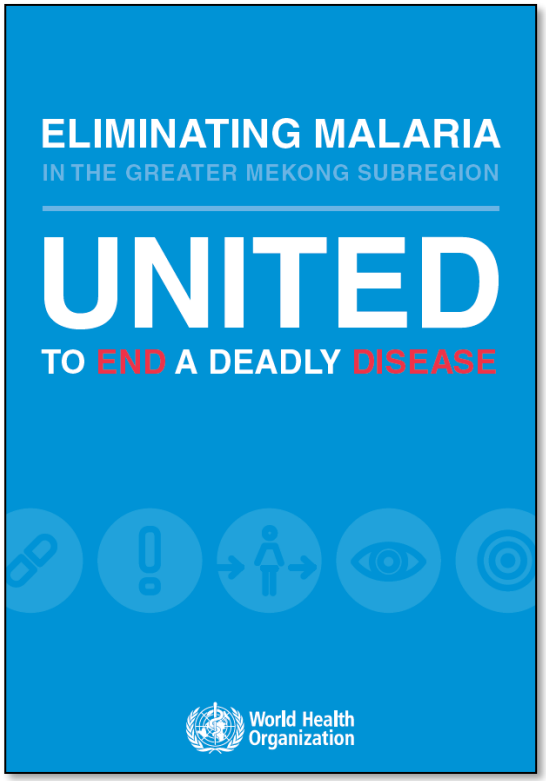
Strategic Advisory Group on malaria eradication

2nd Meeting: 16 – 17 February 2017

GMS: Partners Forum Nov 2016







Vector Control

Multi-country evaluation of implications of insecticide resistance for malaria vector control

Key outcomes

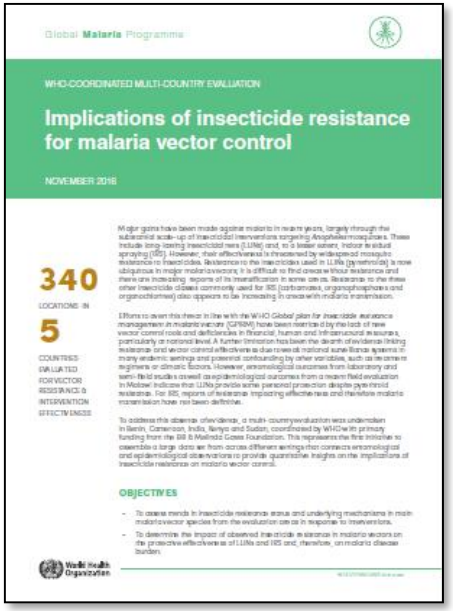
1. Insecticide resistance was highly variable between years and was heterogeneous on a relatively fine scale.
2. There was a trend of increasing pyrethroid resistance in the main malaria vector species.
3. There was **no evidence of an association between malaria disease burden and pyrethroid resistance** across all locations.
4. There was **evidence that LLINs provided personal protection against malaria in areas with pyrethroid resistance**. There was no difference detected in LLIN effectiveness between higher and lower pyrethroid resistance.
5. There was evidence from an area (Galabat) with high LLIN coverage that IRS with an insecticide to which there is resistance provided no additional protection whereas **IRS with an insecticide to which there is susceptibility almost halved malaria incidence** relative to LLINs alone.
6. The development of pyrethroid resistance was slower in areas with LLINs plus a non-pyrethroid IRS than in an area with LLINs only.

Multi-country evaluation of implications of insecticide resistance for malaria vector control

Implications for malaria vector control and surveillance

- Universal coverage with effective vector control of all at-risk populations is essential to protect against malaria. LLINs continue to provide protection even in the face of resistance.
- Despite gains made against malaria, transmission is still occurring. New tools and strategies are required.
- Countries are urged to develop and implement national insecticide resistance monitoring and management plans.
- Better measures of insecticide resistance are needed.

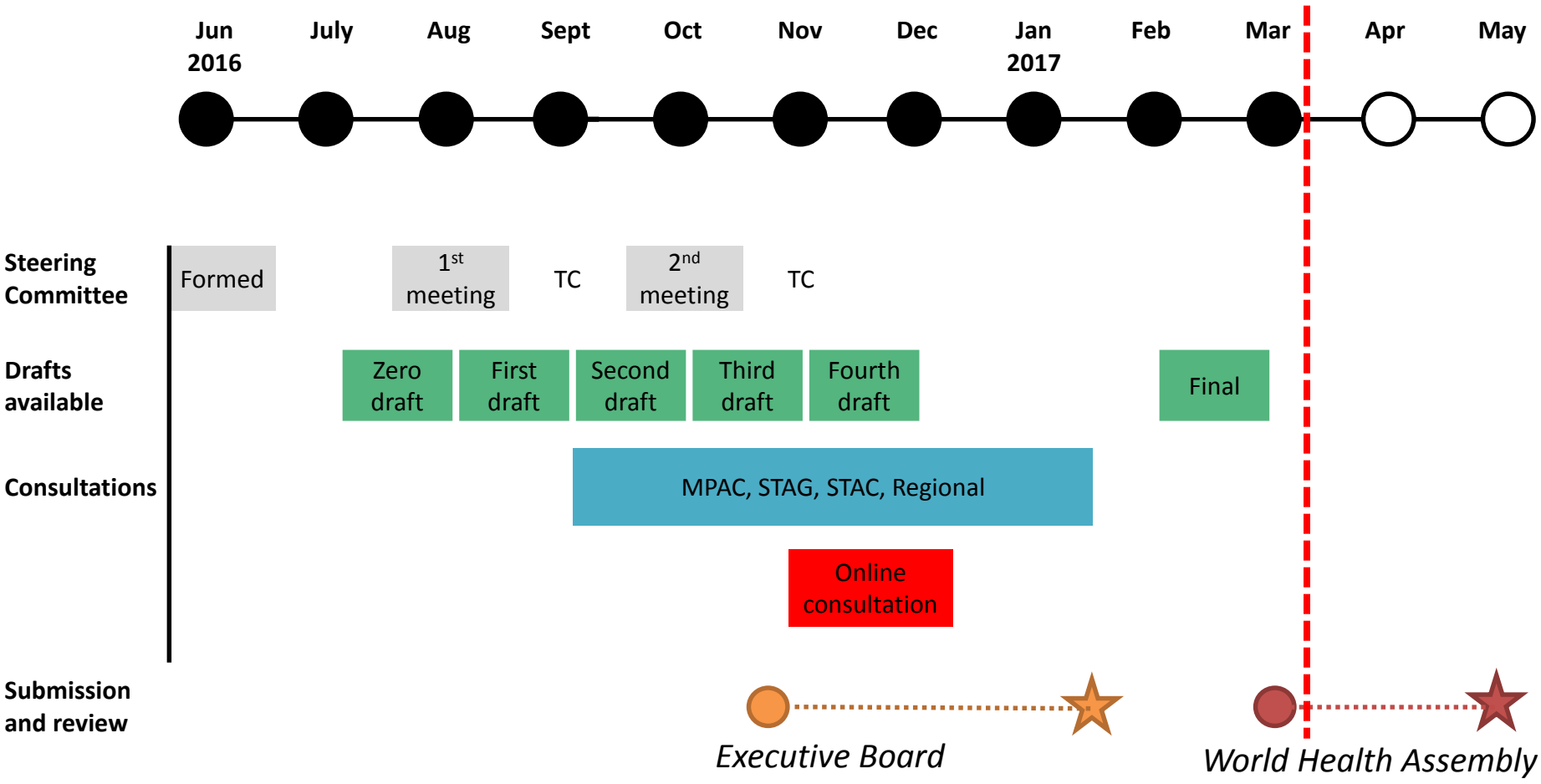
November 2016



http://www.who.int/malaria/publications/atoz/insecticide-resistance-implications/en/

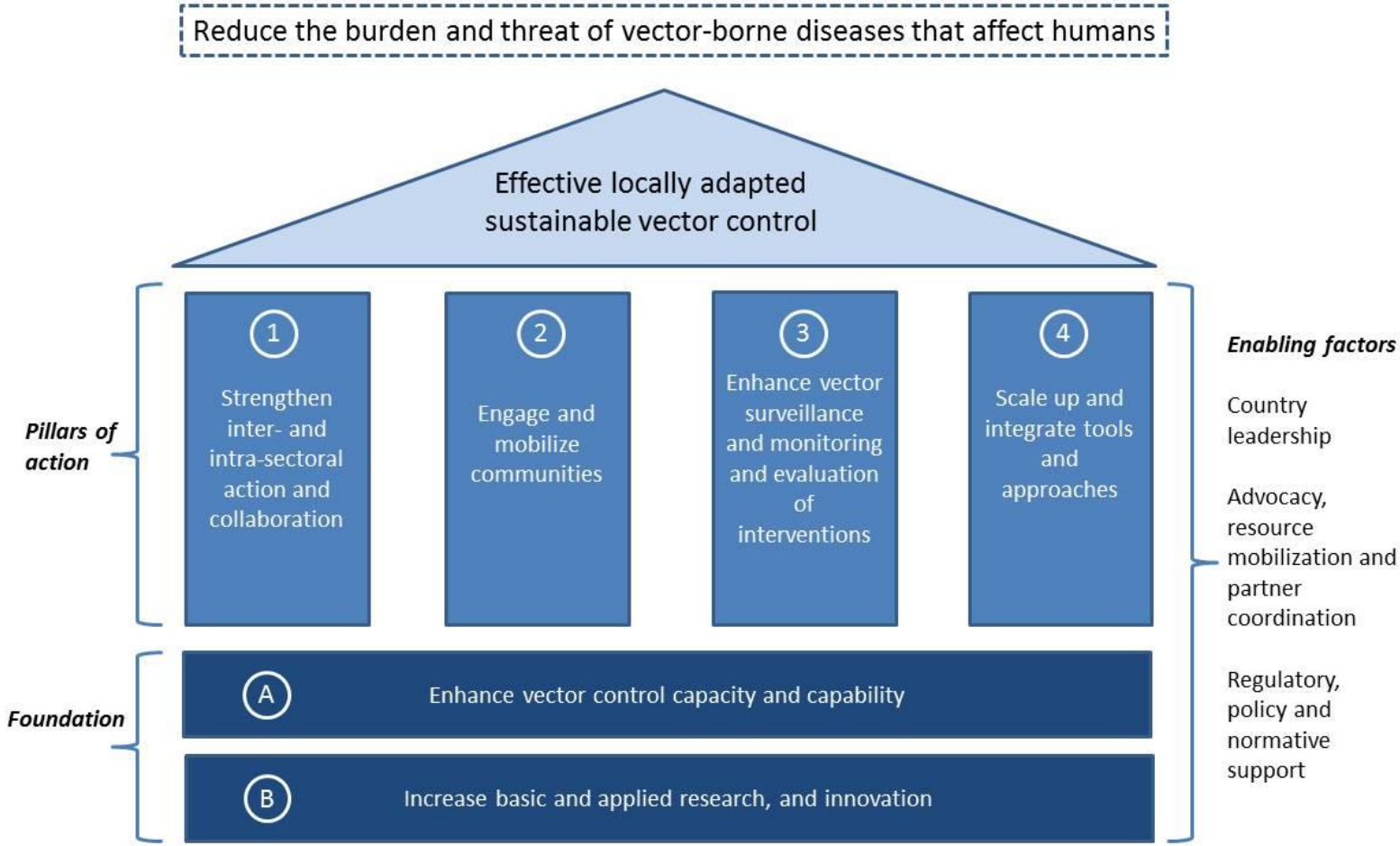
Draft Global vector control response

Status: Fifth draft (v5.1) produced based on feedback from online consultation and Executive Board 140th session (held 28 January 2017)



Draft Global vector control response

Provides strategic guidance to countries and development partners for urgent strengthening of vector control as a fundamental approach to preventing disease and responding to outbreaks



http://www.who.int/malaria/global-vector-control-response/en/

Reformed process for WHO evaluation of vector control products

Vector control product with community effect for potential use in public health

WHO pre-submission coordination committee (WHO-PQT/WHO-GMP/WHO-NTD) determines product pathway

Product class **and** claim <u>WITH</u> a WHO policy recommendation

Pre-Qualification Process
(WHO-PQT)

Screening
Complete screen of application

Assessment
Expert group assessment of submitted data on product efficacy, safety and quality against established standards

Inspection
Manufacturing facilities are inspected to ensure compliance with WHO-recommended quality standards

Product pre-qualified by WHO
(WHO-PQT)

Post-Prequalification activities
(WHO-PQT)

Product class and/or claim <u>WITHOUT</u> a WHO policy recommendation

New Interventions Verification Process
(VCAG, WHO-NTD + WHO-GMP)

Concept review and data definition
Review of concept and determination of data required to a) assess product class/claim and b) support formulation of WHO policy recommendation

Assessment standards development
Test guidelines, SOPs, standards and criteria developed

Assessment and recommendation to WHO
Evaluation of evidence and (a) completion of the TPP for new product class or (b) claim validation for new product claim

Public health value of product class/claim validated
(WHO-GMP + WHO-NTD)

WHO policy recommendation
(WHO-GMP + WHO-NTD with support of VCTEG / MPAC / STAG)

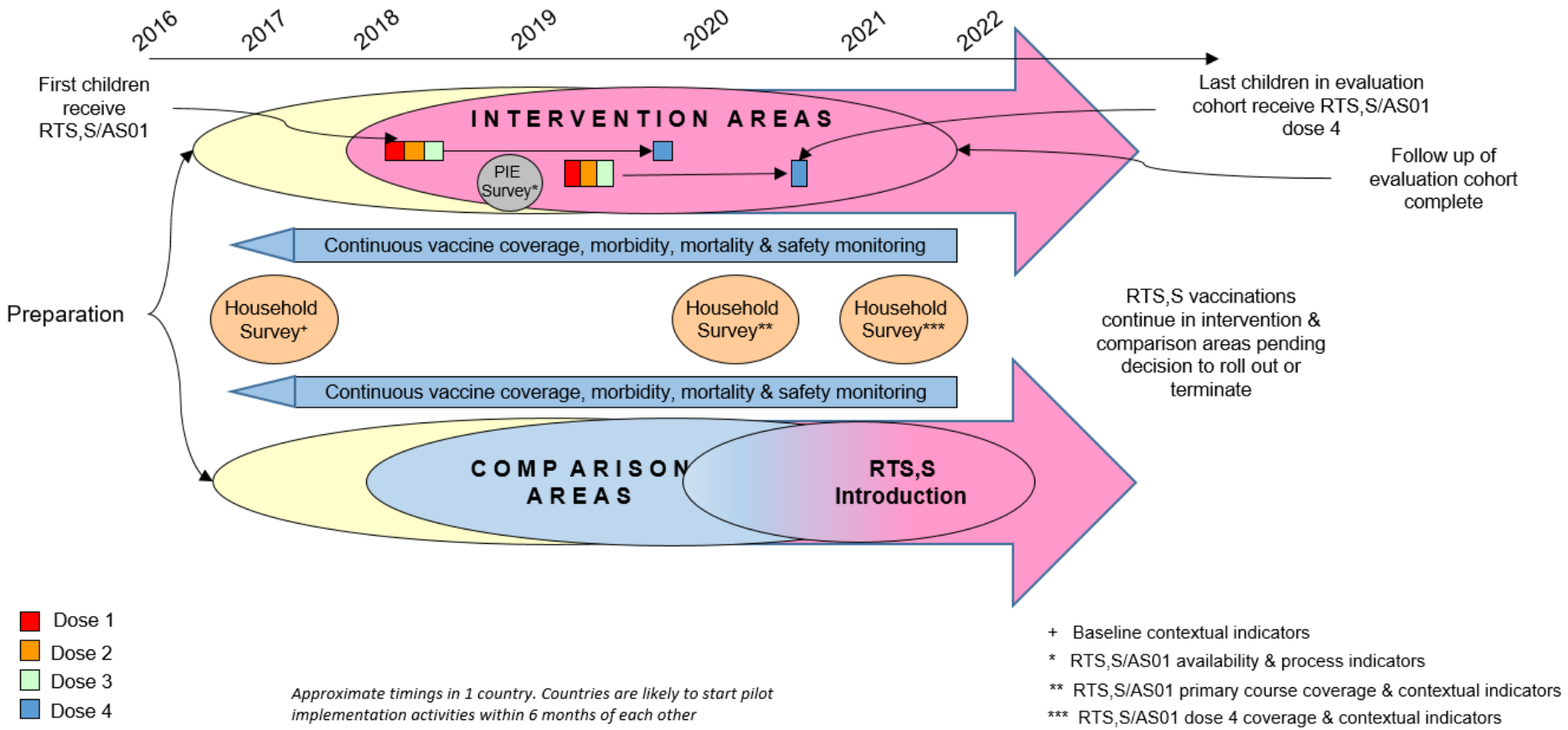
Operational guidance on conditions for use in programmes
(WHO-GMP and WHO-NTD with support of, VCTEG / MPAC/ STAG)

RTS,S malaria vaccine

- RTS,S/AS01 – the first malaria vaccine
  - 39% reduction in clinical malaria
  - 31% reduction in severe malaria
  - Considerable potential for public health impact

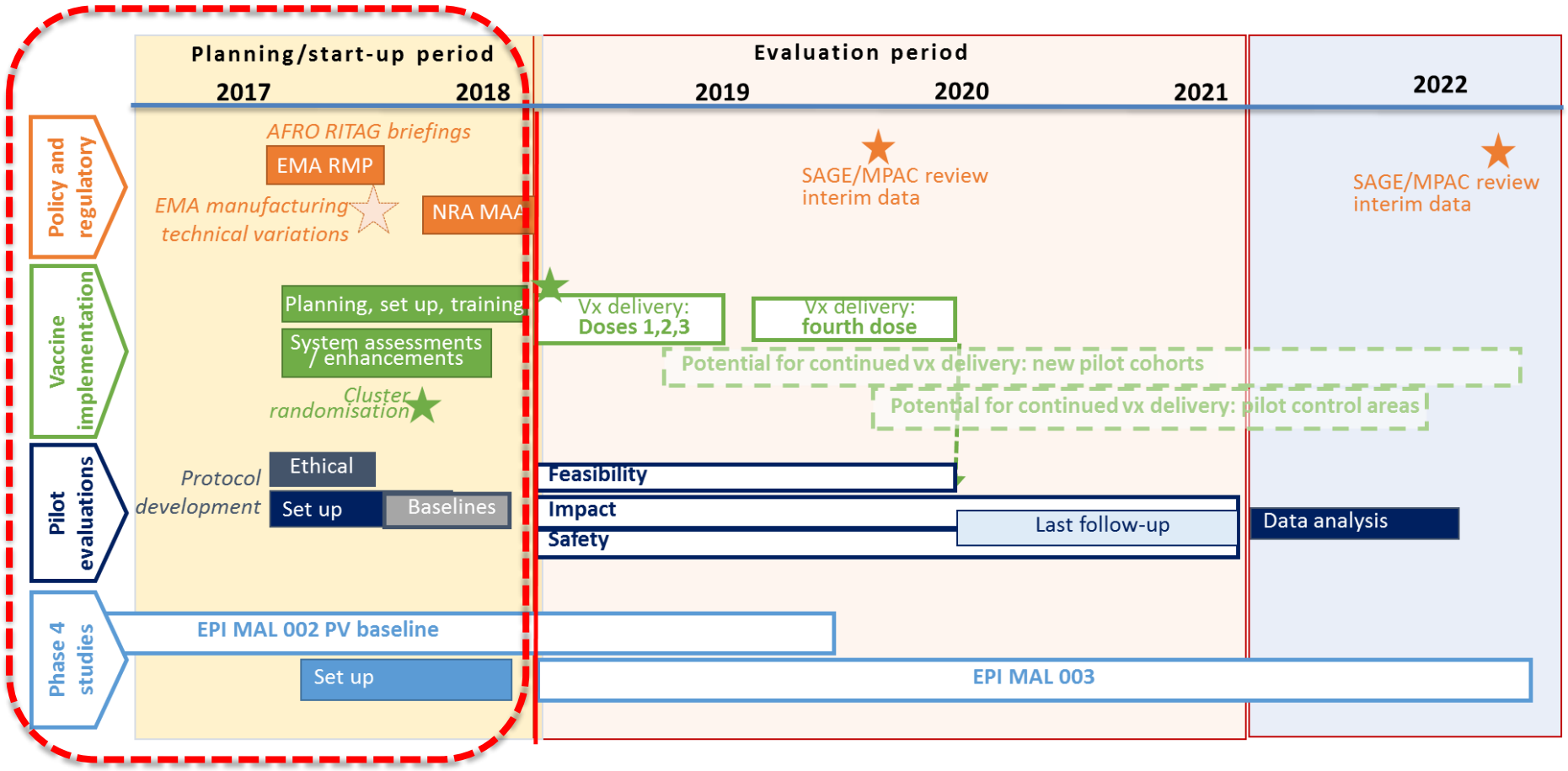
  } Over 4 years follow-up
- WHO recommendation to pilot implementation in 3 countries: rigorous evaluation of
  - **Feasibility**
  - **safety**
  - **impact**
- Master protocol to form basis of country-specific protocols
- Target date for start of vaccinations: Q2:2018
  - Discussion needed on duration of RTS,S deployment in implementation areas, and potential roll out of RTS,S/AS01

Overview of pilot implementation of RTS,S, S/A01



Indicative overall timeline 2017–2022

Target: first vaccine introduction Q1 2018

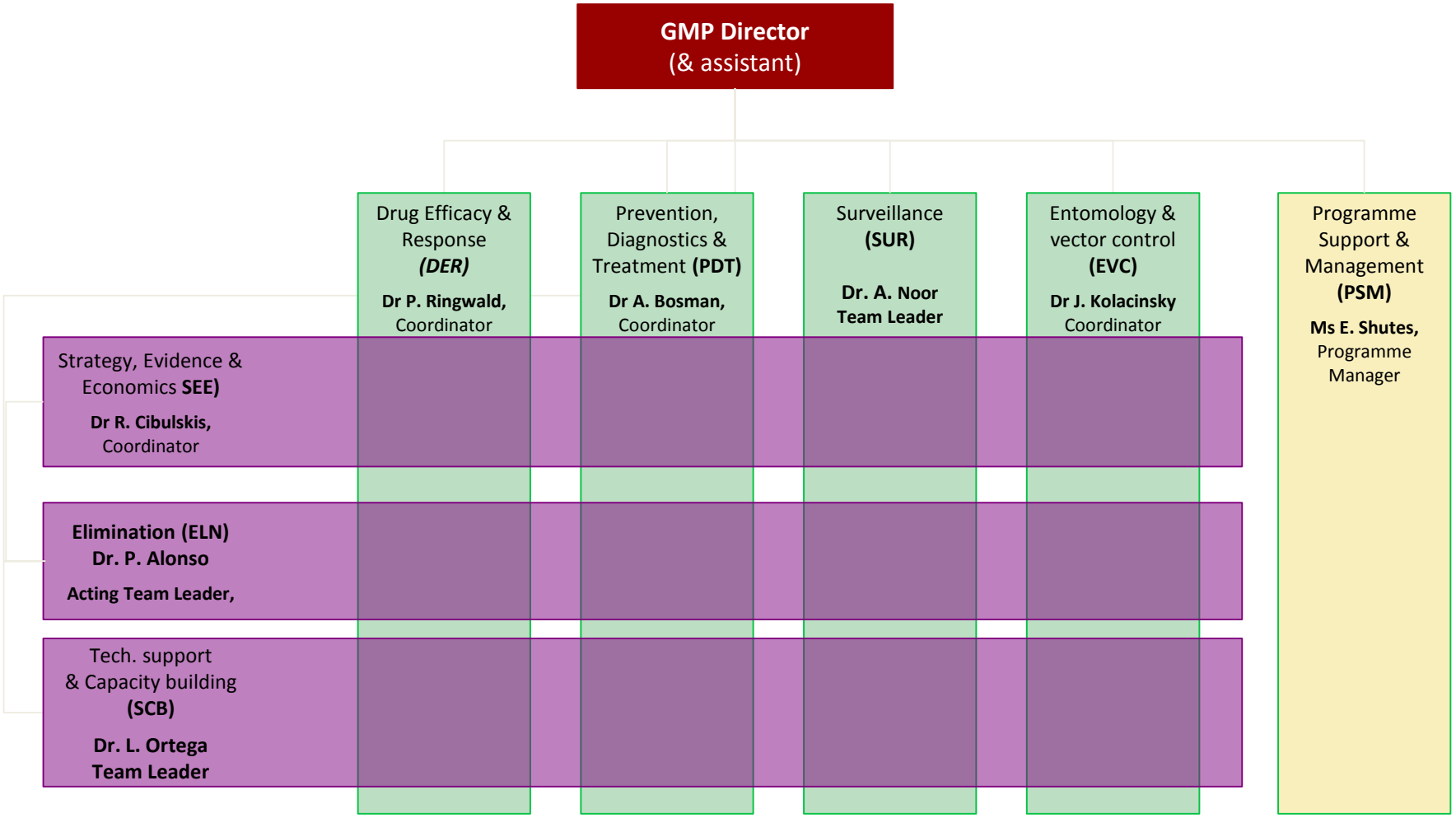


Roll Back Malaria Partnership update

- New RBM Board named in June 2016
- New RBM by-laws approved
- Revitalised RBM Partnership hosted by UNOPs
- Dr Kesete Admasu, CEO announced February 2017
- Partnership Committees being formed
- GMP looks forward to working closely with the new RBM to ensure complementarity of work to achieve the GTS milestones

ROLL BACK MALARIA PARTNERSHIP

THANK YOU


GMP Director
(& assistant)
Drug Efficacy & Response (DER)
Dr P. Ringwald, Coordinator
Prevention, Diagnostics & Treatment (PDT)
Dr A. Bosman, Coordinator
Surveillance (SUR)
Dr. A. Noor Team Leader
Entomology & vector control (EVC)
Dr J. Kolacinsky Coordinator
Programme Support & Management (PSM)
Ms E. Shutes, Programme Manager
Strategy, Evidence & Economics SEE)
Dr R. Cibulskis, Coordinator
Elimination (ELN)
Dr. P. Alonso
Acting Team Leader,
Tech. support & Capacity building (SCB)
Dr. L. Ortega
Team Leader

Proposed adjustments on the definition of GMP "core roles"

I

In collaboration with the malaria community, address key **strategic questions** related to malaria control and elimination

II

Set, communicate & disseminate **normative guidance**, policy advice and implementation guidance to support country action

III

Coordinate WHO **capacity building & technical support** to member states, jointly with Regions, ISTs and countries

V

Keep an **independent score** of global progress in malaria control and elimination, including **drug & insecticide resistance**

IV

Enable countries to develop & implement robust **surveillance** systems to generate quality data and use that data to achieve greater impact

1. Global Technical Strategy objectives for 2020

Malaria Policy Advisory Committee Meeting

22–24 March 2017, Geneva, Switzerland
Background document for Session 2

World Health Organization

Update on RTS,S Malaria Vaccine Implementation Programme

March 2017, Geneva, Switzerland

Background

Following the joint review and advice from MPAC and the Strategic Advisory Group of Experts on Immunization (SAGE) in October 2015, WHO published its position paper on RTS,S, the first malaria vaccine. WHO recommends pilot implementation of the RTS,S vaccine in distinct settings in sub-Saharan Africa in order to generate the evidence necessary for an updated WHO policy recommendation on the use of the RTS,S malaria vaccine in children in sub-Saharan Africa. The key objectives are:

- To assess the operational feasibility of providing RTS,S at the recommended schedule of four doses;
- To evaluate the impact of the vaccine on all-cause child mortality (overall and by gender), malaria-specific mortality and severe malaria;
- To evaluate the frequency of adverse events following vaccination, with an emphasis on meningitis and cerebral malaria.

WHO has taken the lead in developing the Malaria Vaccine Implementation Programme (MVIP), raising the necessary funds and starting to establish partnerships with relevant organizations.

Update since September 2016

In November 2016, the Global Fund to Fight AIDS, Tuberculosis and Malaria approved US$ 15 million from its catalytic funds for the malaria vaccine pilots. Together with previous funding commitments made by Gavi, the Vaccine Alliance (up to US$ 27.5 million, matching other sources 1 to 1) and UNITAID (US$ 9.6 million), a total of US$ 49.2 million has now been pledged for the first 4 years of the Programme (2017–2020). These commitments enable the initiation of the Programme in three countries at the recommended scope and sample size of the observational studies.

WHO received expressions of interest from 10 countries to participate in the pilot implementation programme. Selection criteria were applied to identify three countries, and a joint delegation from WHO, PATH, and the vaccine manufacturer, GlaxoSmithKline Biologicals (GSK), made initial visits to the countries in October–November 2016. The proposed Malaria Vaccine Implementation Programme was discussed with senior representatives from the Ministries of Health, as well as the National Malaria Control Programmes, the Expanded Programme on Immunization, regulatory authorities, research organizations and other partners. The visits confirmed the countries' continued interest and suitability to participate in the pilot

WHO/HTM/GMP/MPAC/2017.1

programme, and the countries have now been formally notified of their selection. A public announcement of the country selection will be made by the end of April 2017.

Intensive preparation activities are under way, with follow-up visits to the pilot countries scheduled for March 2017. An advanced draft of the master protocol for the evaluation of the cluster-randomized pilot implementation of RTS,S has been developed. The draft will be included in GSK's revised RTS,S Risk Management Plan, to be submitted to the European Medicines Agency in March 2017. The WHO Ethics Review Committee as well as relevant bodies in the three countries will subsequently conduct protocol reviews.

WHO will release a Request for Proposals (RFP) in order to identify suitable research partners to conduct the evaluations in each of the three countries. The successful applicants will lead the development of country-specific protocols for subsequent review by local ethics review committees.

A collaboration agreement between WHO, PATH and GSK defining roles and responsibilities in the RTS,S Malaria Vaccine Implementation Programme is currently being finalized.

To explore the potential for a joint regulatory review and shared or collaborative oversight mechanisms for RTS,S use in the pilots, representatives of the three pilot countries' national regulatory agencies convened as part of the African Vaccine Regulatory Forum (AVAREF) on 18–19 February 2017.

Preparation activities for vaccine introduction, regulatory approval, pharmacovigilance and evaluation readiness will continue over the course of this year, with the aim of starting implementation of the RTS,S malaria vaccine in pilot areas in 2018.

RTS,S Malaria Vaccine Implementation Programme

A joint initiative of GMP & IVB

Update to the Malaria Policy Advisory Committee

David Schellenberg, Scientific Advisor, GMP
Mary Hamel, Coordinator MVIP, IVR, IVB
22nd March 2017

Background

- RTS,S - 30 years in development, a Phase 3 trial in >16,000 children, positive scientific opinion from the European Medicines Agency
- SAGE and MPAC unequivocal on the need to determine the public health role of this vaccine

- The RTS,S Malaria Vaccine Implementation Programme (MVIP) is a joint project between WHO's Global Malaria Programme and the Immunization, Vaccines and Biologicals Department, developed in collaboration with participating countries, PATH and GSK

- Proposal submitted to funding agencies mid-2016
  - Design based on WHO technical consultation in January 2016

Update since September 2016
Funding Situation: Phase 1 (2017-2020)

- June 2016:
  - Gavi Board approved up to $27.5 million for the first 4 years, on condition of matched funding
  - UNITAID Executive Board approved strategic fit
- September 2016:
  - UNITAID committed up to $9.6 million for Phase 1
- November 2016:
  - Global Fund committed $15 million
- Expect to sign funding agreements in coming weeks

Update since September 2016
In-country preparations

- First round of joint WHO/PATH/GSK visits to 3 countries in October-November 2016
  - Continued interest at technical and leadership levels confirmed
- Countries officially informed of selection
- Second round of visits in March 2017
  - Work started to plan vaccine introduction, routine pharmacovigilance strengthening and evaluation components
- Public announcement planned for World Malaria Day

Update since September 2016
Regulatory review

- 18-19 February 2017: Pre-AVAREF meeting convened representatives from National Regulatory Agencies of the 3 pilot countries.
- Potential regulatory strategies discussed to authorise use of RTS,S in pilots
- Suggestion for joint regulatory review process to be facilitated by WHO

Update since September 2016
Evaluation protocol & selection of evaluation partners

- Master protocol developed, to be submitted by GSK as part of their Risk Management Plan
- Country-specific protocols to be developed following selection of in-country evaluation partners
- Request for Proposals to select evaluation partners will be published in coming weeks
  - Expect to confirm evaluation partners by Q2/Q3 2017
- Potential for joint ethics review of protocol facilitated by WHO under discussion

Malaria Vaccine Pilot Implementation

Overall design (1)

- **Sub-national introduction of the approved RTS,S vaccine**
  - Introduced and delivered by EPI using existing mechanisms
  - In close collaboration with NMCP, ensuring continued use of other malaria prevention and treatment measures
- Sub-national introduction enables some areas (clusters) to introduce RTS,S at the beginning of the programme, while other clusters act as comparison areas
  - Allocation of clusters into implementation or comparison areas will be randomized
  - Clusters defined (e.g. district, sub-country) based on country context and evaluation requirements

RTS,S Malaria Vaccine Pilot Evaluation

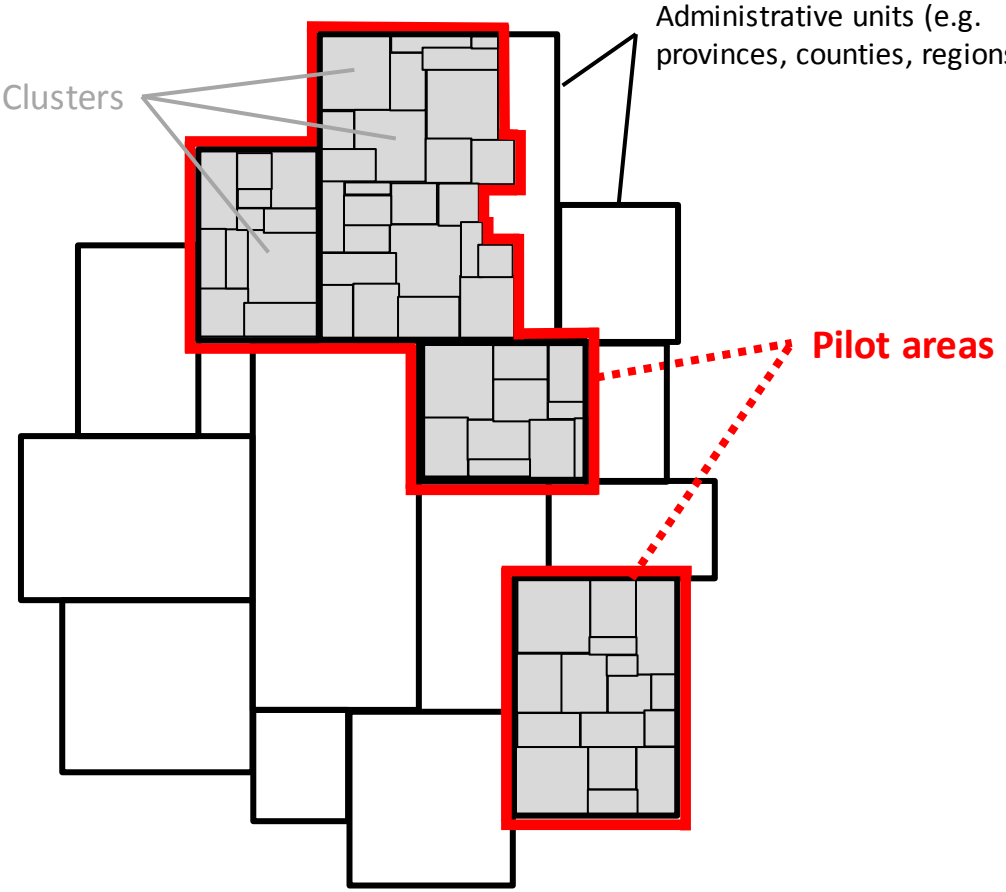
Overall design (2)

- **Rigorous Evaluation, by country-based research institutions, of**:
  - **Operational feasibility** of providing RTS,S at the recommended four-dose schedule when implemented through the routine EPI;
  - **Impact** of the vaccine on all cause child mortality (overall and by gender), malaria-specific mortality and severe malaria;
  - **Safety**: frequency of adverse events following immunisation (AEFI), with an emphasis on meningitis and cerebral malaria

- Essential that standardised monitoring systems are set up in RTS,S and comparison areas to record outcomes of interest

Illustration of cluster-randomized design

Hypothetical Country A



1. Identification of pilot area targeting approx. 240,000 children in ~ 60 clusters (≈4000 children/cluster) + 4 additional clusters for Phase IV

2. Set up of standardized monitoring systems in all clusters to monitor safety and survival

3. Randomization of clusters

   RTS,S implementation

   Comparison areas

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SAFETY EVALUATION

Malaria Vaccine Implementation Programme

Key safety questions

- What is the frequency and profile of RTS,S/AS01 reported AEFI?
- Is administration of RTS,S associated with rare or unexpected adverse events?
- Is RTS,S/AS01 vaccination associated with an increased risk of meningitis or cerebral malaria?
- Is RTS,S/AS01 vaccination associated with gender specific mortality?
- Is the relative impact of RTS,S/AS01 positive overall?
  - Some risks may be present, as with other vaccines, but are the risks outweighed by benefits such that the overall impact is beneficial?

3 pillars of RTS,S safety assessment in the MVIP

MOH Strengthened Pharmacovigilance

Passive / enhanced passive / active
All Pilot areas: N=240,000*
All AEFI, includes rare/unanticipated AEFI; AESI
Gender specific mortality

WHO Pilot Evaluation In-Patient Surveillance

Active
8 clusters: N=32,000*
Focus on meningitis and cerebral malaria

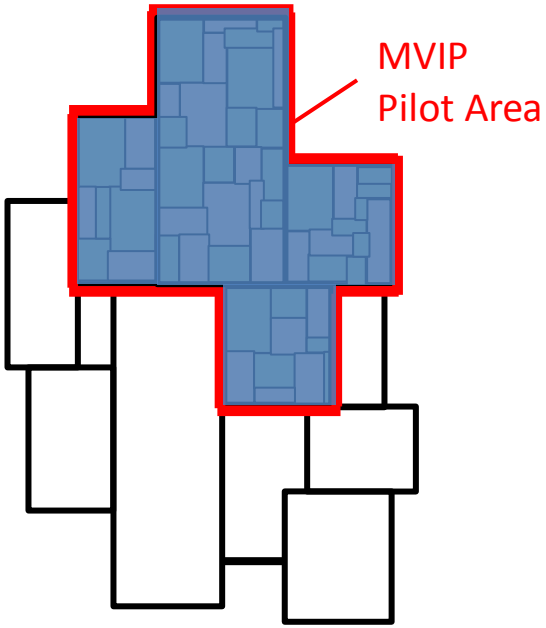
GSK Phase IV Study

Active with HH visits
4 clusters: N=16,000*
Focus on meningitis, malaria, as well as AESI

* Half of N located in vaccinated clusters, half in unvaccinated clusters. A sample of at least 240,000 children, including the first 120,000 children vaccinated in each country, will contribute to the evaluation

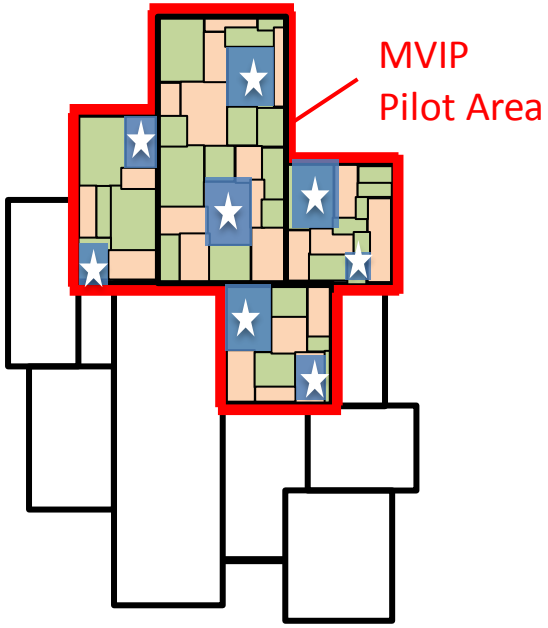
MVIP safety evaluation for RTS,S

Routine spontaneous AEFI reporting
Focus on rare and unexpected AEFI



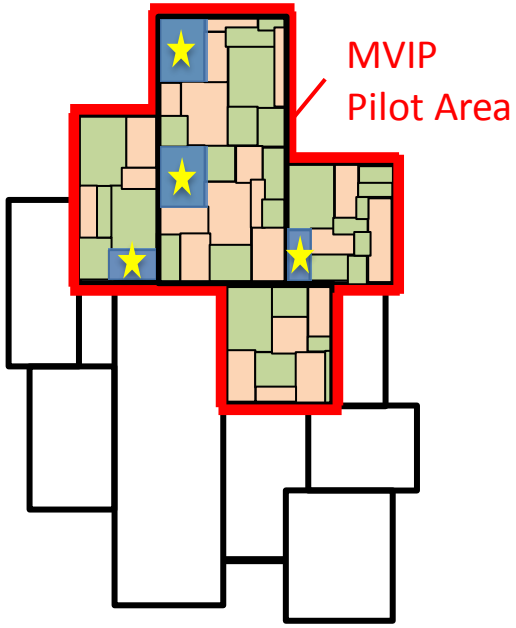
Strengthened in all areas

Pilot evaluation in-patient surveillance
Focus on meningitis and cerebral malaria



8 sentinel hospitals

Phase IV in-patient surveillance
Focus on meningitis, cerebral malaria and AESIs



4 sentinel hospitals
+ home visits

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Paediatric Inpatient Surveillance

- Quality assured, inpatient surveillance at sentinel hospitals
- Systematic, standardised clinical and laboratory assessment and management of all admissions

- All under 5 year admissions to paediatric wards:
  - Demographic and vaccination data, outcome of admission
  - Key clinical signs, including criteria for lumbar puncture
  - Lab results: malaria status, CSF results

- Relevant clinical staff trained in inpatient management algorithm
  - Includes collection of blood and CSF samples to assess study endpoints
  - Standardised case definitions

Statistical Considerations

- Sample size of 96,000 across the pilot implementation countries
- 12 clusters of 4,000 births per arm will detect a 2.1 fold increase in meningitis
  - Assumes meningitis rate in comparison areas of ~0.1% from age 6-35m (inter-cluster correlation coefficient=0.4)
    - If meningitis rate is lower (0.04%), able to detect a 2.6 fold increase

IMPACT EVALUATION

Objectives of impact evaluation

- To assess the impact of the RTS,S vaccine on:
  - all cause child mortality (overall and by gender)
  - malaria-specific mortality
  - severe malaria

- Implementation in the setting of concomitant recommended malaria interventions

Proposed approach: Mortality surveillance at community level

- Network of Village Reporters (VR) documents all deaths among children aged up to 48 months in the implementation & comparison areas
  - Dependent on country-specific practices, VRs will either:
    - Visit all households in their catchment area regularly, or
    - Build and maintain a network to ensure VRs are informed of fatal events among children
- Deaths in the age range have a standardized, WHO-approved Verbal Autopsy (VA) performed, according to locally acceptable practices
- All deaths and VAs are reported to the local Evaluation Partner(s), national coordinating bodies & national vital statistics registry / CRVS
- Community-based data complemented by cause-specific hospital data

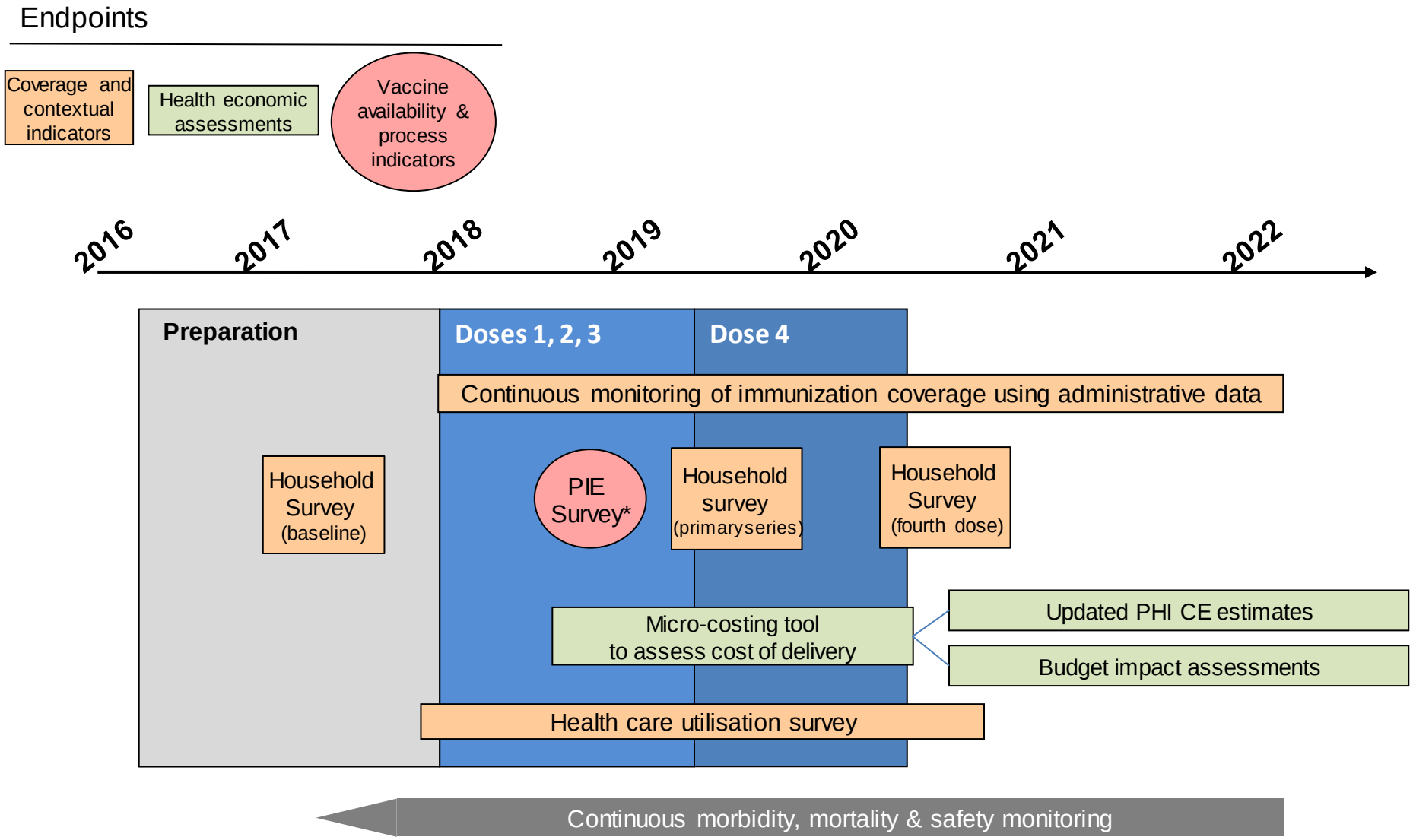
Statistical Considerations

- 240,000 children per country (120,000 in RTS,S areas and 120,000 in comparison areas) should enable detection of a 10% reduction in mortality
  - Assumes ~2.5% mortality from 6 – 35 months of age in those not vaccinated
    - Inter-cluster coefficient of variation of 0.1
  - 80% power, 5% significance level
- Final analysis of impact occurs at the end of the follow-up period

FEASIBILITY EVALUATION

Feasibility evaluation components

Approximate timings in 1 country. Countries are likely to start pilot implementation activities within 6 months of each other



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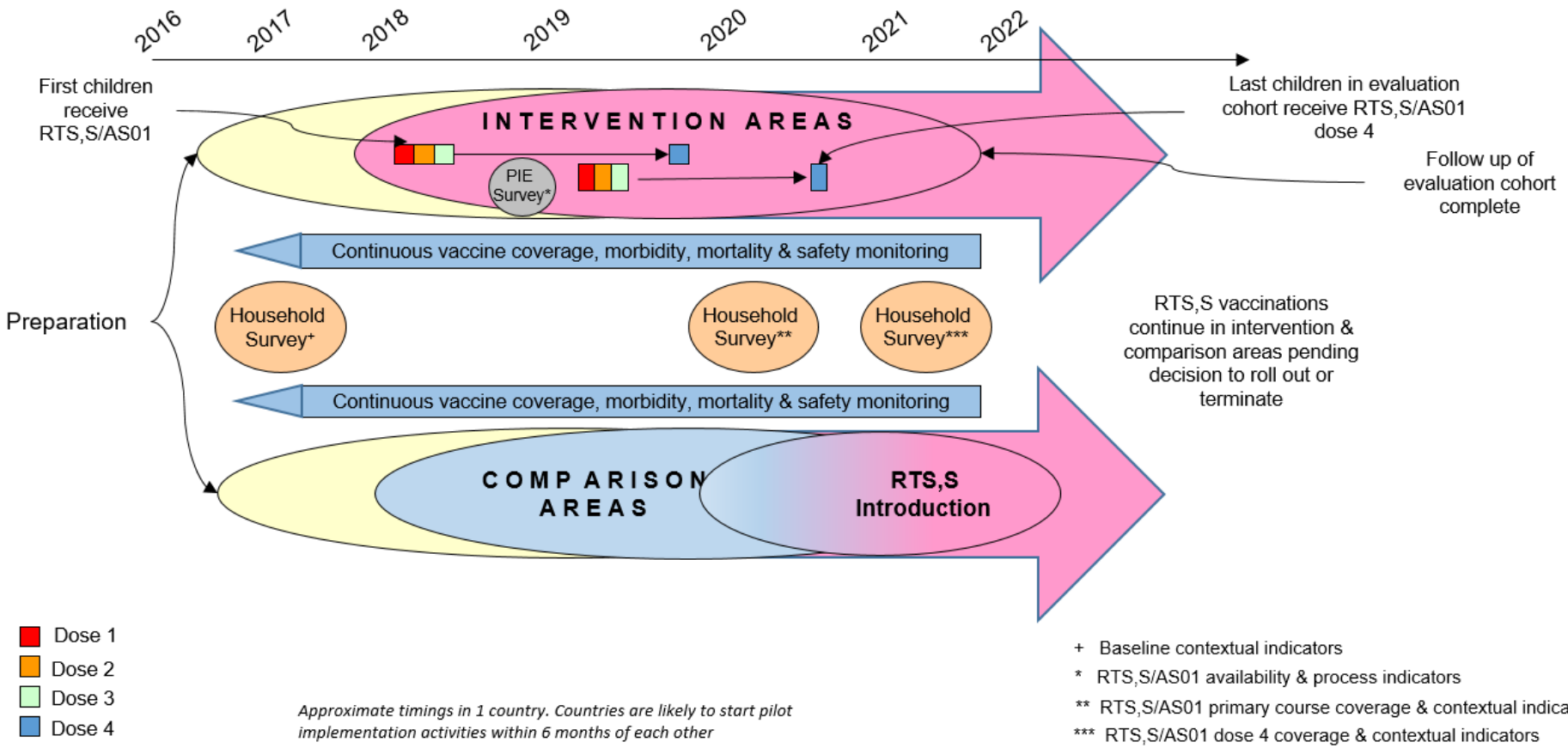
Overview of Pilot Implementation of RTS,S/AS01



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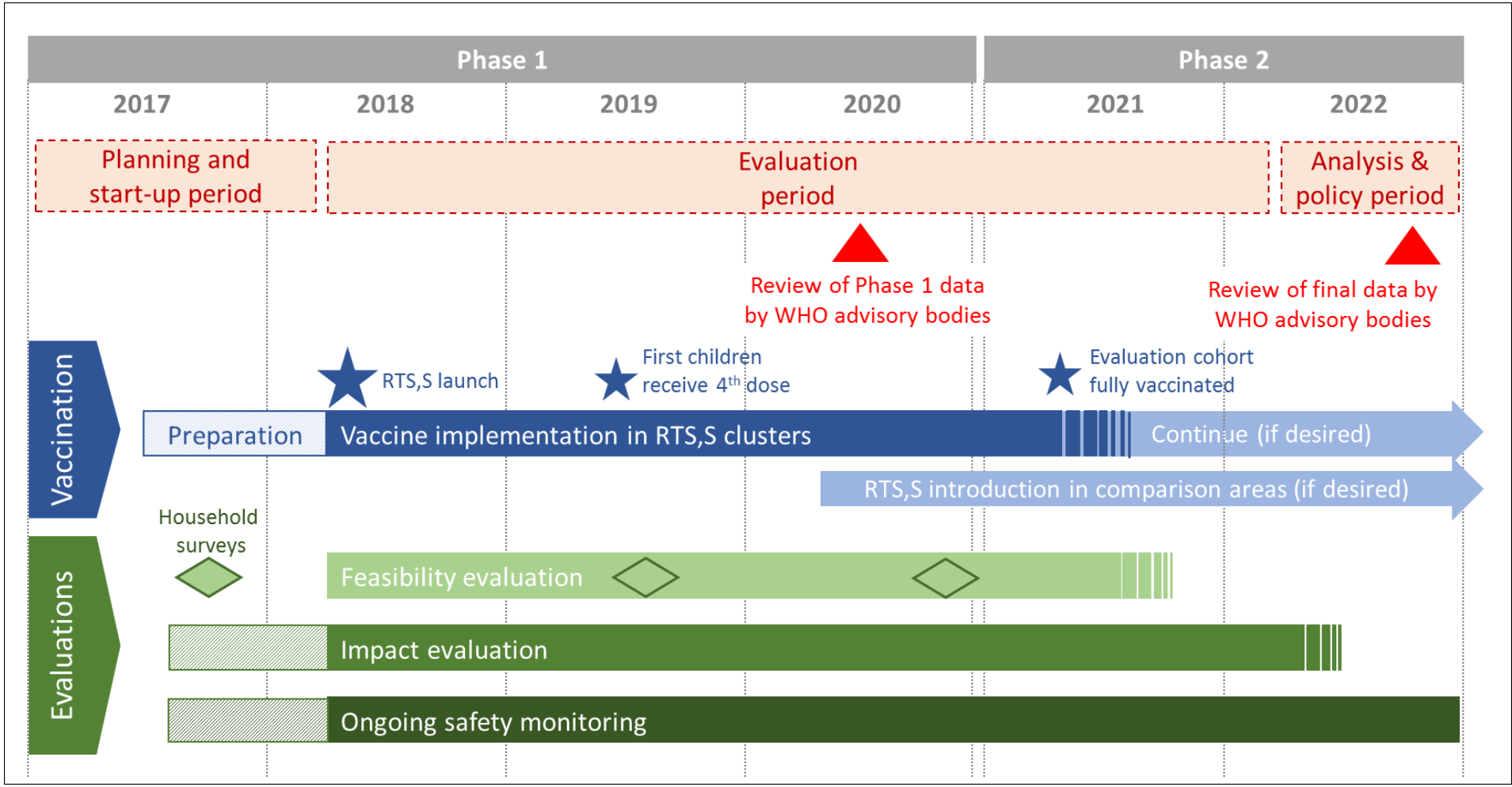
Key aspects that need to be ready before vaccine introduction

- Regulatory review
- Vaccine implementation
- Country-specific protocols & their ethical review
- Evaluation readiness – following RFP-based selection of Evaluation Partners
  - Baseline household survey
  - Sentinel hospital clinical surveillance
  - Community mortality surveillance
- Pharmacovigilance

Readiness for all these aspects is a pre-requisite for programme start

Indicative overall timeline 2017-2022

Target: first vaccine introduction Q2 2018



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Co-ordination with GSK's Phase IV Study

- Regular interactions WHO, PATH, GSK since April 2016
  - Bi-weekly leadership call, weekly Protocols & Methods sub-group calls, communications sub-group calls
- Tripartite collaboration agreement being finalised
- Initial joint WHO/PATH/GSK country visits Oct/Nov 2016
  - Introduction to WHO-led and Phase IV evaluations
- Master protocol for the WHO-led evaluation developed by WHO, reviewed by PATH & GSK
  - WHO protocol to be included in GSK's Risk Management Plan submitted to European Medicines Agency

Conclusion

- RTS,S/AS01 – the first malaria vaccine
  - 39% reduction in clinical malaria
  - 31% reduction in severe malaria

  } Over 4 years follow-up

  - Considerable potential for public health impact
- WHO recommendation to pilot implementation in 3 countries: rigorous evaluation of feasibility, safety and impact
- Master protocol to form basis of country-specific protocols
- Target date for start of vaccinations: Q2:2018
  - Discussion needed on duration of RTS,S deployment in implementation areas, and potential roll out of RTS,S/AS01

Malaria Policy Advisory Committee Meeting

22–24 March 2017, Geneva, Switzerland
Background document for Session 2

The cardiotoxicity of antimalarials

WHO Evidence Review Group Meeting, 13–14 October 2016
Varembé Conference Centre, Geneva, Switzerland

Executive summary

The cardiotoxicity of antimalarial medicines has received renewed interest in recent years following the 'Thorough QT' assessment of the dihydroartemisinin-piperaquine formulation approved by the European Medicines Agency, which showed evidence of QT interval prolongation. Piperaquine is a bisquinoline antimalarial that is structurally related to chloroquine. Many drugs among the quinoline and structurally-related medicines affect myocardial depolarization and repolarization. WHO currently recommends the artemisinin-based combination treatment dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria. This treatment is being considered alongside other antimalarial medicines for preventive therapy and mass drug administration.

To inform WHO recommendations, a group of experts met in October 2016 to review evidence on the cardiotoxicity risk of quinoline antimalarials and structurally-related medicines in people with and without clinical malaria.

The following recommendations were proposed by the WHO Evidence Review Group for consideration by the WHO Malaria Policy Advisory Committee and the WHO Advisory Committee on Safety of Medicinal Products.

WHO/HTM/GMP/MPAC/2017.2

Summary of findings and proposed recommendations

1. Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, chloroquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine, have been associated with a low risk of cardiotoxicity.

2. Drug-induced QT/QTc interval prolongation is a surrogate indicator for increased risk of drug-induced torsade de pointes (TdP), a potentially lethal polymorphic ventricular tachycardia. Risk factors for drug-induced QT/QTc prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels. Antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution in individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmias, or who are already taking medicines that can prolong the QT/QTc interval.

3. Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most intensively studied antimalarial drugs. No sudden deaths have been attributed to cardiotoxicity following artemether-lumefantrine. However, among ~200 000 treated individuals with close follow-up, one possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported. This finding is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc-prolonging medicines in current use.

4. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, reveals no evidence of a significant difference in the risks of cardiotoxicity following exposure to piperaquine, chloroquine or amodiaquine at the current recommended doses. The risks of cardiotoxicity of piperaquine-containing medicines are probably similar for healthy volunteers and malaria patients.

5. Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk. Further studies are needed to identify genetic polymorphisms and other pre-existing conditions that may contribute to the risk of drug-induced cardiotoxicity. More evidence on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine is needed.

1. Introduction

Quinoline antimalarials and structurally-related compounds have long been associated with cardiovascular side effects; it is well known that they prolong the QT interval of the surface electrocardiogram (ECG). Of these antimalarials, WHO currently recommends quinine, chloroquine, amodiaquine, mefloquine, lumefantrine and piperaquine for the treatment of clinical malaria in combination with either an artemisinin derivative or another antimalarial medicine. Quinidine, the dextrorotatory diastereoisomer of quinine, has been associated with significant cardiotoxicity; therefore, WHO recommends that quinidine be given with careful clinical and ECG monitoring for the treatment of severe malaria only in cases where no other parenteral antimalarial is available. Halofantrine causes marked QT interval prolongation and has been associated with over 30 reports of sudden cardiac death; it has never been recommended by WHO for the treatment of malaria.

A prolonged corrected QT interval (QTc) is a sensitive but not specific indicator of increased risk of torsade de pointes (TdP), a polymorphic ventricular tachycardia that can degenerate in some cases into ventricular fibrillation and lead to sudden cardiac death. However, the relationship between QTc interval prolongation and TdP is not straightforward. Drugs that cause QTc interval prolongation have been inconsistently associated with life-threatening tachyarrhythmias, and only a small proportion of patients with QTc interval prolongation have developed such conditions.

The risk of cardiotoxicity of antimalarial drugs has received renewed interest following the European Medicines Agency's (EMA) marketing authorization of Eurartesim® (dihydroartemisinin-piperaquine) in 2011. The regulatory review identified a potential risk of arrhythmia based on a 'Thorough QT' (TQT) study in healthy volunteers that showed evidence of QTc interval prolongation. Dihydroartemisinin-piperaquine (DHA-PPQ) has since been used extensively in the treatment of uncomplicated malaria and in large studies of mass treatment in healthy subjects. It is now being considered alongside other antimalarial medicines for preventive therapy and mass drug administration (MDA).

Abbreviations

ACT	artemisinin-based combination therapy
ADR	adverse drug reaction
AL	artemether-lumefantrine
ASAQ	artesunate-amodiaquine
ASMQ	artesunate-mefloquine
C_{max}	peak plasma concentration
DHA-PPQ	dihydroartemisinin-piperaquine
DNDi	Drugs for Neglected Diseases Initiative
DOT	directly observed therapy
ECG	electrocardiogram
EMA	European Medicines Agency
EMP	Essential Medicines and Health Products
ERG	Evidence Review Group
FDA	United States Food and Drug Administration
GMP	Global Malaria Programme
GSK	GlaxoSmithKline
HDSS	health and demographic surveillance system
hERG	human ether-à-go-go related gene
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
IDRC	Infectious Diseases Research Collaboration
INESS	INDEPTH Effectiveness and Safety Studies
IPT	intermittent preventive therapy
IPTi	IPT of infants
IPTp	IPT of pregnant women
LSTM	Liverpool School of Tropical Medicine
MDA	mass drug administration
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
MORU	Mahidol-Oxford Tropical Medicine Research Unit
OUCRU	Oxford University Clinical Research Unit
PDP	product development partnership
PK/PD	pharmacokinetic/pharmacodynamic
QTc	corrected QT interval
QTcB	QTc with Bazett's correction
QTcF	QTc with Fridericia's correction
SMC	seasonal malaria chemoprevention
SMQ	Standardised MedDRA Query
SMRU	Shoklo Malaria Research Unit
SP	sulfadoxine-pyrimethamine
TdP	torsade de pointes
TQT	thorough QT
WANECAM	West African Network for Antimalarial Drugs
WWARN	Worldwide Antimalarial Resistance Network

The other antimalarials in current use that have this same qualitative effect – i.e., quinine, chloroquine and amodiaquine – were introduced over 50 years ago, at a time when the potential risk of drug-induced TdP was not appreciated. Despite their extensive use, these drugs have not been subject to the same pre-registration scrutiny as dihydroartemisinin-piperaquine.

To inform the risk assessment of antimalarial drugs, the WHO Global Malaria Programme (GMP) initiated an evidence review of antimalarial cardiotoxicity, in collaboration with the WHO Essential Medicines and Health Products (EMP) Department.

2 Overview

2.1 Objectives

The objectives of the evidence review were to:

1. Inform the risk assessment of antimalarial cardiotoxicity;
2. Evaluate the risk of sudden unexplained death following exposure to quinoline antimalarials;
3. Examine pharmacokinetic/pharmacodynamic (PK/PD) studies of the main artemisinin-based combination therapies (ACTs) to evaluate the dose-response effect and risk factors of QTc interval prolongation;
4. Examine comparative clinical trials of DHA-PPQ and other piperaquine-containing combination antimalarials to evaluate PK/PD relationships for piperaquine in healthy volunteers compared to malaria patients;
5. Identify evidence sources and gaps, and provide recommendations for additional studies to inform risk assessments.

2.2 Process

The Evidence Review Group (ERG) was approved by the WHO Advisory Committee on Safety of Medicinal Products in June 2016 and by the Malaria Policy Advisory Committee in September 2016.

In order to document sudden unexplained death and/or TdP following antimalarial drug exposure, as recommended by the expert cardiologists consulted before the meeting, WHO identified and collated relevant reviews and studies with large individual patient data series based on a literature search and in collaboration with the malaria research community, contract research organizations, and manufacturers of originator pharmaceutical products of interest.

Information was collected about the following quinoline and structurally-related antimalarial medicines, either as monotherapy or as part of a combination treatment:

- Artemether-lumefantrine
- Artesunate-amodiaquine
- Dihydroartemisinin-piperaquine
- Arterolane-piperaquine
- Artefenomel-piperaquine
- Pyronaridine-artesunate
- Quinine
- Chloroquine
- Mefloquine
- Halofantrine
- Ferroquine
- Primaquine

Evidence was drawn from publications/manuscripts, reports, data, and presentations (see Annex A for summary). Publications/manuscripts and suitable reports were shared as meeting pre-reads (see Annex B for list), while data were pooled, analysed and presented at the ERG meeting.

Professor Josep Brugada and Professor Nick White co-chaired the meeting. Dr Xin Hui Chan was the meeting rapporteur and WHO technical resource person for the preparation of the meeting. A list of meeting participants is available in Annex C.

During the meeting, presentations and discussions were organized around five thematic sessions:

1. Introduction and Background
2. Sudden Death Following Antimalarial Therapy
3. Studies on the Effects of Antimalarial Medicines on the ECG
4. PK/PD Analyses on the Effects of Antimalarial Medicines on the ECG
5. Priority Research Gaps and Planned Studies on the Effects of Antimalarials on the ECG

3 Evidence reviewed

3.1 Introduction and background

3.1.1 Drug-induced QT interval prolongation

The assessment of QT/QTc interval prolongation is an important part of the regulatory evaluation of new medicines and has become a common reason for drugs being withdrawn from the market. Both the EMA and United States Food and Drug Administration (FDA) have adopted the International Conference on Harmonisation (ICH) preclinical S7B *(1)* and clinical E14 *(2)* ('Thorough QT') guidelines for evaluating QT/QTc prolongation and the proarrhythmic potential of new medicines.

The electrocardiographic QT interval represents the ventricular action potential, i.e., the interval between ventricular depolarization and repolarization, as determined by the dynamic and fine balance of electrical currents mediated by ion channels on ventricular cardiomyocytes. These action potentials vary from cell layer to cell layer. The QT interval reflects the summation of these potentials (Fig. 1).

By far the most common mechanism by which drugs cause QT interval prolongation is by blocking the human ether-à-go-go related gene (hERG) potassium channel, the voltage-gated ion channel that mediates the rapid component of the delayed rectifier potassium current, I_{Kr}. Blockade of the hERG channel lengthens ventricular repolarization and the duration of ventricular action potential. This is reflected on the surface ECG as a prolonged QT interval; it may also result in the reactivation of inward, mainly calcium, depolarizing currents, thereby generating early afterdepolarizations. Under the right spatial and temporal heterogeneity of refractoriness in ventricular cardiomyocytes, early afterdepolarizations can trigger TdP. In the majority of cases, TdP is self-terminating, but if sustained, it can degenerate into ventricular fibrillation and cause sudden cardiac death *(3)*.

The relationship between QT/QTc interval prolongation and TdP is not straightforward. Drugs that cause QT/QTc interval prolongation lead to life-threatening tachyarrhythmias in only a small proportion of patients. Sudden cardiac death can also occur in individuals whose QT/QTc intervals are within the normal range. Prolongation of the QT/QTc interval is therefore a sensitive but not specific marker of an increased risk of TdP. Although imperfect, QT/QTc interval prolongation remains at present the best available surrogate indicator for TdP risk.

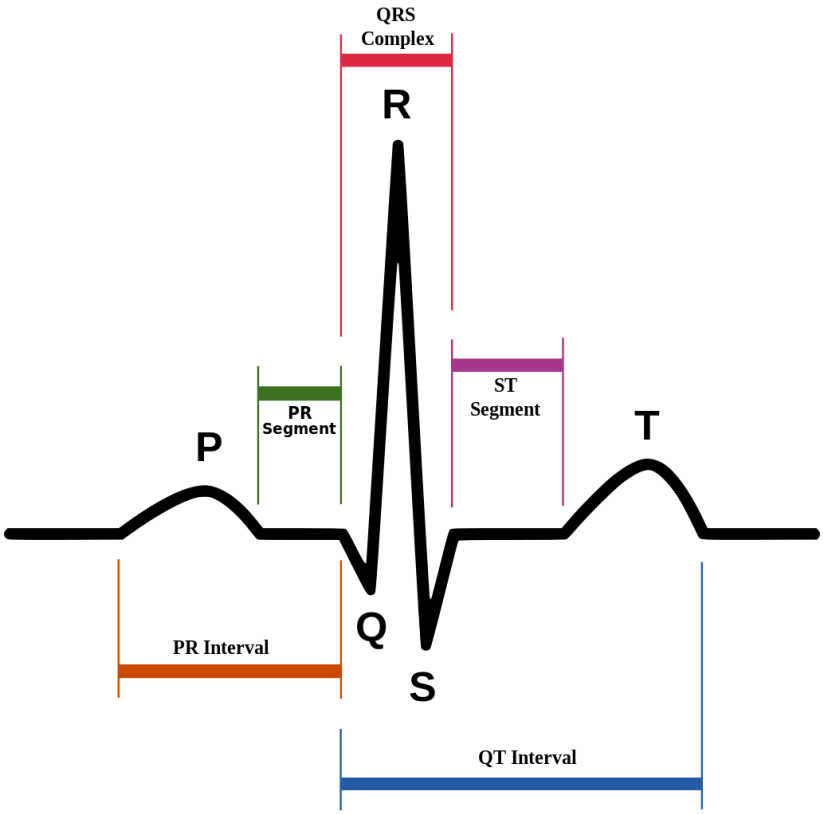


Fig. 1. The surface electrocardiogram in normal sinus rhythm

Experience with both QT/QTc interval-prolonging medicines and congenital long QT syndrome suggests:

- A QT/QTc[i] interval >500ms[ii] is associated with a higher risk of TdP and sudden cardiac death;
- Among drugs with QT/QTc interval-prolonging potential, antiarrhythmics have been associated with TdP in 1–5% of exposed subjects, while non-cardiovascular drugs have been associated with TdP at much lower frequencies, e.g., one in 100 000 exposures for moxifloxacin *(4)*;

[i] The measured QT interval is routinely adjusted for heart rate using one of a range of correction formulae to account for the inverse relationship between QT interval and heart rate. QTc refers to this corrected QT value.

[ii] There is a no consensus concerning the choice of upper limit values for absolute QT/QTc interval and changes from baseline. While lower limits increase the false-positive rate, high limits increase the risk of failing to detect a signal for concern. In clinical trials, a QTc prolongation >500ms during therapy has been a threshold of particular concern. Conducting multiple analyses using different limits is a reasonable way to approach this uncertainty, including:

- Absolute QTc interval prolongation:
  - QTc interval >450ms
  - QTc interval >480ms
  - QTc interval >500ms
- Change from baseline in QTc interval:
  - QTc interval increases from baseline >30ms
  - QTc interval increases from baseline >60ms

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf

- TdP degenerates into ventricular fibrillation in ~10% of cases.
- The incidence of drug-induced TdP and life-threatening ventricular arrhythmias has been reported as 3.2–13 per million person years in active surveillance studies conducted in Europe *(5–7)*; very little evidence has emerged from tropical areas.

Apart from hERG blockade, several risk factors decrease the repolarization reserve *(8)* and facilitate the development of arrhythmias in individual patients. These include:

- PK/PD effects, e.g., CYP450 inhibition from drug interactions leading to higher drug levels;
- Female gender, which is associated with a risk that is approximately two-fold greater after puberty *(9)*;
- Structural heart disease, e.g., ischaemic cardiomyopathy, left ventricular hypertrophy;
- Genetic defects of cardiac ion channels, including subtle genetic polymorphisms;
- Electrolyte disturbances, e.g., hypokalaemia, hypomagnesaemia, hypocalcaemia;
- Bradycardia, e.g., from increased vagal tone;
- Hepatic impairment, e.g., from alcoholic cirrhosis;
- Concomitant use of medicines that prolong the QT/QTc interval, see http://crediblemeds.org.

As there are no simple screening tests to identify people who may develop TdP and fatal ventricular tachyarrhythmias, it is important to study outliers in drug safety studies (i.e., those with abnormal electrocardiographic intervals) in order to identify the factors that increase the risk of individuals developing life-threatening arrhythmias associated with drug-induced QT/QTc interval prolongation.

To identify better predictors of drug-induced TdP, the FDA has invested in a research programme that includes a Comprehensive *in vitro* Proarrhythmia Assay *(10)*, which assesses the effects of drugs on multiple ion channels; the use of detailed ECG collection in early clinical studies with exposure-response analysis *(11)*; and the use of ECG biomarkers to distinguish between patterns of drug blockade of multiple ion channels *(12)*. This programme is expected to be completed over the next 2 years.

Key conclusions

- Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk.
- Drug-induced QT/QTc interval prolongation is a sensitive but not specific surrogate indicator for drug-induced TdP risk; despite its limited specificity, it is the best marker available.
- A QT/QTc interval >500ms is associated with a higher risk of TdP and sudden cardiac death:
    - Among drugs that prolong the QT/QTc interval, antiarrhythmics have been associated with TdP in 1–5% of exposed individuals, while non-cardiovascular drugs have been associated with a much lower risk of TdP. Around one in 10 cases of TdP degenerate into life-threatening tachyarrhythmias.
- Risk factors for drug-induced QT/QTc interval prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels.

3.1.2 Malaria, antimalarial medicines and cardiotoxicity

Antimalarial medicines are a vital tool for reducing malaria-related morbidity and mortality in individual patients, as well as for controlling and eliminating malaria. These medicines are deployed on a vast scale, with over 400 million treatments now distributed annually, and 2.2 billion courses of ACTs delivered between 2005 and 2015.

In malaria-endemic regions, antimalarial medicines are used for the treatment of clinical malaria, for preventive therapy in high-risk populations, and in the form of MDA for malaria control and elimination. The objectives of treatment with oral antimalarial medicines are as follows:

1. Case management

   ACTs have been the mainstay of recommended treatments for uncomplicated malaria. A complete therapeutic course is taken over 3 days. The clinical objectives of treating uncomplicated malaria are to achieve cure and to prevent progression to severe disease or chronic infection by ensuring as rapid and as complete elimination of the parasite from the blood as possible. The public health objectives of treatment are to reduce onward transmission of malaria and to prevent the emergence and spread of resistance to antimalarial drugs.

2. Preventive Treatment

   Administration of full therapeutic courses of an antimalarial either alone or in combination to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk. Preventive treatment includes chemoprophylaxis, intermittent preventive therapy of pregnant women (IPTp), intermittent preventive therapy of infants (IPTi), and seasonal malaria chemoprevention (SMC) of children aged 3–59 months.

3. Mass drug administration

   MDA is the 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. WHO now recommends that MDA of antimalarial medicines be considered for the elimination of malaria in areas approaching interruption of transmission, where there is good access to treatment, effective implementation of vector control and surveillance, and minimal risk of infection being reintroduced, as well as for epidemics and complex emergences . Use of time-limited MDA is also recommended to reduce malaria morbidity and mortality rapidly 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.

Quinoline antimalarials and structurally-related compounds have long been associated with cardiovascular side effects. These include *(13)*:

1. Exacerbation of malaria-related orthostatic hypotension, e.g., quinine, chloroquine, mefloquine;
2. Acute hypotension with rapid parenteral injection, e.g., chloroquine, quinine, quinidine;
3. Sinus bradycardia, e.g., mefloquine;
4. QRS complex widening, e.g., quinidine, quinine, chloroquine;
5. QT interval prolongation, e.g., halofantrine, quinidine, quinine, chloroquine, amodiaquine, piperaquine.

Chloroquine hypotension from peripheral vasodilation and negative inotropy was the probable cause of sudden death reported following the rapid parenteral administration of chloroquine for the treatment of malaria in children. PK/PD assessments found that toxicity resulted from transiently very high plasma concentrations following parenteral administration. This effect was circumvented by using a slow, continuous, rate-controlled infusion or smaller, more frequent intramuscular or subcutaneous doses to administer the drug *(14)*.

Quinidine, the diastereoisomer of the cinchona alkaloid quinine, is the prototype for drugs causing QT interval prolongation; it is a well-known cause of syncope and, rarely, sudden death. In the 1920s, the Dutch cardiologist Wenckebach began to use quinidine as an antiarrhythmic *(15)*. In the 1960s, it became the first drug to be associated with marked QT interval prolongation and symptomatic TdP *(16)*, such that iatrogenic QT interval prolongation was termed the 'quinidine effect'. WHO now recommends that quinidine be given with careful clinical and ECG monitoring for the treatment of severe malaria only in cases where no other parenteral antimalarial is available. Halofantrine is a lipophilic phenanthrene methanol compound that was discovered by the Walter Reed Army Institute of Research. Since the initial case reports from the Thai-Burmese border *(17)*, halofantrine has been associated with TdP *(18)* and more than 30 reports of sudden cardiac death *(19)*. WHO has never recommended halofantrine for the treatment of malaria. In April 2016, GlaxoSmithKline (GSK) discontinued production of proprietary halofantrine (Halfan®).

Hundreds of metric tonnes of chloroquine have been dispensed annually since the 1950s, making chloroquine one of the most widely used drugs in humans. Despite this extensive use, the lethality of the 4-aminoquinoline chloroquine in overdose has caused concern over the use of chloroquine for the treatment of malaria. More recently, there has been uncertainty over the potential risk of QT interval prolongation associated with bisquinoline piperaquine; in fixed-dose combination with dihydroartemisinin, bisquinoline piperaquine is the latest addition to the ACTs recommended by WHO for the treatment of malaria. Piperaquine has also been used on a large scale; 140 million piperaquine treatments were consumed in China between 1978 and 1992, until piperaquine resistance prompted a change in treatment policy. As both chloroquine and piperaquine have

terminal elimination half-lives of approximately 1 month, there has been considerable exposure to both drugs without apparent or reported cardiovascular concerns.

In assessing the iatrogenic effects of antimalarial drugs on the heart, it is important to also consider the underlying disease effects of malaria on the cardiovascular system.

Uncomplicated malaria is a febrile illness associated with nausea, vomiting and orthostatic hypotension. Severe falciparum malaria is characterized by multiple vital organ dysfunction caused mainly by the extensive sequestration of parasitized red blood cells in the microvasculature, including the myocardial capillaries. Despite this, there is no evidence of myocarditis or a negative inotropic effect, and myocardial dysfunction is unusual in acute malaria. Patients with severe malaria tend to have a low systemic vascular resistance with a high cardiac index. They are usually not hypovolaemic, hypokalaemic, hypomagnesaemic or markedly hypocalcaemic, although metabolic acidosis, hypoglycaemia and acute kidney injury are common.

For a disease with an extensive range of systemic complications and multiple vital organ dysfunction, it is notable that arrhythmias have only very rarely been reported in malaria patients, even in severe cases.

Acute malaria illness has significant effects on the QT interval. Before treatment, patients are usually febrile, anxious, upright, tachycardic and often anorexic. The sympathetic nervous system is activated and the QT interval is shortened. As the patient recovers, often lying in bed, the fever settles, appetite returns, the heart rate declines and the QT interval lengthens. The difference between the shortened QT interval before treatment and the day-3 normalized QT interval (which often coincides with peak antimalarial drug levels) may be misattributed to a drug effect. If there is a drug effect, it may be compounded by this systemic physiological response to recovery *(13)*. In addition, usual QT correction formulae designed to normalize the QT interval tend to "overcorrect" (i.e., the QTc interval appears longer) at fast heart rates and "undercorrect" (i.e., the QTc interval appears shorter) at normal or slow heart rates. These factors should be taken into account when interpreting results from ECG safety studies in malaria patients.

Central to the selection of appropriate drugs for emerging and current indications for antimalarial medicines is the risk–benefit assessment of their intended use in the target population. This risk–benefit assessment differs when antimalarials are to be used for case management, preventive therapy or MDA. Malaria causes significant morbidity, can progress to severe illness and death in vulnerable groups, and is endemic in settings with limited access to health care services. Among people with malaria – whether symptomatic or asymptomatic – or otherwise healthy subjects, it is not possible to predict who may develop TdP and fatal tachyarrhythmia as a result of drug-induced QT interval prolongation. Making ECG recording and interpretation a requirement, even with the presence of mobile technologies, would be operationally impossible in the field and severely limit the use of any drug. Screening for family history is limited, as it is difficult to ascertain whether arrhythmia was the cause of sudden unexplained death. Further work is required to develop appropriate tools with which to identify and monitor people at higher risk of life-threatening arrhythmias, e.g., those with congenital long QT syndrome, in malaria-endemic regions, as well as in the context of antimalarial therapy with QT interval-prolonging drugs.

Key conclusions

- Antimalarial drugs are vital for malaria treatment, prevention, control and elimination.
- Drugs structurally related to quinine may affect cardiac myocyte depolarization and repolarization.
- Quinidine and halofantrine have been associated with significant cardiotoxicity. WHO has never recommended halofantrine for the treatment of malaria.
- Apart from halofantrine, the oral antimalarial drugs, particularly chloroquine and piperaquine, have been used extensively with very few reports of cardiotoxicity.
- Rapid parenteral administration of chloroquine, quinine or quinidine may cause life-threatening hypotension.

3.2 Sudden death following antimalarial therapy

Understanding the frequency of drug-related sudden death is key to assessing the risk of antimalarial cardiotoxicity, particularly in malaria-endemic regions with very limited access to ECG monitoring for arrhythmia detection.

3.2.1 Overall

DHA-PPQ was the only antimalarial drug for which high-quality adverse event data from research studies were available for all indications of antimalarial therapy in malaria-endemic areas, i.e., MDA, preventive therapy and case management. This information is summarized in Table 1, and further analysis by treatment indication is presented in sections 3.2.2 to 3.2.4.

Table 1. Sudden unexplained deaths following antimalarial therapy with DHA-PPQ

Study type	Subjects	Courses	Doses	Sudden unexplained deaths	Source(s)
MDA	154 762	~428 929	1 179 523	1*	Table 2
IPT & non-MDA repeated courses	14 014	~28 376	~85 128	0	Systematic review *(20)* & START-IPT (unpublished)
Case management	25 198	~25 198	~75 594	0	Table 4 & INESS *(21)*
Total	**193 974**	**482 503**	**1 340 245**	**1***	

*In all of these reviews, one sudden unexplained death following MDA was considered to be possibly drug-related.
~Derived from another denominator.

This analysis suggests that the risk of sudden unexplained death following DHA-PPQ is one in 193 974 individuals treated in studies with confirmed active follow-up over 3 days from initiation of drug treatment. Of note:

- Follow-up over 3 days from drug administration captures adverse events during the period when the risk of drug-induced QT/QTc interval prolongation is highest, as piperaquine levels are at their peak;
- The choice of number of subjects as the main denominator for exposure reflects expert advice that individuals' repolarization reserve is unlikely to change considerably during the period of repeated dosing in MDA and IPT;
- Sudden unexplained death may be caused by TdP degenerating into life-threatening ventricular tachyarrhythmias, but other causes cannot be excluded with certainty.

3.2.2 Mass drug administration

High-quality pharmacovigilance data from populations exposed to MDA are essential for defining the cardiotoxicity risk of antimalarials used for this indication. Compared to healthy volunteer study populations examined in the pre-approval clinical development phase, populations exposed to MDA with antimalarial medicines differ in terms of age (6 months to >80 years versus 18–50 years), ethnic composition *(22)*, presence of comorbidities, exposure to concomitant medications, and possible low-level parasitaemia. Target populations for antimalarial IPT and SMC also differ (i.e., pregnant women and young children, respectively). Furthermore, there are different risk–benefit ratios associated with exposure to antimalarials in MDA or preventive therapy compared to the use of the same medicines for the treatment of uncomplicated malaria. In particular, the evaluation of medicines for case management is based on clinical trials in populations with a confirmed diagnosis of acute malaria, which often specifically exclude patients with risk factors for QT/QTc interval prolongation.

In addition, given the rarity of drug-induced TdP and life-threatening tachyarrhythmias, as indicated by available evidence (presented in section 3.1.1), the number of patients exposed to antimalarial drugs in pre-approval clinical trials alone is not sufficiently large to detect these very rare events *(23)*.

Present experience and recent studies on malaria MDA

Because of its high efficacy, good tolerability and long post-treatment prophylaxis resulting from the 20- to 30-day terminal elimination half-life of piperaquine, DHA-PPQ is currently being evaluated for its potential role in MDA as part of malaria elimination efforts. Four studies in Asia and Africa yielded information on MDA with DHA-PPQ; these data are summarized in Table 2.

Table 2. Malaria elimination studies incorporating antimalarial MDA with DHA-PPQ

Study	Location(s)	No. of participants	No. of courses	No. of doses	No. of deaths within 30 days of drug* unexplained / total	Adverse event surveillance in addition to passive spontaneous reporting
MACEPA *(24)*	Zambia	103 963ˆ	336 821 in four rounds	903 600ˇ	0 / 1	DOT – first and third doses of each course, line listing surveillance/adherence visit with or after third dose
CISM	Mozambique	36 820	~57 913 in two rounds	173 738ˇ	1 / 1	DOT – first dose of each course, HDSS record linkage
TME	Thailand, Myanmar, Cambodia, Viet Nam, Lao PDR	10 042	22 384 in three rounds	67 152	0 / 17	DOT – all three doses of each course, line listing/census follow-up at health facility or home at 3, 6, 9 and 12 months
BMEP	Myanmar	3937	11 811 in three rounds	35 433	0 / 0	DOT – all three doses of each course, line listing follow-up following MDA rounds only
Total		**154 762**	**~428 929**	**1 179 523**	**1 / 19**	

MACEPA = Malaria Control and Elimination Partnership in Africa. CISM = Centro de Investigação en Saúde Manhiça. TME = Targeted Malaria Elimination. BMEP = Border Malaria Elimination Programme. DOT = directly observed therapy. HDSS = Health and Demographic Surveillance System. ˆThis is probably an underestimation by approximately 30–50 000 participants, as it assumes that MDA was received by the same individuals in all rounds of treatment; this is unlikely to be the case, however, as the focal MDA component of this programme targeted only malaria rapid diagnostic test-positive households, which would have varied from one round to another. ˇThese figures take into account subsample adherence figures provided by each programme. ˜Number of courses was derived from number of doses. *As detected by the adverse event surveillance system of each programme described in the final column of the table.

In all four MDA studies, participants were given multiple rounds of a 3-day treatment course of DHA-PPQ tablets. Participants were divided into age- or weight-based treatment groups in order to achieve daily therapeutic dose ranges of dihydroartemisinin (2–10 mg/kg body weight) and piperaquine (16–26 mg/kg body weight). Each round was conducted at least 1 month from the next. In the studies conducted in Asia, primaquine (0.25 mg base/kg body weight) was also administered with the first dose of each treatment course. All participants were exposed to at least one course of DHA-PPQ. All studies had a lower age limit of ~6 months (range = 3 to 12 months), and excluded individuals who were pregnant, had contraindications to study drugs, or had acute illness at the time of drug administration.

There was one sudden unexplained death following DHA-PPQ administration in this MDA group. An otherwise healthy 16-year-old female in Mozambique collapsed and died on the way to hospital after complaining of palpitations. This occurred several hours after the second dose of her first course of DHA-PPQ. She had no history of previous hospital admissions or any other medical conditions, and no past or concomitant intake of any other medication. According to her stepmother, the girl had self-administered her second dose of 40/320mg DHA-PPQ about 20 minutes after a meal of rice, cooked salad, and bread. Both the malaria rapid diagnostic test and pregnancy test performed at her enrolment the day before were negative. No autopsy or ECG was performed. Cardiology experts at the ERG reviewed this case and deemed her death to be consistent with sudden cardiac death, possibly causally related to drug exposure.

The remaining 18 deaths recorded in these studies had alternative explanations (see Table 3): accidents and infections accounted for seven deaths each, reflecting the risks inherent in the resource-limited rural and peri-urban settings of these MDA studies; three were due to complications of gastrointestinal conditions; and the final death was attributed to vascular disease in a patient with known predisposing factors.

Table 3. Causes of death in malaria elimination studies following MDA with DHA-PPQ

Cause of death	No. of deaths	Autopsy?	Study	Further information
Traffic accident	4	No	TME	
Tuberculosis	3	No	TME	
Septic abortion	2	No	TME	
Melioidosis	1	No	TME	
Diphtheria	1	No	TME	
Diarrhoea	1	No	TME	
Haematemesis	1	No	TME	12-year-old female who died 2 weeks after completing second course of DHA-PPQ
Abdominal pain	1	No	TME	30-year-old male who died 8 days after completing third course of DHA-PPQ
Drowning	1	No	TME	Three other drownings over 18 months of study in control group or in MDA group >30 days after drug administration

Cause of death	No. of deaths	Autopsy?	Study	Further information
Homicide	1	No	TME	35-year-old male found dead with gunshot wound in forest 16 days after completing second course of DHA-PPQ
Choking	1	Yes	MACEPA	2-year-old male seen to choke on pill, and upper tracheal obstruction by white powder with oedema of both lungs confirmed on autopsy
Vascular disease	1	No	TME	56-year-old male with chronic heart disease and hypertension on enalapril suddenly collapsed and died while chopping a tree after climbing a hill more than 24 hours after completing his second course of DHA-PPQ
Total	**18**			

TME = Targeted Malaria Elimination. MACEPA = Malaria Control and Elimination Partnership in Africa.

A conservative approach was adopted for this analysis, in that exposure figures from individual programmes were retained only if there was a system in place for following individual patients over time. All studies had confirmed active follow-up of individual subjects over at least 3 days from the initiation of the drug treatment, i.e., during the period of maximum risk. However, as with other spontaneous reporting systems, deaths could have been underreported in programmes with only passive surveillance of subjects between 3 and 30 days post-treatment. At the same time, sudden deaths are notable events in communities where MDA is conducted; therefore, if they did occur, they would have the potential to undermine confidence in the MDA programme. In light of this, it is noteworthy that there was no evidence of such concerns about deaths or other adverse events in any of the four programmes contributing data to this review.

Historical studies on malaria MDA

Two key published reviews *(25,26)* on past MDA with antimalarial medicines were also analysed for reports of sudden unexplained deaths. The systematic review *(25)* included 32 published studies between 1931 and 2013, while the second review *(26)* also included unpublished work and grey literature. Overall, the safety data were of low quality, reflecting passive reporting from routine pharmacovigilance systems. Few studies reported mortality, only 10 studies reported adverse events, and only four studies included some form of active surveillance. From these studies, the only two deaths reported were from haemoglobinuria following intramuscular mepacrine (quinacrine, Atabrine) and plasmochin (plasmoquine, pamaquine).

3.2.3 Preventive treatment and other indications requiring repeated dosing

Literature review

DHA-PPQ has been studied as a potential alternative for IPT. In order to assess the efficacy and safety of repeated exposure to 3-day treatment courses of DHA-PPQ, a systematic review and random effects meta-analysis *(20)* of previously published studies was performed, comparing DHA-PPQ with other antimalarials and placebo. A total of 11 recent studies were included.

Of the nine IPT studies:

- five were in children aged <5 years (*n* = 5481) *(27–31)*
- one was in schoolchildren (*n* = 740) *(32)*
- one was in adult men at occupational risk of malaria (*n* = 961) *(33)*
- two were in pregnant women (*n* = 1846) *(34,35)*

Of the two case management studies:

- one was a randomized controlled trial in children aged <5 years (*n* = 312) *(36)*
- one was a cohort study in pregnant women (*n* = 5288) *(37)*

The 4511 participants exposed to DHA-PPQ received a total of 18 873 courses, with 18 297 courses taken by the 3935 participants who received ≥2 courses; 9131 participants were exposed to placebo or comparator therapies. Comparator interventions were placebo, artemether-lumefantrine (AL), sulfadoxine-pyrimethamine (SP), SP + amodiaquine, SP + piperaquine, SP + chloroquine, and co-trimoxazole + piperaquine. Treatments were administered at 1-, 2- and 3-month intervals, or as three courses during the second and third trimesters of pregnancy. Antimalarials were administered as directly observed therapy (DOT) for at least the first dose of each course (10 studies), or intake was recorded by the subjects' parents (one trial).

None of the 11 studies reported sudden or unexplained deaths, or serious adverse events consistent with sudden cardiac death. Risk of death was similar between DHA-PPQ and comparator arms. DHA-PPQ was also not associated with increased loss to follow-up compared to comparator drugs, but was associated with a higher loss to follow-up compared to placebo; however, this finding was driven primarily by the high loss to follow-up in a single study *(33)* and probably unrelated to the drug.

IPT studies in progress

Data were also presented from three recently completed preventive therapy studies that used DHA-PPQ at standard weight-based doses to achieve daily therapeutic dose ranges of dihydroartemisinin (2–10 mg/kg body weight) and piperaquine (16–26 mg/kg body weight).

There were two deaths reported among the 10 079 participants of the START-IPT cluster randomized trial of monthly SMC in schoolchildren in Jinja, Uganda. These deaths were due to a road traffic accident and tetanus, respectively, and were considered unrelated to DHA-PPQ (Duocotexin®). Participants received up to six rounds of SMC, and all three doses of each treatment course were administered as DOT.

There were no deaths or cardiac events among 2279 pregnant women in the STOPMIP study in Papua, Indonesia, approximately 700 of whom received monthly IPTp with DHA-PPQ (Eurartesim®) during antenatal care visits in their second and third trimesters of pregnancy. The first and third doses of each course were administered as DOT. All women were followed up until 6–8 weeks after delivery.

There were no deaths or cardiac events among 100 HIV-infected pregnant women exposed to DHA-PPQ (Duocotexin®) in the PROMOTE BC2 IPTp study in Tororo, Uganda. Participants received DHA-PPQ every 4 weeks during antenatal care visits in their second and third trimesters of pregnancy, with the first dose of each course administered as DOT. A total of 468 courses of DHA-PPQ were administered, and all 100 women were followed up until delivery.

There were no cases of TdP or ventricular tachyarrhythmia in the START-IPT, STOMIP and PROMOTE BC2 nested ECG substudies (discussed in further detail in section 3.4.2); these included 155 schoolchildren, 33 women and 13 women, respectively.

3.2.4 Case management

Literature review

A systematic review of all published antimalarial clinical efficacy trials was undertaken using the WWARN publication library to identify deaths following antimalarial therapy with quinoline and structurally-related antimalarials. SP was included as a comparator. The review yielded publications on 810 clinical trials that tested in at least one arm a quinoline compound or SP for the treatment of uncomplicated falciparum malaria. A total of 210 156 participants were enrolled in these trials, with 194 845 patients treated with a quinoline drug or SP. Participants received up to one course of each antimalarial. The vast majority of efficacy trials had a follow-up period of ≥14 days. Further information was obtained by contacting the corresponding authors or interrogating the WWARN data repository. The 2005 WHO-Uppsala Monitoring Centre system *(38)* was used for standardized case causality assessment.

The data showed 80 deaths following treatment with the antimalarial medicines of interest (listed in section 2.2), details of which are summarized in Table 4. Mortality in the treatment of uncomplicated falciparum malaria generally ranges from 0.1% to 1%. Exposures and deaths following quinine were not included in Table 4, as severe rather than uncomplicated malaria was the primary indication for the use of this antimalarial.

Table 4. Deaths following antimalarial therapy in historical case management efficacy trials

	Subjects/ courses	Sudden unexplained	Severe malaria	Infections other than malaria	Trauma/ accidents	Poisoning	>28 days after drug	Other	Unknown aged 6–59 months	Total
Halofantrine	2027	2								2
AL	34 576		9	6	3	1	5			24
ASAQ	18 815		4	4		1	1	1	1	12
Amodiaquine	5981		1	1	1		1			4
ASMQ	18 815		2		1		2	1		6
Mefloquine	6606							1		1
Pyronaridine-artesunate	4422				1					1
DHA-PPQ	14 273		3	3	1		3	3		13^
Chloroquine	23 773		2	3		1	1	1	2	10
SP	17 568		5						2	7
Quinolines	*129 288*	*2*	*21*	*17*	*7*	*3*	*13*	*7*	*3*	*73*
Grand Total	**146 856**	**2**	**26**	**17**	**7**	**3**	**13**	**7**	**5**	**80**

AL = artemether-lumefantrine. ASAQ = artesunate-amodiaquine. ASMQ = artesunate-mefloquine. DHA-PPQ = dihydroartemisinin-piperaquine. SP = sulfadoxine-pyrimethamine. ^These 13 deaths were from nine clinical trials also reviewed either as part of a Cochrane review of the efficacy and safety of DHA-PPQ *(39)* or the Sigma Tau meta-analysis on the clinical use of piperaquine; eight of the nine studies were reviewed in both.

Only two cases were assessed as probably drug-associated: two sudden unexplained deaths following halofantrine treatment. One death occurred in a 37-year-old woman with a lifelong history of syncope and palpitations; after having been treated with mefloquine 21 days before, she had a cardiac arrest just before receiving the final dose of a 3-day course of high-dose halofantrine *(17)*. Another death of a 22-year-old man occurred during the recovery phase after receiving micronized halofantrine *(40)*. Two other deaths were assessed as possibly drug-related: One was of an 11-month-old girl *(41)* with severe malaria who died 3 days after artesunate-amodiaquine (ASAQ) with uncontrolled administration of traditional medicine of an unknown nature; the other was of an 18-month-old girl *(42)* who died from severe malaria 7 hours after a single dose of AL, but investigators could not exclude other aetiologies, including sepsis and hypoglycaemia.

Of the 80 cases of death listed in Table 4, 53 had age documentation: 4% (3/53) of the deaths occurred in infants aged <6 months, and 60% (32/53) in children aged 6–59 months. In keeping with the life-threatening nature of acute malaria, 32.5% (26/80) of the deaths were consistent with the progression to severe malaria, while 21% (17/80) were associated with other infections, including HIV/AIDS, pneumonia and diarrhoea, which reflect the main causes of mortality in children under 5 in low- and middle-income countries where malaria is endemic. Deaths from trauma, 9% (7/80), were due to gunshots (2), landmines (2) and other injuries. Given the elimination half-lives of the antimalarial drugs in question, the 16% (13/80) of deaths that occurred >28 days after treatment were thought very unlikely to be drug-related.

There were five deaths of children aged 6–59 months for which a cause had not been determined, but further assessment of these cases was not possible with the limited information available. However, considering the more common causes of death for children of that age group in malaria-endemic regions, it was thought unlikely that sudden cardiac death would be the most probable explanation for these deaths.

Plasmodium falciparum infections are much more likely to progress to severe malaria than *P. vivax* infections. In the case of chloroquine, 10 deaths out of 23 773 participants were reported following chloroquine treatment in falciparum malaria, while no deaths were reported among 11 848 participants receiving chloroquine for vivax malaria ($P < 0.01$). Given that the pharmacokinetic properties of chloroquine are similar in these two malarias, it is more likely that the difference was caused by the disease rather than the drug.

This review was limited by the quality of information available about causes of death and the subjectivity of causality assessment, as well as by the heterogeneity of adverse event monitoring and rates of loss to follow-up in individual trials.

Cochrane review on DHA-PPQ

A 2014 Cochrane review *(39)* evaluated the effectiveness and safety of DHA-PPQ compared to other WHO-recommended ACTs for the treatment of uncomplicated falciparum malaria. The review included 27 randomized controlled trials conducted between 2002 and 2010 enrolling 16 382 participants. The risks of serious adverse events including death were similar when comparing DHA-PPQ with AL and also with artesunate-mefloquine (ASMQ). No cardiac arrhythmias were reported.

Phase 4 safety monitoring assessment of DHA-PPQ

Between 2013 and 2014, the INDEPTH Effectiveness and Safety Studies platform (INESS) conducted a phase 4 prospective observational study on DHA-PPQ (Eurartesim®) at eight Health and Demographic Surveillance System (HDSS) sites of the INDEPTH network in Tanzania, Burkina Faso, Mozambique and Ghana, as part of the EMA risk management plan for the drug. This study

is significant for being the largest and most rigorously conducted post-marketing safety monitoring assessment of any antimalarial medicine in real-life conditions in sub-Saharan Africa. A total of 10 925 patients with uncomplicated malaria aged >6 months were treated with at least one dose of DHA-PPQ. Of these, 10 591 patients received a full course of DHA-PPQ and completed follow-up visits on day 5 ± 2 days and day 28. Out of all the 10 925 patients who received DHA-PPQ, six deaths were reported, of which three were assessed as being unrelated to DHA-PPQ. It was assessed that the remaining three deaths were unlikely to be related to DHA-PPQ: One was of a 17-month-old boy who presented 14 days after DHA-PPQ with severe diarrhoea secondary to acute gastroenteritis and died within 24 hours of admission; one was of a 4-year-old girl who presented within 24 hours of recruitment with severe anaemia and died on the way to a higher referral facility for blood transfusion; and the last was of a 3-year-old girl who died at home from severe malaria 3 days after recruitment, as suggested by verbal autopsy. Among the 1002 patients in the nested cardiac safety cohort who underwent ECG monitoring at baseline before and after the third dose and on day 7, there was no documented report of clinically relevant cardiotoxicity, TdP or ventricular fibrillation *(21)*.

3.2.5 Case safety report databases

Spontaneous reports to pharmacovigilance centres and drug manufacturers are another important source of information that can be used to detect rare adverse events. The goal of such spontaneous reporting systems is to highlight possible signals of adverse drug reactions (ADRs) and not to make estimates of their incidence. These systems provide information throughout the lifetime of a drug. However, there is significant and widespread underreporting of ADRs (including serious or severe ADRs) to spontaneous reporting systems *(43)*. Reports also vary in quality and completeness. The subjectivity and use of different methods to perform causality assessment are further limitations *(44)*.

WHO global database of individual case safety reports

VigiBase® is the WHO Global Database of Individual Case Safety Reports, i.e., spontaneous reports of ADRs, received from national pharmacovigilance centres that are members of the WHO Programme for International Drug Monitoring. Three summary reports were generated on:

1. Sudden death and TdP/QT interval prolongation with any antimalarial
2. Suspected ADRs and TdP/QT interval prolongation with halofantrine
3. Suspected ADRs and TdP/QT interval prolongation with DHA-PPQ

A total of 40 cases of sudden death and/or death as an outcome of TdP/QT interval prolongation following any antimalarial were reported, all of which originated in Europe and North America. In 22 cases, the antimalarial was used for an indication other than malaria, with drug dosages and durations varying accordingly. In 16 cases, concomitant use of another medicine that could potentially increase the risk of QT/QTc interval prolongation was reported. Quinidine was the suspected antimalarial in 16 cases; in 12 of these cases, there was evidence of a cardiac-related indication and/or concomitant medications, suggesting quinidine was used as an antiarrhythmic. Exposure to chloroquine and hydroxychloroquine was reported in six and five cases of sudden death, respectively. In four of these cases, overdose was listed as the indication. Hydroxychloroquine was used to treat rheumatoid arthritis, systemic lupus erythematosus and small cell lung carcinoma in one case each. Long-term use of chloroquine or hydroxychloroquine may cause myopathy, which may involve cardiac muscle. Collagen vascular diseases are also associated independently with cardiomyopathy and conduction defects. Exposure to mefloquine was reported in six cases of sudden death; in one of these cases, mefloquine was administered concomitantly with halofantrine. Halofantrine, quinine (as treatment for restless legs syndrome in one case, and as an intentional overdose in another), and pyrimethamine (as treatment for

toxoplasmosis in two cases) were the antimalarials in the remaining cases identified. Only four reports were of good quality, i.e., had a completeness score ≥0.8.

Halofantrine was associated with 30 reports of TdP/QT interval prolongation based on a search using broad Standardised MedDRA Queries (SMQ)[iii]. These included two reports of TdP, three of ventricular fibrillation, and four that resulted in death. In three of these deaths, concomitant medications included chloroquine in two cases and mefloquine in one case (also reported as a death after mefloquine). Of the 30 reports, 18 were from France, where the drug was used more extensively than in other countries. A further four deaths were identified among reports of sudden death and general cardiac-related ADRs.

For DHA-PPQ, four reports were identified through the broad SMQ for TdP/QT interval prolongation. There was one report of QT interval prolongation that was transient and resolved; this was also the only report that was identified using a narrow SMQ term specific to the condition of interest, i.e., QT interval prolongation. The remaining three reports were found using broad SMQ terms of syncope and loss of consciousness, which are symptoms that can be presentations of TdP/QT interval prolongation, along with a range of other conditions, including orthostatic hypotension and vasovagal episodes. In two of these cases, tamsulosin, which is known to cause orthostatic hypotension, was a concomitant medication. Another medication potentially causing QT/QTc interval prolongation, ciprofloxacin, was a concomitant medication in the final case. All patients had malaria, which itself is associated with orthostatic hypotension, listed as the indication.

Pharmaceutical company safety databases

The sales figures and number of sudden unexplained deaths following exposure to halofantrine, artemether-lumefantrina and dihydroartemisinin-piperaquine based on the safety database of the respective manufacturers are presented in Table 5.

Table 5. Sudden unexplained deaths from pharmaceutical company safety database searches

	Halofantrine (Halfan®)	AL (Coartem®/Riamet®)	DHA-PPQ (Eurartesim®)
Period	1988–October 2016	1998–October 2016	2011–October 2016
Sales figures[†] (doses)	23.2 million^	>840 million	2.8 million
Sudden unexplained or cardiac deaths	36	0	1

[†]Pharmaceutical company sales figures represent a proportion of the total sales of these antimalarials, which are mostly sold as generics (with the exception of halofantrine). ^Halfan® sales figures were available only up until 2012, while global safety database information was available to October 2016; the product was discontinued in April 2016, so it is unlikely that up-to-date sales figures would be much higher than those reported here.

Fatal cardiotoxicity related to halofantrine was reviewed *(19)* based on a systematic literature search and access to the GSK global safety database. Cases added to the GSK database after this first review's March 2005 cut-off were assessed for the ERG using the same methodology. Thirty-six cases were identified, the majority of which – 58% (21/36) – had received concomitant drugs that could also induce QT/QTc interval prolongation. There were 32 cases for which the time from the first dose to death was available: All occurred within 3 days of the first dose, and 84% (27/32) of these died within 24 hours. While reporting bias cannot be ruled out, the reported time of

[iii] SMQ are validated, standardized sets of search terms used to facilitate retrieval of MedDRA-coded data.

occurrence of these deaths is consistent with the timing of peak drug concentrations following halofantrine administration in uncomplicated malaria, when drug-induced cardiotoxicity risk is at its highest *(45)*. All cases identified in VigiBase® had corresponding records with identical demographic details and case descriptions in the GSK global safety database; these records were all included in the halofantrine cardiotoxicity review *(19)*. Both sudden unexplained deaths identified in the case management literature review (presented in section 3.2.4) were also included in the GSK database and halofantrine cardiotoxicity review *(19)*.

Of the six cases with fatal outcomes following AL reported by Novartis, the investigators reported no drug-related causality: One death was from severe malaria, three were neonatal deaths from other causes, one occurred 151 days after dosing, and one had insufficient detail for assessment.

The Sigma Tau safety database yielded two cases of possible serious cardiovascular events following DHA-PPQ. The first was the sudden death of a 16-year-old female following MDA (as presented in section 3.2.2). The other was of a 36-year-old healthy male volunteer in a clinical trial *(46)* who reported feeling lightheaded in the evening, about 10 hours after having taken the third dose of DHA-PPQ with breakfast. At the time of the adverse event, ECG monitoring showed that he had an irregular bradycardic rhythm. He then became unresponsive and apnoeic with a similar irregular bradycardia followed by asystole for 43 seconds. After at least 10 seconds of cardiopulmonary resuscitation, he reverted to normal sinus rhythm at a rate of 66 beats per minute and a blood pressure of 118/62mmHg. The subject stated retrospectively that he had had bloating and diarrhoea on the day of the event. After review of the case report, the ERG considered it consistent with vasovagal syncope rather than TdP. Two other cases of sudden unexplained death following DHA-PPQ were also presented. The first death was of a 28-month-old boy who had been frequently unwell from birth. He had presented with fever and abdominal pain to the health centre, where he underwent a malaria rapid diagnostic test, which was negative. He was then treated with a 3-day course of mebendazole for an intestinal parasitic infection. The day after his last dose of mebendazole, he died 5–15 minutes after his first dose of DHA-PPQ, which was given as SMC. The investigators considered his death to be potentially related to a drug interaction between DHA-PPQ and mebendazole. However, in light of the very brief interval between DHA-PPQ intake and death, the pharmacokinetics of piperaquine, as well as the short terminal elimination half-life of mebendazole of 3–6 hours after oral dosing, the ERG considered it unlikely that the death had been drug-related. The second case was of a 5-year-old boy who died the day after receiving the third dose of DHA-PPQ in an observational malaria treatment study. The verbal autopsy indicated that the child had died after a tonic-clonic seizure following repeated vomiting that had started on the first day of treatment. The ERG concluded that the repeated vomiting would have probably interfered with drug absorption, making it unlikely that the drug had caused the child's death.

The 2011 Sigma Tau meta-analysis on the clinical use of piperaquine reported no excess risk of death between DHA-PPQ and comparator arms in both IPT and case management studies. In total, 19 446 patients treated with DHA-PPQ were considered in 55 trials: 9015 in 34 controlled and 561 in seven uncontrolled studies for the treatment of uncomplicated malaria; 192 in nine PK studies; and 9678 in five IPT studies. Comparators in case management studies included AL, ASAQ and ASMQ. Comparators in IPT studies included SP, SP + amodiaquine, and placebo. The Cochrane systematic reviews of case management with DHA-PPQ *(39)* (see section 3.2.4) and repeated doses of DHA-PPQ *(20)* (see section 3.2.3) included 22 out of 34 of the controlled trials and two out of five of the IPT studies, respectively. Both reviews had similar findings to this meta-analysis. None of the 10 deaths identified following DHA-PPQ was thought to be consistent with sudden cardiac death. Eight of the nine deaths identified from case management studies were also assessed independently in the case management literature review (presented in section 3.2.4), while the one death in IPT was also included in the repeated doses of DHA-PPQ review *(20)* (discussed in section 3.2.3).

No ventricular tachyarrhythmias or TdP have been documented following exposure to AL or DHA-PPQ.

Liverpool School of Tropical Medicine (LSTM) Centralised Antimalarial Safety Database

This database of adverse events following antimalarial administration includes safety data collected from studies conducted by the ACT Consortium and Malaria in Pregnancy Consortium. There were no reports of serious adverse events of sudden death, TdP/QT interval prolongation or cardiac arrhythmias within 14 days of follow-up after antimalarial therapy. In a mix of healthy volunteer, IPT and case management studies, 4694 subjects received AL, 2316 received DHA-PPQ, 843 received ASAQ, 849 received ASMQ, 4111 received SP, 1365 received chloroquine + SP, and 1370 received azithromycin + SP. One of the published IPTp studies was also included in the systematic review on repeated doses of DHA-PPQ *(20)* (section 3.2.3). It was not clear if the unpublished studies were also included in other evidence considered.

Key conclusions

- DHA-PPQ treatment has been associated with one possible sudden cardiac death post-MDA out of 193 974 trial subjects with close follow-up in malaria MDA, IPT and case management studies, the majority of whom were exposed to repeated courses in MDA and IPT studies.
- IPT studies and therapeutic clinical trials did not show a different risk of death between DHA-PPQ and other antimalarials recommended by WHO for the treatment of uncomplicated malaria.
- Neither DHA-PPQ nor AL has been associated with documented life-threatening arrhythmias.
- AL treatment has not been associated with any sudden unexplained deaths.
- Reported deaths following chloroquine and hydroxychloroquine have been associated with use in overdose or for chronic indications other than the treatment of malaria.
- Concomitant use of QT/QTc interval-prolonging drugs has been found to increase the risk of antimalarial cardiotoxicity.

3.3 Studies of the effects of antimalarial medicines on the ECG

3.3.1 Halofantrine

The FDA approved halofantrine as Halfan® in 1992 under SmithKline Beecham (now GSK).

The absorption of halofantrine is highly variable and enhanced substantially by fatty foods and bile salts. The drug is highly bound to plasma lipoproteins and has a large apparent volume of distribution with a moderately long distribution phase. Halofantrine is metabolized to desbutylhalofantrine by CYP3A4 and inhibits CYP2D6. It undergoes enterohepatic recycling with faecal elimination of both parent drug and metabolite.

Halofantrine blocks hERG channels and has been associated with a dose- and concentration-related prolongation of the QTc interval in preclinical models *(47)*, healthy volunteers *(48,49)* and patients with uncomplicated malaria *(17)*. QTc interval prolongation with halofantrine has been associated with TdP, syncope and >30 cases of sudden death (section 3.2.5). Prior exposure to mefloquine is a risk factor that increases QTc interval prolongation with halofantrine *(17)*. Food-

mediated lymphatic absorption and consequent high thoracic duct drug concentrations may also increase risk *(50)*.

3.3.2 Artemether-lumefantrine

Artemether-lumefantrine was first registered as Coartem® in Gabon in 1998 and as Riamet® in Switzerland in 1999. It is currently registered in around 86 countries worldwide, including the European Union and the United States.

In the *in vitro* whole cell patch clamp study, lumefantrine and its metabolite desbutyl-lumefantrine showed a concentration-dependent inhibition of the hERG current, but at a much higher 50% inhibitory concentration (IC_{50}) than mefloquine, chloroquine and halofantrine; only halofantrine had an IC_{50} lower than its free therapeutic plasma maximum concentration (C_{max}) *(51)*. No QTc interval prolongation was seen *in vivo* in dogs with AL administered orally, except at extremely high total doses of 600mg/kg/day.

Following the experience with halofantrine, ECG evaluations have been included in most studies of AL treatment. In a randomized, double-blind, double-dummy, two-period crossover, single-dose study conducted in 13 fed, healthy, male volunteers, halofantrine had a mean maximum increase in QTcB of 28ms, but no QTcB interval prolongation was observed with AL *(52)*. In a randomized, double-blind, parallel group, 4-week trial to compare the safety and efficacy of AL with halofantrine in adult male and female travellers returning to Europe with acute falciparum malaria, 26.9% (14 subjects) had a QTc interval increase of >15% from baseline with halofantrine as compared to 7.8% (four subjects) with AL *(53)*.

The TQT study performed in healthy adult volunteers showed that, relative to placebo, AL was associated with a mean maximum increase in QTcF of 7.45ms at the 68-hour time point. The period of QTcF prolongation over zero effect, as defined in the ICH E14 guideline, was 3.5–4 days after the last dose of the standard six-dose regimen. Post-hoc analysis showed an association between the maximum observed values of QTcF change from baseline adjusted from placebo and concentrations of lumefantrine. At typical clinical concentrations of lumefantrine, an increase of >10ms was excluded. In clinical trials conducted with the six-dose AL regimen, a post-baseline QTcF interval >500ms was reported in 0.2% of adult patients, while no paediatric patient aged <12 years had a post-baseline QTcF interval >500ms.

The small increase in QTc interval associated with AL does not appear to be associated with a significant risk of arrhythmia. The small number of adverse events affecting the cardiovascular system were almost all of mild intensity and resolved without intervention.

3.3.3 Dihydroartemisinin-piperaquine

Dihydroartemisinin-piperaquine (Eurartesim®) received EMA marketing authorization in 2011.

Preclinical *in vitro* studies were performed comparing the effects of DHA-PPQ with those of other antimalarials *(54)*. In the whole cell patch clamp study, only halofantrine had an IC_{50} lower than its free therapeutic C_{max}, while chloroquine, mefloquine, lumefantrine, piperaquine, dihydroartemisinin, and the positive control dofetilide blocked hERG with IC_{50}s ranging from 3- to 30-fold their C_{max} values. Neither DHA-PPQ nor AL induced potential torsadogenic effects in the rabbit ventricular wedge preparation, affected hERG trafficking, or inhibited the sodium or slow potassium currents. Chloroquine facilitated hERG trafficking at 30-fold its C_{max}, showed a medium risk of torsadogenic effects in the rabbit ventricular wedge preparation, and blocked the sodium current at about 30-fold its C_{max}.

The TQT study performed in healthy adult volunteers showed that DHA-PPQ administered in the fasting state was associated with a mean maximum time-matched increase in QTcF relative to

placebo of 21.0ms compared with 9.9ms for AL. Time to C_{max} was reported as 4–6 hours post-dose for piperaquine. QTcF interval prolongation was transient for both DHA-PPQ and AL.

The results of a phase 2 PK/PD and safety study comparing a new paediatric DHA-PPQ dispersible formulation with crushed film-coated DHA-PPQ tablets in 300 infants aged 6–12 months with uncomplicated malaria were also presented. Both formulations had similar piperaquine pharmacokinetic and adverse effect profiles. There was a ~15–20% reduction in mean heart rate between day 0 and 4 hours post-dose on day 2 consistent with fever resolution, accompanied by an increase in mean QTcF of ~20ms in both groups. Mean QTcF returned to day 0 levels by day 7. There were no cardiovascular adverse events.

Two accidental cases of overdose with DHA-PPQ have been reported in paediatric patients with fever treated with DHA-PPQ for microscopy-confirmed malaria. The first was of a 9-year-old African girl who received nine tablets instead of three of DHA-PPQ at 17:45 on 2 April 2016. Her QTcF interval at 06:30 on 3 April was 464ms compared to 413ms at admission on 1 April. The second was of a 5-year-old African boy who received three tablets instead of one of DHA-PPQ at 17:30 on 7 September 2016. At 09:30 the next day, he had a QTcF interval of 381ms compared to 346ms at admission. Neither child had clinical signs of arrhythmia.

3.3.4 Pyronaridine-artesunate

In 2012, pyronaridine-artesunate (Pyramax®) became the first ACT to be granted a positive scientific opinion under the EMA Article 58 procedure. Pyronaridine tetraphosphate was first synthesized in the 1970s.

In *in vitro* hERG studies, pyronaridine inhibited the hERG current at an IC_{50} of 0.65µM, ~28 times the free therapeutic C_{max} in humans and ~8 times the maximum concentration of pyronaridine achieved in clinical trials. Up to 300µM artesunate, ~1000 times the C_{max} in humans, had no effect on the hERG current. No QTc interval prolongation was seen in the *in vivo* QT assay in dogs, except at doses several times greater than the human equivalent dose of pyronaridine-artesunate used in phase 3 trials.

In phase 1 studies, QTc data were available for 222 healthy subjects who received pyronaridine-artesunate either as a single dose or for 3 days. The maximum mean change of QTcB from baseline was 7ms to 13ms and that of QTcF was -1ms to 1ms. The maximum QTcB interval measured in any individual was 470ms, while the maximum QTcF interval – in a different subject – was 469ms.

In phase 2 and 3 studies in patients with uncomplicated malaria, QTc data were available for 2817 patients who received pyronaridine-artesunate. The maximum QTcB interval measured in any individual was 475ms, while the maximum QTcF individual – in a different subject – was 473ms. There were no cardiovascular adverse events following pyronaridine-artesunate that were potentially attributable to QTc interval prolongation.

In the phase 3b West African Network for Antimalarial Drugs (WANECAM) repeat dosing study, pyronaridine-artesunate had the least potential to prolong the QTc interval compared to AL, ASAQ and DHA-PPQ. There were no cases of QTcB or QTcF interval >500ms among patients who received pyronaridine-artesunate. In addition, repeat dosing did not have an appreciable effect on QTc parameters.

In granting the positive Article 58 opinion, the EMA agreed that a TQT study was not mandatory for Pyramax®.

3.3.5 Artefenomel-piperaquine

Artefenomel (OZ439) is a novel aromatic trioxolane that is being trialled in combination with piperaquine for the treatment of uncomplicated malaria.

In the *in vitro* hERG assay, OZ439 inhibited the hERG current at an IC_{50} of ~22µM, while the IC_{50} concentrations of two of its main metabolites were >10µM. Considering that the average free therapeutic plasma C_{max} after a single OZ439 dose of 800mg is 0.12µM, taking into account 96% protein binding, this suggests a 180-fold safety margin. There was no effect on QTc in the *in vivo* assay in conscious dogs with OZ439 exposures equivalent to the C_{max} of free therapeutic plasma *(55)*.

Exposure-response analysis was performed on data from a placebo-controlled, single-dose, phase 1 study with OZ439 and piperaquine. In the study, 59 healthy subjects aged 18 to 55 years received OZ439 alone or placebo in the first period, followed by OZ439 + piperaquine or matching placebos in the second period. OZ439 and piperaquine doses ranged from 100mg to 800mg and 160mg to 1440mg, respectively. Pre- and post-dosing, 12-lead ECG tracings and PK samples were collected serially. A significant relationship between plasma concentrations and placebo-corrected change from baseline QTcF was demonstrated for piperaquine, but not for OZ439, with a mean slope of 0.047ms/ng/ml (90% confidence interval: 0.038–0.057). This result suggests that piperaquine, but not OZ439, prolongs the QTcF interval in a concentration-dependent way. A linear mixed effects model accounting for the plasma concentrations of both piperaquine and OZ439 predicted a largest mean QTcF effect of 14ms (90% confidence interval: 10–18ms) and 18ms (14–22ms) at expected plasma concentrations following administration in the fasted state of a single dose of OZ439 800mg combined with piperaquine 960mg (188ng/ml) and 1440mg (281ng/ml), respectively *(55)*.

3.3.6 Ferroquine

Ferroquine is a 4-aminoquinoline analogue with a structural homology to chloroquine that is currently in pre-approval clinical trials.

In the *in vitro* hERG assay, ferroquine inhibited the hERG current at an IC_{50} of 2.0µM, and its more slowly-eliminated active metabolite SSR97213 had an IC_{50} of 0.183µM – respectively ~200–500 times and ~40–80 times the free therapeutic C_{max} in human subjects. In the conscious dog *in vivo* QT assay, ferroquine had no effect on QTc at 3, 10 and 30mg/kg doses.

In phase 1 studies in healthy subjects, 117 subjects received up to 1600mg of ferroquine, either alone or in combination with artesunate; 55 subjects received ferroquine up to a dose of 1200mg in combination with OZ439. Preclinical and clinical studies have shown that artesunate *(56)* (section 3.3.4) and OZ439 *(55)* (section 3.3.5) are not associated with QTc interval prolongation. Of these 172 subjects, only one had a QTcF interval >450ms and none had a QTcF interval >500ms. ECG analysis from pooled phase 1 studies showed an estimated mean increase in QTcF compared to placebo of 3.1ms (95% confidence interval: 1.4–4.8), 3.3ms (0.8–5.8), and 5.9ms (3.9–7.8) at the higher single doses of 800, 900, and 1200mg, respectively. In the 3-day repeated ferroquine monotherapy ascending-dose study, morphological changes were observed at the 800mg dose of ferroquine on day 1, with four out of six subjects developing T wave flattening, and one out of six patients developing an inverted U wave. Due to the T wave changes observed at the 800mg dose level, enrolment was discontinued for the 1000mg dose level.

3.3.7 Other antimalarial drugs

Amodiaquine and primaquine both affect cardiac electrophysiology and both are used widely; however, very few studies have recorded ECGs. The limited data available suggest that artesunate-amodiaquine is associated with QTc interval prolongation similar to that following

chloroquine *(57)*, and that primaquine does not cause significant QTc interval prolongation *(58–60)*. However, more information is needed. It is notable that with the extensive global usage of quinine in the first half of the 20th century and the enormous use of chloroquine (and to a lesser extent amodiaquine) in the second half, there have been no reports of sudden unexplained death suggestive of cardiac arrhythmia at the doses used for malaria treatment.

Key conclusions

- Halofantrine treatment has been associated with substantial dose- and concentration-dependent QTc interval prolongation at therapeutic doses in healthy volunteers and malaria patients; it has also been associated with conduction abnormalities, TdP, syncope and sudden death.
- Artemether-lumefantrine treatment has been associated with slight concentration-dependent QTc interval prolongation at therapeutic doses, but this transient QTc interval prolongation has not been associated with cardiovascular adverse events.
- DHA-PPQ treatment has been associated with greater QTc interval prolongation than AL at therapeutic doses, but this QTc interval prolongation is transient and has not been associated with cardiovascular adverse events.
- Studies have shown pyronaridine-artesunate treatment to have the lowest potential to prolong the QTc interval compared to AL, ASAQ and DHA-PPQ, even after repeat dosing.
- Artefenomel (OZ439) has not been associated with concentration-dependent QTc interval prolongation.
- More information is needed on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine.

3.4 PK/PD analyses on the effects of antimalarial medicines on the ECG

3.4.1 Pooled analyses

Preliminary analyses from individual subject data shared with the ERG (see Annex A for list) were pooled, analysed and presented. A subset of studies with central ECG readings performed by Cardiabase were also analysed and presented separately. In addition, results from nonlinear mixed effects PK/PD modelling of individual subject measurements from selected studies of chloroquine and DHA-PPQ were presented.

QTc measurement methodologies

A number of QTc measurement methodologies were used in a variety of combinations, including:

- ECGs with automated machine readouts versus semi-automated central digital readings versus manual measurements on paper; in some studies, only a subset of ECGs, such as those with prolonged QTc intervals as determined by other methods, were sent for central reading;
- Superimposed median beat measurements versus averaged measurements of multiple complexes from a particular ECG lead, usually lead II but occasionally others;
- Threshold versus tangent method for determining the end of the T wave;
- 50mm/second versus 25mm/second paper speed.

ECGs were recorded at a variety of time points, although all studies measured ECGs at baseline and at least one other point in time following drug dosing (usually at the expected time of peak drug concentration). The possibility of a detection effect in studies with more frequent ECG

measurements was discussed. Members of the ERG also noted the widely observed inter-observer variability in QTc measurements.

Despite the heterogeneity in ECG measurement methodologies, there was remarkable agreement among individual studies in terms of the findings related to QTc parameters (see sections 3.3 and 3.4.2), as well as between the Cardiabase pooled statistical analyses of studies utilizing relatively standardized ECG measurement procedures and the ERG pooled statistical analysis, which included data from studies using a diverse range of ECG measurement methods.

Correction factor sensitivity analysis

The Bazett ($QT \times RR^{-0.5}$) and Fridericia ($QT \times RR^{-0.333}$) corrections are the two most commonly used in clinical practice to adjust the measured QT interval for heart rate, with the RR interval representing the duration between QRS complexes. In addition, the Fridericia correction has been the subject of increased interest following an April 2012 recommendation from the ICH E14 TQT Implementation Working Group that its use is adequate for the majority of TQT studies.

In both pooled statistical analyses, QTcB was found to be the better correction factor at baseline for patients with malaria, while QTcF was more appropriate for healthy subjects in general. In the Cardiabase analysis, study-specific corrections were close to Bazett's correction for malaria patients and non-Caucasian healthy subjects, while study-specific corrections approximated Fridericia's correction for healthy volunteers from predominantly Caucasian populations. Study-specific sensitivity analyses conducted in the STOPMIP IPTp and ADJusT case management studies with DHA-PPQ confirmed that Bazett's correction offered better heart rate correction, whereas the large START-IPT SMC study in schoolchildren favoured Fridericia's correction.

In the preliminary pooled PK/PD analysis of DHA-PPQ data, the overall population correction in malaria patients was close to Bazett's correction. The daily population correction exponent gradually decreased in absolute value over several days to approach Fridericia's correction as patients recovered from malaria.

Degree of QTc interval prolongation

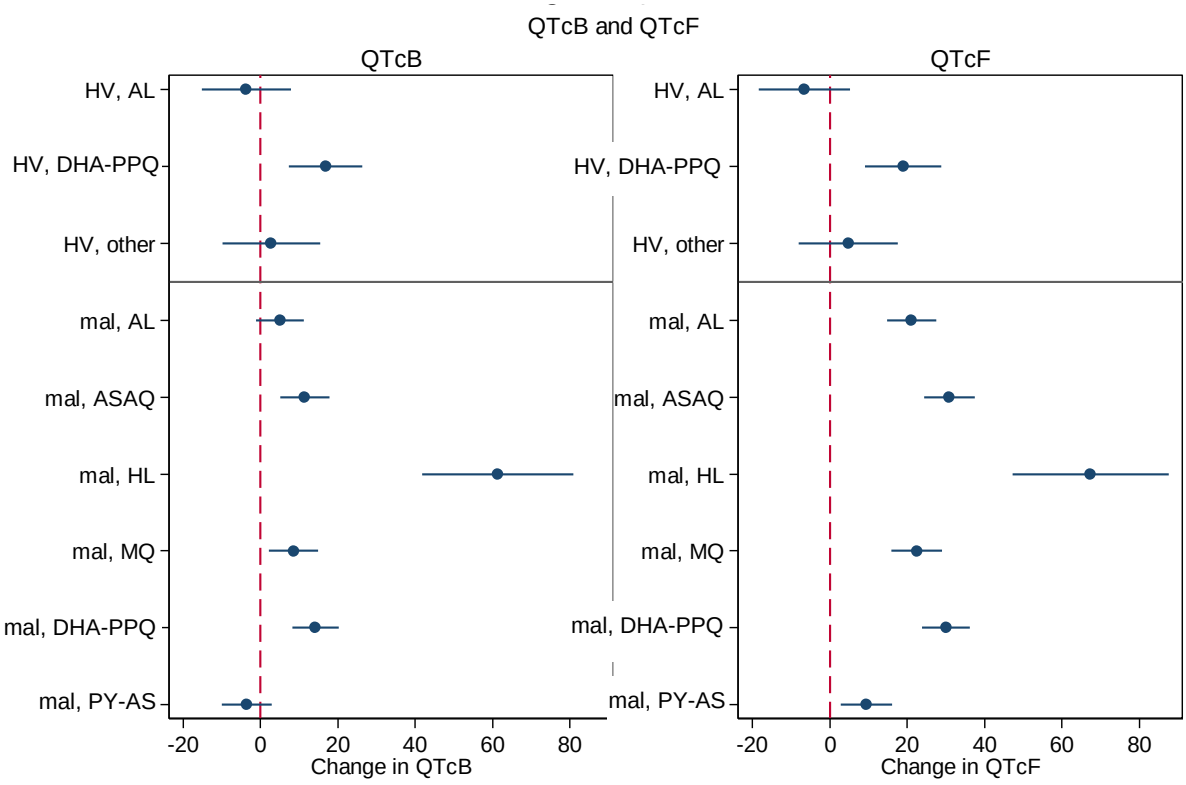
Nonlinear mixed effects PK/PD modelling of measurements from two randomized 3-period crossover studies in healthy Thai volunteers *(58,60)* found chloroquine to be associated with QTc interval prolongation greater than that of DHA-PPQ. The approximate mean concentration–QTcF effect of chloroquine was a 10.2ms increase in QTcF per 100ng/mL increase in plasma chloroquine concentration compared to a 3.12ms increase in QTcF per 100ng/mL increase in plasma piperaquine concentration. In these healthy volunteer studies, patients received single oral doses of each antimalarial drug at standard therapeutic doses. ECGs were recorded pre-dose and over 24 hours post-dose, while pharmacokinetic sampling was performed pre-dose and over 36 days following administration of chloroquine or DHA-PPQ. Pharmacokinetic assessment was performed using both model-independent and nonlinear mixed effects PK/PD modelling approaches.

The preliminary pooled PK/PD modelling analysis of DHA-PPQ found similar slopes for the mean concentration–QTcF effect of piperaquine in healthy volunteers and in malaria patients, with a mean concentration–QTcF effect of 3.3ms of QTcF prolongation per 100ng/mL increase in piperaquine concentration. Healthy volunteer data were included from the crossover study in healthy Thai volunteers *(58)* and the DHA-PPQ (Eurartesim®) TQT study, while uncomplicated malaria patient data were drawn from the 1002 subjects included in the nested ECG and PK substudy of the INESS *(21)* phase 4 safety monitoring assessment of DHA-PPQ (also discussed in section 3.2.4). Three INESS patients had a QTcF interval >500ms at C_{max}, but there were no episodes of TdP, ventricular fibrillation or adverse clinical sequelae *(21)*. Both TQT and INESS patients received full 3-day treatment courses of DHA-PPQ. In the TQT study, subjects who

received DHA-PPQ were in three arms, each with different food conditions: fasting, high-fat/low-calorie, and high-fat/high-calorie.

Individual patient data provided to the ERG to evaluate the effect of full therapeutic courses of antimalarials on QTc measurements were pooled and analysed. Quinine was not included in this analysis, as the data shared were related to its use in the treatment of severe malaria. A preliminary analysis was undertaken to determine the mean change in QTc associated with each antimalarial medicine in patients with uncomplicated malaria and in healthy subjects (where data were available). Change in QTc was defined as the difference in QTc measured at baseline and at a follow-up ECG selected to be either 2–8 hours after the last dose of the treatment course (where time of dose was available) or approximately 52 hours after the baseline ECG (where time of dose was not available). Preliminary results of this ERG pooled analysis using Bazett's and Fridericia's corrections are shown in Fig. 2 and summarized in the paragraph below.

Of the antimalarial drugs studied, halofantrine was associated with the most substantial QTc interval prolongation in patients with uncomplicated malaria. DHA-PPQ and ASAQ had comparable QTc interval prolongation in patients with uncomplicated malaria followed by AL; this was also the case in the Cardiabase pooled analysis. AL was associated with a lesser degree of QTc interval prolongation than DHA-PPQ in healthy subjects. DHA-PPQ was associated with similar QTc interval prolongation both in healthy subjects and in uncomplicated malaria patients with both Bazett's and Fridericia's corrections. AL was associated with similar QTcB interval prolongation in healthy volunteers and uncomplicated malaria patients, but there appeared to be greater QTcF interval prolongation associated with AL in malaria patients than in healthy volunteers. Mefloquine (as monotherapy or in combination with either artesunate or artemether) was associated with a QTc interval prolongation similar to that of AL. Pyronaridine-artesunate was associated with the smallest QTc interval prolongation in both statistical analyses. In the Cardiabase analysis, OZ439 was associated with a QTc interval prolongation comparable to that of pyronaridine-artesunate.



HV = healthy volunteers, mal = patients with uncomplicated malaria.
AL = artemether-lumefantrine, DHA-PPQ = dihydroartemisinin-piperaquine, other = trimethoprim-sulfamethoxazole, ASAQ = artesunate-amodiaquine, HL = halofantrine, MQ = mefloquine / artesunate-mefloquine / artemether-mefloquine, PY-AS = pyronaridine-artesunate.

Fig. 2. Predicted change in QTc in milliseconds with 95% confidence intervals

Disease and non-drug factors affecting QTc interval prolongation

In addition to heart rate, temperature was a significant covariate, accounting for a 16% increase in the slope of the mean concentration–QTcF effect of piperaquine among malaria patients in the PK/PD modelling analysis. As would be expected with recovery from malaria, the median heart rate and temperature of patients with malaria decreased between baseline and time of follow-up ECG in pooled studies. There was no significant change in heart rate between baseline and time of follow-up ECG for healthy subjects.

QTcB interval >500ms following antimalarial therapy

The ERG chose Bazett's correction for this analysis, as the vast majority of subjects in the analysis set had clinical malaria. Of the 4025 individuals who received DHA-PPQ, 24 or 0.6% had a QTcB interval >500ms. Of the 1202 individuals who received AL, four or 0.3% had a QTcB interval >500ms; this figure is similar to the 0.2% with a QTcF interval >500ms drawn from the Novartis database (see section 3.3.2). The median and mean time of QTcB interval >500ms was 2 days from baseline, i.e., on day 3 of antimalarial therapy, when the C_{max} values of piperaquine and lumefantrine are expected to occur.

3.4.2 Special risk groups

Preventive therapy in pregnant women, infants and schoolchildren

PK and ECG substudies were conducted as part of the DHA-PPQ preventive therapy studies of the Uganda Infectious Diseases Research Collaboration (IDRC). Four populations were evaluated in the PROMOTE birth cohort IPTp and IPTi studies, and one population in the START-IPT SMC study:

- BC1 mothers *(35)*: HIV-uninfected women enrolled at 12–20 weeks gestation, randomized to 8-weekly SP, 8-weekly DHA-PPQ, or 4-weekly DHA-PPQ from 20 weeks gestation to delivery;
- BC2 mothers: HIV-infected women on efavirenz-based antiretroviral therapy enrolled at 12–28 weeks gestation, randomized to daily trimethoprim-sulfamethoxazole or daily trimethoprim-sulfamethoxazole + 4-weekly DHA-PPQ until delivery (discussed also in section 3.2.3);
- BC1 women: a subset of BC1 mothers enrolled at 34–54 weeks postpartum as controls for BC1 mothers who received a single 3-day course of DHA-PPQ;
- BC1 children: birth cohort of children born to BC1 mothers, randomized to 12-weekly or 4-weekly DHA-PPQ between 8 and 104 weeks of age;

and

- START-IPT: cluster randomized trial evaluating the impact of monthly SMC of asymptomatic schoolchildren with DHA-PPQ for up to six rounds on community-level malaria indicators (discussed also in section 3.2.3).

ECGs were recorded during each course of DHA-PPQ prior to the first dose and 3–4 hours after the third dose. In the PROMOTE birth cohort populations, venous and capillary blood samples

were collected at different time points post-dose; the venous and capillary blood samples collected simultaneously at 24 hours were used to establish correlations between capillary and venous plasma piperaquine concentration results. In the START-IPT population, only capillary samples were collected. A previous study demonstrated that capillary blood piperaquine concentrations are approximately 3-fold higher than venous plasma concentrations *(61)*.

PROMOTE birth cohort groups receiving DHA-PPQ had a mean 15–20ms increase in QTcF or 12–21ms increase in QTcB from baseline, while groups receiving SP or trimethoprim-sulfamethoxazole only had no significant change in QTc. The QTc increases were similar with both Bazett's and Fridericia's corrections in all study populations receiving DHA-PPQ. The number of prior courses of DHA-PPQ was not related to the degree of QTc interval prolongation. There were no cases of QTcB or QTcF intervals >500ms in the 98 patients who received DHA-PPQ in the ECG substudies. No significant correlation was found between change in QTc and piperaquine exposure or concentrations. This may be related to pregnancy, HIV-positivity with efavirenz treatment, or infancy – each being associated with significantly lower piperaquine exposure and C_{max}.

In START-IPT, treatment was associated with a mean increase in QTcF of 16.6ms (95% confidence interval: 15.1–18.1). Of the 155 participants, 18 in the ECG substudy experienced 22 episodes of QTcF interval prolongation, none of which were clinically significant and all of which were resolved. The risk of QTcF interval prolongation did not appear to increase with repeated rounds of DHA-PPQ. There were three cases of QTcF interval >480ms, of which one was >500ms; all three patients were excluded from further rounds of DHA-PPQ and remained clinically well. Peak piperaquine concentrations were associated with change in QTcF from baseline. Final multivariate analyses are in progress.

In the STOPMIP IPTp study using DHA-PPQ in Papua, Indonesia (also discussed in section 3.2.3), a nested PK and ECG substudy of 33 women was performed. ECGs were performed at baseline and 4–6 hours after the third dose of DHA-PPQ for each course. DHA-PPQ was associated with a mean increase in QTcF of 20ms and in QTcB of 15ms. This prolongation was not affected by the number of previous courses of DHA-PPQ taken. Mean QTc and increase in QTc from baseline decreased with each successive course of DHA-PPQ, regardless of whether Bazett's or Fridericia's correction was used. Two women had a post-baseline QTcF interval >480ms (and a QTcB interval >500ms) and did not receive further courses of DHA-PPQ. Piperaquine drug concentrations are expected to be available in early 2017.

There were no clinically significant cardiovascular adverse events or arrhythmias observed in these substudies or their main trials.

Case management in children in the 5–24.9kg weight band

In the ADJusT dose optimization study to evaluate the cardiac safety of DHA-PPQ in the treatment of uncomplicated falciparum malaria in children weighing 5–24.9kg in Malawi, 96 children received a full 3-day course of DHA-PPQ at daily doses of 1.7–3.8mg/kg body weight of DHA and 13.6–30.0mg/kg body weight of PPQ[iv]. QTc was measured 4–6 hours after the third dose of DHA-PPQ and compared to baseline and day 28 readings. There were no arrhythmias, or QTcF or QTcB intervals >500ms. A linear exposure-response model was fitted to describe the relationship between the change in QTcB from baseline adjusted for the baseline value and the whole blood concentration of piperaquine. An increase of 440ng/mL in the whole blood concentration of piperaquine was associated with an increase of 30ms from baseline in QTcB (95% confidence interval: 402–486ng/mL).

[iv] The current WHO-recommended daily therapeutic dose range of DHA-PPQ for children weighing <25kg is 2.5–10mg/kg body weight dihydroartemisinin and 20–32 mg/kg body weight piperaquine.

Key conclusions

- Halofantrine was associated with the greatest QTc interval prolongation of the antimalarial drugs studied.
- Chloroquine has been associated with a larger QTc interval prolongation than DHA-PPQ in healthy volunteers.
- DHA-PPQ and ASAQ have been associated with comparable degrees of QTc interval prolongation in malaria patients, although more data on amodiaquine are needed.
- QTc interval prolongation associated with DHA-PPQ has been found to be similar in both malaria patients and healthy subjects.
- AL has been associated with smaller QTc interval prolongation than DHA-PPQ in malaria patients and in healthy subjects.
- Pyronaridine-artesunate was associated with the smallest QTc interval prolongation of the antimalarials studied.

3.5 Priority research gaps and planned studies on the effects of antimalarials on the ECG

It was agreed that the preliminary analyses initiated on the data gathered for the ERG should be continued and completed. The following evidence gaps and priorities for further research were identified at the meeting:

- Exploration of alternative dosing strategies to further minimize the cardiotoxicity risk associated with antimalarial medicines, through field trials and PK/PD modelling, including:
  - Age-based dosing in children
  - Weekly drug administration in MDA
- Identification of genetic polymorphisms and other pre-existing conditions that may contribute to the risk of repolarization-related cardiotoxicity, through:
  - Further investigation of individual outliers in antimalarial drug safety studies
  - Further investigation of special risk groups such as malnourished children
  - Pooling data from potential trial participants with a QTc interval >450ms at screening
- Direct comparison of the cardiotoxicity risk of antimalarial drugs in different populations, through:
  - Pooled PK/PD and statistical analyses of individual patient data on QTc interval prolongation
  - Further nested PK/PD studies, especially in populations exposed to MDA
  - Preclinical *in vitro* and *in vivo* assays conducted by independent laboratories

In particular, more evidence is needed with respect to chloroquine, amodiaquine and primaquine.

- Centralization and standardization of the format of reporting adverse events following antimalarial medicines, particularly deaths, in order to improve signal detection for cardiotoxicity, including:

    - Spontaneous reports to international and national pharmacovigilance centres
    - Serious adverse event and loss to follow-up reporting from clinical trials
    - Active pharmacovigilance strategies in populations exposed to MDA
- Harmonization of ECG measurement methodologies in antimalarial cardiotoxicity safety studies.

The plans of the WWARN piperaquine safety study group to further build on the reviews presented at this meeting, including the pooled PK/PD modelling analysis of piperaquine-containing medicines, were introduced.

4 Conclusions and recommendations

The ERG panel addressed the following key questions and made the following recommendations for consideration:

1. What is the frequency of sudden death attributable to the cardiotoxicity of different antimalarial medicines?

Halofantrine has been associated with >30 sudden deaths attributed to cardiotoxicity. This is the only antimalarial considered to have an unacceptable risk.

Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most intensively studied antimalarial drugs. There have been no sudden deaths attributed to cardiotoxicity following artemether-lumefantrine. One possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported among ~200 000 individuals with close follow-up treated in clinical studies of malaria treatment, prevention, control and elimination. This is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc interval-prolonging medicines in current use (see section 3.1.1).

Despite hundreds of millions of doses administered in the treatment of malaria, there have been no reports of sudden unexplained death associated with quinine, chloroquine or amodiaquine, although each drug causes QT/QTc interval prolongation. Unfortunately, there are relatively few prospective studies of the electrocardiographic effects of these drugs.

Intravenous chloroquine, quinine and quinidine may cause lethal hypotension if administered too rapidly. Large doses (>3.5mg base/kg) of intramuscular or subcutaneous chloroquine may also cause hypotension.

2. What is the frequency of life-threatening ventricular tachyarrhythmias and TdP following treatment with antimalarials that prolong the QT interval?

No episodes of TdP or life-threatening ventricular tachyarrhythmias have been documented following dihydroartemisinin-piperaquine or artemether-lumefantrine.

Although drug-induced QT/QTc interval prolongation is an imperfect surrogate indicator for drug-induced cardiotoxicity risk, it is the best currently available. A QT/QTc interval >500ms has been associated with increased risk of TdP and sudden cardiac death. Among drugs that prolong the QT/QTc interval, antiarrhythmics have been associated with TdP in 1–5% of exposed individuals, while non-cardiovascular drugs have a much lower risk of TdP. Approximately one in 10 cases of TdP will degenerate into life-threatening tachyarrhythmias.

Dihydroartemisinin-piperaquine has been associated with a QTc interval >500ms in 0.6% of individuals exposed, while artemether-lumefantrine has been associated with a QTc interval >500ms in 0.2–0.3% of individuals exposed. No data are available for such QTc analyses to predict the risk of drug-induced TdP and life-threatening tachyarrhythmias in the general population, to estimate the differential risks in specific population subgroups, or to quantify these risks for individual antimalarial medicines.

Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, chloroquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine, have been associated with a low risk of cardiotoxicity. Out of ~200 000 people treated with close follow-up, the one reported case of sudden death considered to be possibly causally related to treatment with dihydroartemisinin-piperaquine suggests that, while cardiotoxicity may occur as a very rare *(62)* event, safety monitoring should continue in clinical studies of malaria treatment, prevention, control and elimination. This cardiotoxicity risk is likely to be similar to that following treatment

with chloroquine or artesunate-amodiaquine, and higher than that following treatment with artemether-lumefantrine or pyronaridine-artesunate. These findings are consistent with the risk of TdP and life-threatening ventricular tachyarrhythmias associated with other QT/QTc interval-prolonging medicines in current use.

3. What factors increase the frequency of life-threatening ventricular tachyarrhythmias following exposure to antimalarial medicines that induce QT interval prolongation?

The general risk factors for TdP should also be considered risk factors for antimalarial medicines that prolong the QT/QTc interval. Concomitant medications that can induce QT/QTc interval prolongation or potentiate the effects of QT/QTc interval-prolonging drugs, structural heart disease, genetic defects of cardiac ion channels, electrolyte abnormalities such as hypokalaemia, bradycardia and hepatic impairment increase the risk of life-threatening ventricular tachyarrhythmias following exposure to QT/QTc interval-prolonging drugs, including antimalarial medicines.

4. What strategies for malaria treatment or chemoprevention can reduce the risk of life-threatening ventricular tachyarrhythmias following exposure to antimalarial medicines that induce QT interval prolongation?

In individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmia, or who are already taking medicines that can prolong the QT/QTc interval, antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution. If possible, closer monitoring is advised when giving quinine, chloroquine, artesunate-amodiaquine or dihydroartemisinin-piperaquine to such individuals.

5. Is the risk of cardiotoxicity of piperaquine-containing medicines higher than that of chloroquine?

No. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, provides no evidence of a significant difference in the risk of cardiotoxicity following exposure to the currently recommended doses of piperaquine, chloroquine or amodiaquine.

6. Is the risk of cardiotoxicity of piperaquine-containing medicines higher in healthy volunteers than in malaria patients?

No. Review of pharmacovigilance and clinical data, along with preliminary results from PK/PD modelling, provides no evidence of a difference in the risk of cardiotoxicity of piperaquine-containing medicines in healthy volunteers compared to malaria patients.

7. What evidence sources and gaps can be identified, and what additional studies are recommended to inform the risk assessment for antimalarial cardiotoxicity?

The following evidence gaps and priorities for further research were identified at the ERG meeting:

- Exploration of alternative dosing strategies to further minimize the cardiotoxicity risk associated with antimalarial medicines, through field trials and PK/PD modelling, including:
    - Age-based dosing in children
    - Weekly drug administration in MDA

- Identification of genetic polymorphisms and other pre-existing conditions that may contribute to the risk of repolarization-related cardiotoxicity through:
    - Further investigation of individual outliers in antimalarial drug safety studies
    - Further investigation of special risk groups such as malnourished children
    - Pooling data from potential trial participants with a QTc interval >450ms at screening
- Direct comparison of the cardiotoxicity risk of antimalarial drugs in different populations, through:
    - Pooled PK/PD and statistical analyses of individual patient data on QTc interval prolongation
    - Further nested PK/PD studies, especially in populations exposed to MDA
    - Preclinical *in vitro* and *in vivo* assays conducted by independent laboratories

In particular, more evidence is needed with respect to chloroquine, amodiaquine and primaquine

- Centralization and standardization of the format of reporting of adverse events following antimalarial medicines, particularly deaths, in order to improve signal detection for cardiotoxicity, including:
    - Spontaneous reports to international and national pharmacovigilance centres
    - Serious adverse event and loss to follow-up reporting from clinical trials
    - Active pharmacovigilance strategies in populations exposed to MDA
- Harmonization of ECG measurement methodologies in antimalarial cardiotoxicity safety studies.

Annex A: Summary of evidence

Evidence	Summary
WHO VigiBase® global individual case safety report database analyses	1. Sudden unexplained death or TdP/QT interval prolongation following **any antimalarial** 2. Adverse drug reactions associated with **halofantrine** 3. Adverse drug reactions associated with **DHA-piperaquine**
LSTM antimalarial drug safety database report	Sudden death, TdP/QT interval prolongation or cardiac arrhythmia adverse events following **antimalarial drug** therapy in ACT Consortium and Malaria in Pregnancy Consortium studies
Literature reviews	1. Cardiotoxicity of **antimalarial drugs** x2 2. Effectiveness and safety of **DHA-piperaquine** treatment in uncomplicated malaria
Pooled analyses and meta-analyses	1. Analysis of sudden deaths following mass drug administration of **antimalarial drugs** 2. Systematic review and meta-analysis of safety, tolerability and efficacy of repeated doses of **DHA-piperaquine** with focus on IPT 3. Analysis of deaths following **antimalarial drug** treatment in uncomplicated malaria 4. Pooled analysis of QT effect of **antimalarial drugs** in contributed clinical studies 5. Pooled analysis of QT effect of **antimalarial drugs** in Cardiabase-supported studies
Pooled PK/PD modelling	Analyses of drug exposure–QT relationship and effects of covariates in selected contributed clinical studies on **chloroquine** and **DHA-piperaquine**
IPT collaboration clinical trial data and study reports	1. STOPMIP IPT with **DHA-piperaquine** in pregnant women in Indonesia 2. PROMOTE IPT with **DHA-piperaquine** in infants as well as pregnant and postpartum women with and without HIV in Uganda 3. START-IPT SMC with **DHA-piperaquine** in schoolchildren in Uganda
Research network clinical trial data	1. MORU, SMRU and OUCRU studies on **quinine, chloroquine, halofantrine, mefloquine, artesunate-mefloquine, artemether-lumefantrine and DHA-piperaquine** 2. INESS phase 4 prospective observational study to evaluate safety of **DHA-piperaquine** in public health facilities in East, West and Southern Africa 3. WANECAM phase 3b/4 randomized trial on **pyronaridine-artesunate** versus **DHA-piperaquine** versus **artesunate-amodiaquine** versus **artemether-lumefantrine** for treatment of repeated episodes of uncomplicated malaria in West Africa

Evidence	Summary
PDP and regulator clinical trial data and study reports	1. MMV phase 1 and phase 2b studies on **OZ439-piperaquine** 2. DNDi phase 2b studies on **artesunate-mefloquine** and **artesunate-amodiaquine** 3. FDA phase 1 study on **halofantrine**
Pharmaceutical company proprietary data and reports	• Proprietary safety database case reports of sudden deaths following **halofantrine** [GSK] • Safety overview report of **artemether-lumefantrine** based on information from preclinical studies, clinical trials and proprietary safety database case reports [Novartis] • Clinical study reports and data from phase 1 food and phase 4 clinical trials on **artesunate-amodiaquine** [Sanofi] • Results from preclinical studies on **ferroquine** as well as phase 1 clinical trials on **ferroquine-artesunate** and **ferroquine-OZ439** [Sanofi] • Electrocardiology safety assessment report of **pyronaridine-artesunate** based on results from preclinical to phase 3b studies [Shin Poong] • Meta-analysis on clinical use of **piperaquine** [Sigma Tau] • Safety overview of **DHA-piperaquine** based on information from sponsored clinical trials and proprietary safety database case reports [Sigma Tau] • Preclinical study results on TdP risk of **piperaquine** and **DHA-piperaquine** [Sigma Tau] • Clinical study reports and data from phase 1 food, phase 2 and phase 3 clinical trials of **DHA-piperaquine** [Sigma Tau]
Piperaquine safety study group analysis plan	Proposal to assess the relationship between piperaquine exposure and cardiac safety, adjusting for the effects of confounders using pooled PK/PD data from healthy volunteers, those given preventive treatment, and uncomplicated malaria patients

Annex B: List of pre-reads

Introduction and background

i. Drug-induced QT interval prolongation

I. Expert summary on preclinical and clinical basis for drug-induced QT prolongation [M Drici]

ii. Review of antimalarial cardiotoxicity

II. Published review on the cardiotoxicity of antimalarial drugs [White, 2007] *(13)*
III. WWARN systematic review manuscript on the cardiotoxicity of antimalarial drugs [N White]

Session 1: Sudden death in antimalarial therapy

i. General

1. WHO VigiBase® reports of sudden death, TdP and QT prolongation with antimalarials [N Iessa]
2. ERG analysis of sudden deaths after antimalarial mass drug administration [X Chan]
3. WWARN review of deaths after antimalarial treatment in uncomplicated malaria [P Guerin]
4. LSTM Centralised Antimalarial Drug Safety Database report [C Pace, D Lalloo & F ter Kuile]

ii. Halofantrine

5. WHO VigiBase® reports of suspected adverse drug reactions with halofantrine [N Iessa]
6. Published review on cardiac deaths from literature and GSK safety database [Bouchaud *et al.*, 2009] *(19)*

iii. Dihydroartemisinin-piperaquine/DHA-PPQ

7. WHO VigiBase® reports of suspected adverse drug reactions with DHA-PPQ [N Iessa]
8. Published review and meta-analysis on the efficacy and safety of repeated DHA-PPQ [Gutman *et al.,* 2016] *(20)*

Session 2: Studies on antimalarial effects on the ECG

i. General

9. Published preclinical studies on TdP risk of antimalarial drugs [Borsini *et al.*, 2012] *(54)*

ii. Dihydroartemisinin-piperaquine/DHA-PPQ

10. Sigma Tau meta-analysis on the clinical use of piperaquine [G Valentini]
11. Cochrane review on DHA-PPQ for the treatment of uncomplicated malaria [Zani *et al.*, 2014] *(39)*
12. STOPMIP IPTp study cardiac monitoring report [F ter Kuile & R Ahmed]

iii. Artemether-lumefantrine

13. Novartis Coartem® safety overview [C Winnips]

iv. Pyronaridine-artesunate

14. Shin Poong Pyramax® electrocardiology assessment report [R Miller & J Shin]

v. Artefenomel-piperaquine/OZ439-PPQ

15. Published article on the evaluation of the QT effect of OZ439-PPQ in healthy subjects [Darpo *et al*., 2015] *(55)*

Session 3: PK/PD analyses of antimalarial effects on the ECG

i. Dihydroartemisinin-piperaquine/DHA-PPQ

16. IDRC Uganda IPT study summaries [P Jagannathan, S Staedke & G Dorsey]
17. Published article on the efficacy and safety of DHA-PPQ for IPTp [Kakuru *et al.,* 2016] *(35)*
18. PROMOTE IPTp study manuscript on the results of intensive PK-PD sampling [P Jagannathan] *(63)*

Annex C: List of participants

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References

1. ICH Harmonised Tripartite Guideline S7B: The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. Geneva: ICH; 2005.
2. ICH Harmonised Tripartite Guideline E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Geneva: ICH; 2005.
3. Roden DM, Drici MD. Drug-induced sudden death. In: Priori SG, Zipes DP, editors. Sudden cardiac death: a handbook for clinical practice. Oxford: Blackwell Publishing; 2005.
4. Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. J Physiol. 2016;594:2459–68.
5. Sarganas G, Garbe E, Kimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. Europace. 2014;16:101–8.
6. Molokhia M, Pathak A, Lapeyre-Mestre M, Caturla L, Montastruc JL, CRPV, et al. Case ascertainment and estimated incidence of drug-induced long-QT syndrome: study in Southwest France. Br J Clin Pharmacol. 2008;66:386–95.
7. Darpo B. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. Eur Heart J Suppl. 2001;K:K70–K80.
8. Roden DM. Taking the "idio" out of "idiosyncratic": predicting torsades de pointes. Pacing Clin Electrophysiol. 1998;21:1029–34.
9. Drici MD, Clement N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. Drug Saf. 2001;24:575–85.
10. Cavero I, Holzgrefe H. Comprehensive in vitro Proarrhythmia Assay, a novel in vitro/in silico paradigm to detect ventricular proarrhythmic liability: a visionary 21st century initiative. Expert Opin Drug Saf. 2014;13:745–58.
11. Darpo B, Benson C, Dota C, Ferber G, Garnett C, Green CL, et al. Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. Clin Pharmacol Ther. 2015;97:326–35.
12. Johannesen L, Vincente 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. Clin Pharmacol Ther. 2014;96:549–58.
13. White NJ. Cardiotoxicity of antimalarial drugs. Lancet Infect Dis. 2007;7:549–58.
14. White NJ, Miller KD, Churchill FC, Berry C, Brown J, Williams SB, et al. Chloroquine treatment of severe malaria in children: pharmacokinetics, toxicity, and new dosage recommendations. N Engl J Med. 1988;319:1493–1500.
15. Wenckebach K. Cinchona derivates in the treatment of heart disorders. JAMA. 1923;81:472–4.
16. Selzer A, Wray HW. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation. 1964;30:17–26.
17. Nosten F, ter Kuile FO, Luxemburger C, Woodrow C, Kyle DE, Chongsuphajaisiddhi T, et al. Cardiac effects of antimalarial treatment with halofantrine. Lancet. 1993;341:1054–56.
18. Monlun E, Pillet O, Cochard JF, Favarel Garrigues JC, le Bras M. Prolonged QT interval with halofantrine. Lancet. 1993;342:1541–2.

19. Bouchaud O, Imbert P, Touze JE, Dodoo AN, Danis M, Legros F. Fatal cardiotoxicity related to halofantrine: a review based on a worldwide safety data base. Malar J. 2009;8:289.
20. Gutman J, Kovacs S, Dorsey G, Stergachis A, ter Kuile FO. Safety, tolerability, and efficacy of repeated doses of dihydroartemisinin-piperaquine for prevention and treatment of malaria: a systematic review and meta-analysis. Lancet Infect Dis. 2017;17(2):184–93.
21. Baiden R, Oduro A, Halidou T, Gyapong M, Sie A, Macete E, et al. Prospective observational study to evaluate the clinical safety of the fixed-dose artemisinin-based combination Eurartesim(R) (dihydroartemisinin/piperaquine), in public health facilities in Burkina Faso, Mozambique, Ghana, and Tanzania. Malar J. 2015;14:160.
22. Shah RR. Drug-induced QT interval prolongation: does ethnicity of the thorough QT study population matter? Br J Clin Pharmacol. 2013;75:347–58.
23. Shah RR. Drug-induced prolongation of the QT interval: why the regulatory concern? Fundam Clin Pharmacol. 2002;16:119–24.
24. Eisele TP, Silumbe K, Finn T, Chalwe V, Kamuliwo M, Hamainza B, et al. Assessing the effectiveness of household-level focal mass drug administration and community-wide mass drug administration for reducing malaria parasite infection prevalence and incidence in Southern Province, Zambia: study protocol for a community randomized controlled trial. Trials. 2015;16:347.
25. Poirot E, Skarbinski A, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. Cochrane Database Syst Rev. 2013;12:CD008846.
26. Newby G, Hwang J, Koita K, Chen I, Greenwood B, von Seidlein L, et al. Review of mass drug administration for malaria and its operational challenges. Am J Trop Med Hyg. 2015;93:125–34.
27. Bigira V, Kapisi J, Clark TD, Kinara S, Mwangwa F, Muhindo MK, et al. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. PLoS Med. 2014;11:e1001689.
28. Bojang K, Akor F, Bittaye O, Conway D, Bottomley C, Milligan P, et al. A randomised trial to compare the safety, tolerability and efficacy of three drug combinations for intermittent preventive treatment in children. PLoS One. 2010;5:e11225.
29. Cisse B, Cairns M, Faye E, NDiaye O, Faye B, Cames C, et al. Randomized trial of piperaquine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children. PLoS One. 2009;4:e7164.
30. Kamya MR, Kapisi J, Bigira V, Clark TD, Kinara S, Mwangwa F, et al. Efficacy and safety of three regimens for the prevention of malaria in young HIV-exposed Ugandan children: a randomized controlled trial. AIDS. 2014;28:2701–9.
31. Zongo I, Milligan P, Compaore YD, Some AF, Greenwood B, Tarning J, et al. Randomized noninferiority trial of dihydroartemisinin-piperaquine compared with sulfadoxine-pyrimethamine plus amodiaquine for seasonal malaria chemoprevention in Burkina Faso. Antimicrob Agents Chemother. 2015;59:4387–96.
32. Nankabirwa JI, Wandera B, Amuge P, Kiwanuka N, Dorsey G, Rosenthal PJ, et al. Impact of intermittent preventive treatment with dihydroartemisinin-piperaquine on malaria in Ugandan schoolchildren: a randomized, placebo-controlled trial. Clin Infect Dis. 2014;58:1404–12.
33. Lwin KM, Phyo AP, Tarning J, Hanpithakpong W, Ashley EA, Lee SJ, et al. Randomized, double-blind, placebo-controlled trial of monthly versus bimonthly dihydroartemisinin-piperaquine chemoprevention in adults at high risk of malaria. Antimicrob Agents Chemother. 2012;56:1571–7.

34. Desai M, Gutman J, L'Ianziva A, Otieno K, Juma E, Kariuki S, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. Lancet. 2015;386:2507–19.
35. Kakuru A, Jagannathan P, Muhindo MK, Natureeba P, Awori P, Nakalembe M, et al. Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. N Engl J Med. 2016;374:928–39.
36. Wanzira H, Kakuru A, Arinaitwe E, Bigira V, Muhindo MK, Conrad M, et al. Longitudinal outcomes in a cohort of Ugandan children randomized to artemether-lumefantrine versus dihydroartemisinin-piperaquine for the treatment of malaria. Clin Infect Dis. 2014;59:509–16.
37. Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Sugiarto P, Tjitra E, et al. Dihydroartemisinin-piperaquine treatment of multidrug resistant falciparum and vivax malaria in pregnancy. PLoS One. 2014;9:e84976.
38. The use of the WHO-UMC system for standardised case causality assessment. Uppsala: Uppsala Monitoring Centre; 2012.
39. Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev. 2014;CD010927.
40. Ramsay AR, Msaki EP, Kennedy N, Ngowi FI, Gillespie SH. Evaluation of the safety and efficacy of micronized halofantrine in the treatment of semi-immune patients with acute, Plasmodium falciparum malaria. Ann Trop Med Parasitol. 1996;90:461–6.
41. Nhama A, Bassat Q, Enosse S, Nhacolo A, Mutemba R, Carvalho E, et al. In vivo efficacy of artemether-lumefantrine and artesunate-amodiaquine for the treatment of uncomplicated falciparum malaria in children: a multisite, open-label, two-cohort, clinical trial in Mozambique. Malar J. 2014;13:309.
42. Bassat Q, Mulenga M, Tinto H, Piola P, Borrmann S, Menéndez C, et al. Dihydroartemisinin-piperaquine and artemether-lumefantrine for treating uncomplicated malaria in African children: a randomised, non-inferiority trial. PLoS One. 2009;4:e7871.
43. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:385–96.
44. Théophile H, Arimone Y, Miremont-Salamé G, Moore N, Fourrier-Réglat A, Haramburu F, et al. Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre. Drug Saf. 2010;33:1045–54.
45. Krishna S, ter Kuile F, Supanaranond W, Pukrittayakamee S, Teja-Isavadharm P, Kyle D, et al. Pharmacokinetics, efficacy and toxicity of parenteral halofantrine in uncomplicated malaria. Br J Clin Pharmacol. 1993;36:585–91.
46. Green JA, Mohamed K, Goyal N, Bouhired S, Hussaini A, Jones SW, et al. Pharmacokinetic interactions between tafenoquine and dihydroartemisinin-piperaquine or artemether-lumefantrine in healthy adult subjects. Antimicrob Agents Chemother. 2016;60:7321–32.
47. Wesche DL, Schuster BG, Wang WX, Woosley RL. Mechanism of cardiotoxicity of halofantrine. Clin Pharmacol Ther. 2000;67:521–9.

48. Abernethy DR, Wesche DL, Barbey JT, Ohrt C, Mohanty S, Pezzullo JT, et al. Stereoselective halofantrine disposition and effect: concentration-related QTc prolongation. Br J Clin Pharmacol. 2001;51:231–7.
49. Milton KA, Edwards G, Ward SA, Orme ML, Breckenridge AM. Pharmacokinetics of halofantrine in man: effects of food and dose size. Br J Clin Pharmacol. 1989;28:71–7.
50. Khoo SM, Edwards GA, Porter CJ, Charman WN. A conscious dog model for assessing the absorption, enterocyte-based metabolism, and intestinal lymphatic transport of halofantrine. J Pharm Sci. 2001;90:1599–607.
51. Traebert M, Dumotier B, Meister L, Hoffmann P, Dominguez-Estevez M, Suter W. Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells. Eur J Pharmacol. 2004;484:41–8.
52. Bindschedler M, Lefevre G, Degen P, Sioufi A. Comparison of the cardiac effects of the antimalarials co-artemether and halofantrine in healthy participants. Am J Trop Med Hyg. 2002;66:293–8.
53. van Agtmael M, Bouchaud O, Malvy D, Delmont J, Danis M, Barette S, et al. The comparative efficacy and tolerability of CGP 56697 (artemether + lumefantrine) versus halofantrine in the treatment of uncomplicated falciparum malaria in travellers returning from the Tropics to The Netherlands and France. Int J Antimicrob Agents. 1999;12:159–69.
54. Borsini F, Crumb W, Pace S, Ubben D, Wible B, Yan GX, et al. In vitro cardiovascular effects of dihydroartemisin-piperaquine combination compared with other antimalarials. Antimicrob Agents Chemother. 2012;56:3261–70.
55. Darpo B, Ferber G, Siegl P, Laurijssens B, Macintyre F, Toovey S, et al. Evaluation of the QT effect of a combination of piperaquine and a novel anti-malarial drug candidate OZ439, for the treatment of uncomplicated malaria. Br J Clin Pharmacol. 2015;80:706–15.
56. Maude RJ, Plewes K, Faiz MA, Hanson J, Charunwatthana P, Lee SJ, et al. Does artesunate prolong the electrocardiograph QT interval in patients with severe malaria? Am J Trop Med Hyg. 2009;80:126–32.
57. Siqueira AM, Alencar AC, Melo GC, Magalhaes BL, Machado K, Alencar Filho AC, et al. Fixed-dose artesunate-amodiaquine combination vs chloroquine for treatment of uncomplicated blood stage P. vivax infection in the Brazilian Amazon: an open-label randomized, controlled trial. Clin Infect Dis. 2017;64:166–74.
58. Hanboonkunupakarn B, Ashley EA, Jittamala P, Tarning J, Pukrittayakamee S, Hanpithakpong W, et al. Open-label crossover study of primaquine and dihydroartemisinin-piperaquine pharmacokinetics in healthy adult thai subjects. Antimicrob Agents Chemother. 2014;58:7340–6.
59. Jittamala P, Pukrittayakamee S, Ashley EA, Nosten F, Hanboonkunupakarn B, Lee SJ, et al. Pharmacokinetic interactions between primaquine and pyronaridine-artesunate in healthy adult Thai subjects. Antimicrob Agents Chemother. 2015;59:505–13.
60. Pukrittayakamee S, Tarning J, Jittamala P, Charunwatthana P, Lawpoolsri S, Lee SJ, et al. Pharmacokinetic interactions between primaquine and chloroquine. Antimicrob Agents Chemother. 2014;58:3354–9.
61. Ashley EA, Stepniewska K, Lindegardh N, Annerberg A, Tarning J, McGready R, et al. Comparison of plasma, venous and capillary blood levels of piperaquine in patients with uncomplicated falciparum malaria. Eur J Clin Pharmacol. 2010;66:705–12.
62. Uppsala Monitoring Centre. Glossary of terms used in pharmacovigilance; 2011.
63. Kajubi R, Huang L, Jagannathan P, Chamankhah N, Were M, Ruel T, et al. Antiretroviral therapy with efavirenz accentuates pregnancy-associated reduction of

dihydroartemisinin-piperaquine exposure during malaria chemoprevention. Clin Pharmacol Ther. 2017. doi:10.1002/cpt.664.

The cardiotoxicity of antimalarials

Report of the WHO Evidence Review Group Meeting on 13-14 October 2016

Malaria Policy Advisory Committee (MPAC) Meeting

22-24 March 2017, World Health Organization, Geneva, Switzerland

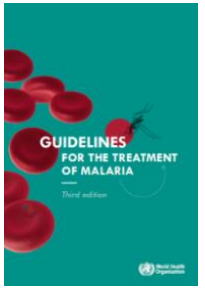
Global **Malaria** Programme

World Health Organization

Presentation Outline

- Malaria treatment, preventive therapy and MDA
- WHO plans to review the cardiotoxicity of antimalarials
- List of studies included in the review
- Panel members, participants, observers & secretariat
- Process for review by ERG, MPAC and ASCoMP
- Summary of findings and proposed recommendations

The benefits of antimalarial medicines



Case management

- The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. The public health objectives of treatment are to reduce onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

Preventive therapy

- The administration of full treatment courses to vulnerable groups to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk. Current WHO-recommended malaria preventive therapies are IPTp, IPTi and SMC.

Mass drug administration

- The coordinated administration of full treatment courses to as much of the at-risk population as possible to clear infections from asymptomatic individuals, to reduce onward transmission and to prevent re-infection during periods of post-treatment prophylaxis.

Recent 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.

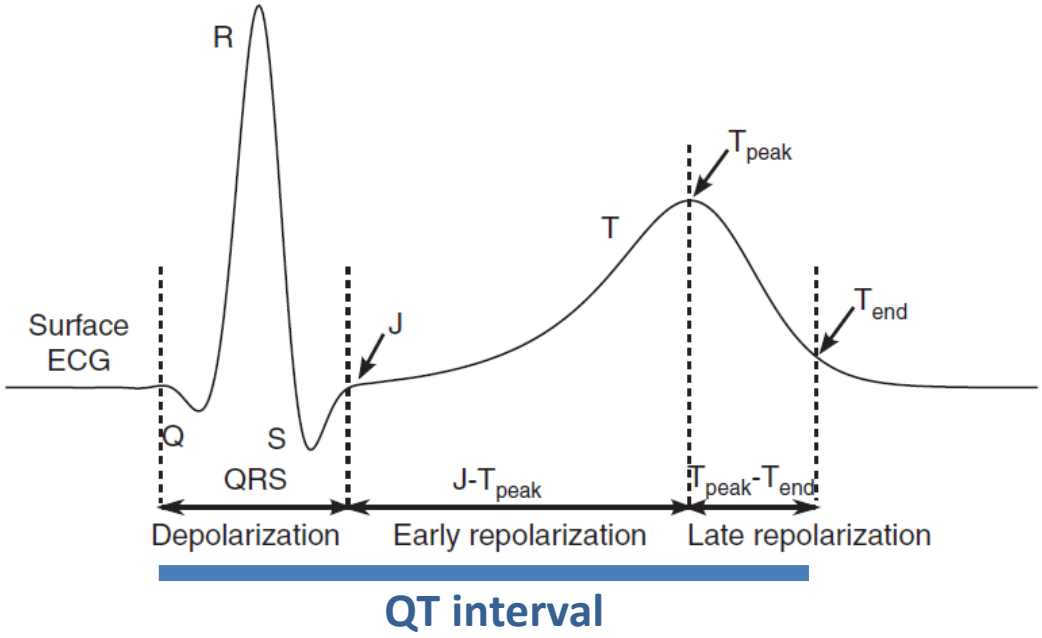
2. Use of time-limited MDA to reduce malaria morbidity and mortality rapidly may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions, as well as in complex emergencies during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.

Cardiovascular side effects of antimalarials

Quinoline antimalarials and structurally-related compounds have long been associated with cardiovascular side effects:

- Exacerbation of malaria-related orthostatic hypotension, e.g., quinine, chloroquine, mefloquine;
- Acute hypotension with rapid parenteral injection, e.g., chloroquine, quinine, quinidine;
- Sinus bradycardia, e.g., mefloquine;
- QRS complex widening, e.g., quinidine, quinine, chloroquine;
- QT interval prolongation, e.g., halofantrine, quinidine, quinine, chloroquine, amodiaquine, piperaquine.

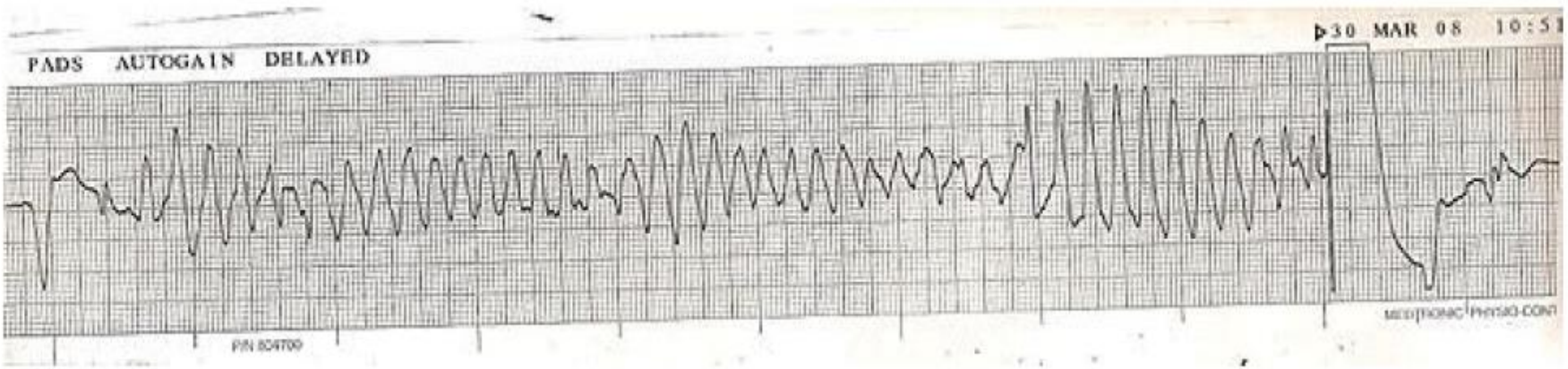
QT prolongation and cardiotoxicity



The **QT interval** represents the ventricular action potential, i.e. the interval between ventricular depolarization and repolarization. QT prolongation increases vulnerability to premature action potentials during the late phase of repolarization which may trigger torsade de pointes (TdP).

- A prolonged corrected QT interval (QTc) is a sensitive but not specific indicator of increased risk of torsade de pointes (TdP), a polymorphic ventricular tachycardia that can degenerate in some cases to ventricular fibrillation and lead to sudden cardiac death. Drugs which prolong the QT interval are variably associated with life-threatening ventricular tachyarrhythmias in a small proportion of patients.

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 QT interval prolongation

Experience with both QT/QTc interval-prolonging medicines and the congenital long QT syndrome suggests:

- A QT/QTc interval >500ms is associated with a higher risk of TdP and sudden cardiac death;
- Among drugs with QT/QTc interval-prolonging potential, antiarrhythmics have been associated with TdP in 1–5% of exposed subjects, while non-cardiovascular drugs have been associated with much lower risk, e.g., one in 100,000 for moxifloxacin;
- TdP degenerates into ventricular fibrillation in ~10% of cases.
- Apart from drug-induced QT interval prolongation, several risk factors decrease the repolarization reserve and facilitate the development of arrhythmias in individual patients

Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk.

Antimalarials and QTc prolongation

- Quinoline antimalarials and structurally-related compounds have been associated with cardiovascular side effects. Antimalarial medicines that prolong the QT interval include **quinine, chloroquine, amodiaquine, mefloquine, lumefantrine** and **piperaquine**. All are recommended currently by WHO for malaria treatment (alone or in fixed-dose combinations with artemisinin derivatives).
- **Quinidine** is associated with significant cardiotoxicity and is recommended for the treatment of severe malaria with careful clinical and ECG monitoring only if no other antimalarials are available.
- **Halofantrine** induces marked QT interval prolongation, has been associated with over 30 reports of sudden cardiac death and has never been recommended by WHO for treatment of malaria.

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 to plan a review of the cardiotoxicity of antimalarials.
- The experts recommended that WHO analyses 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 also possible exposure to concomitant medicines which prolong the QTc interval. There was consensus not to include drug associated "syncope" to avoid many confounders.
- ERG plans were presented to the WHO Advisory Committee on Safety of Medicinal Products and to the Malaria Policy Advisory Committee.

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, MDA, WWARN, Pharma)
- Examine PK/PD studies of the main ACTs to evaluate the dose-response effect and risk factors for QTc interval prolongation
- Evaluate comparative clinical trials of dihydroartemisinin-piperaquine and other piperaquine-containing combination antimalarials to characterise PK/PD relationships for piperaquine in healthy volunteers compared to malaria patients
- Identify evidence sources and gaps, and provide recommendations for additional studies to inform risk assessments

Evidence compiled for the ERG

	Evidence		Summary
1	Vigibase global individual case safety report database analyses	1.	Sudden unexplained death or TdP/QT prolongation following any antimalarial
		2.	Adverse drug reactions associated with **halofantrine**
		3.	Adverse drug reactions associated with **DHA-piperaquine**
2	LSTM antimalarial safety database report	Sudden death, TdP/QT prolongation or arrhythmia adverse events following antimalarial drug therapy in ACT Consortium and Malaria in Pregnancy (MiP) Consortium studies	
3	Literature reviews	1.	Cardiotoxicity of antimalarial drugs
		2.	Deaths following antimalarial drug treatment in uncomplicated malaria
		3.	Effectiveness and safety of **DHA-piperaquine** in treatment of uncomplicated malaria
4	Pooled analyses and meta-analyses	1.	Sudden deaths following mass drug administration (MDA) of antimalarial drugs
		2.	Systematic review and meta-analysis of safety, tolerability, and efficacy of repeated doses of **DHA-piperaquine** with focus on IPT
		3.	Pooled analysis of QT effect of antimalarial drugs in contributed clinical studies
		4.	Pooled analysis of QT effect of antimalarial drugs in Cardiabase-supported studies
5	IPT collaborations contributing individual patient data and analysis reports including PK/PD	1.	STOPMIP IPT with **DHA-piperaquine** in pregnant women in Indonesia
		2.	PROMOTE IPT with **DHA-piperaquine** in infants as well as pregnant and post-partum women with and without HIV in Uganda
		3.	START-IPT with **DHA-piperaquine** in schoolchildren in Uganda

Evidence compiled for ERG (cont'd)

	Evidence		Summary
6	Research networks contributing individual patient data	1.	MORU, SMRU, and OUCRU studies on **quinine, chloroquine, halofantrine, mefloquine, artesunate-mefloquine, artemether-lumefantrine,** and **DHA-piperaquine**
		2.	INESS phase 4 prospective observational study to evaluate safety of **DHA-piperaquine** in public health facilities in East, West, and Southern Africa
		3.	WANECAM phase 3b/4 randomised trial on **pyronaridine-artesunate** versus **DHA-piperaquine** versus **artesunate-amodiaquine** versus **artemether-lumefantrine** for treatment of repeated episodes of uncomplicated malaria in West Africa
7	Product Development Partnerships and Regulators clinical trial data and study reports	1.	MMV phase 1 and phase 2b studies on **OZ439-piperaquine**
		2.	DNDi phase 2b studies on **artesunate-mefloquine** and **artesunate-amodiaquine**
		3.	FDA phase 1 study on **halofantrine**
8	Pharmaceutical companies contributing safety reports and individual patient data	1.	Safety database case reports of sudden deaths after **halofantrine (GSK)**
		2.	Safety overview of **artemether-lumefantrine** based on information from global clinical trials and proprietary safety database reports (**Novartis)**
		3.	Clinical study reports and individual patient data from phase 1 food and phase 4 studies on **artesunate-amodiaquine (Sanofi)**
		4.	Results from phase 1 studies on **ferroquine-artesunate** and **ferroquine-OZ439 (Sanofi)**
		5.	Electrocardiology safety assessment report of **pyronaridine-artesunate** based on information from pre-clinical to phase 3b studies **(Shin Poong)**
		6.	Meta-analysis on clinical use of **piperaquine (Sigma Tau)**
		7.	Safety overview of **DHA-piperaquine** based on information from sponsored clinical trials and proprietary safety database case reports **(Sigma Tau)**
		8.	Pre-clinical study on TdP risk of **DHA-piperaquine** versus other **antimalarial drugs (Sigma Tau)**
		9.	Clinical study reports and individual patient data from phase 1 food, phase 2, and phase 3 studies of **DHA-piperaquine (Sigma Tau)**

Evidence compiled for ERG (cont'd)

	Evidence	Summary
9	PK/PD analyses of individual studies	Analyses of drug exposure-QT relationship and effects of covariates in selected contributed clinical studies on **chloroquine** and **dihydroartemisinin-piperaquine**
10	Piperaquine study group analysis plan	Proposal to assess the relationship between piperaquine exposure and 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,

List of participants

Panel Members

- Karen BARNES
- Josep BRUGADA (Co-chair)
- Xin Hui CHAN (Rapporteur)
- Albertino DAMASCENO
- Milou-Daniel DRICI
- Nilima KSHIRSAGAR
- Peter KREMSNER
- Eugène van PUIJENBROEK
- Nicholas WHITE (Co-chair)

Participants

- Rita BAIDEN
- Pras JAGANNATHAN
- Eva Maria HODEL
- Yasmin KHAN
- Feiko ter KUILE
- Clement NARH
- Issaka SAGARA
- Joel TARNING
- Anja TERLOUW
- Pascal VOIRIOT
- David WESCHE

List of participants (cont'd)

Observers

Representatives of:

- MMV (Stephan DUPARC)
- Novartis (Cornelis WINNIPS)
- Sanofi (Marie-José CABANIS & Rita MERINO)
- Shing Poon (Robert M. MILLER & Jangsik SHIN)
- Sigma Tau (Marco CORSI & Giovanni VALENTINI)
- Sun Pharma (Victoria BODEA)
- WWARN (Philippe GUERIN)

WHO Secretariat

- Pedro ALONSO
- Andrea BOSMAN
- Noha IESSA
- Piero OLLIARO (partial)
- Peter OLUMESE
- Shanthi PAL
- Pascal RINGWALD (apologies)
- Marian WARSAME (partial)

Outline agenda

DAY 1 – Plenary sessions

- Pre-clinical and clinical basis for drug-induced QT prolongation
- Review of Antimalarial Cardiotoxicity
- Sudden Death in Antimalarial Therapy
  - WHO ICSR database, MDA operations, DP repeated doses review, case management review
- Studies of Antimalarial effects on the ECG
  - Halofantrine, Artemether-lumefantrine, Artesunate-amodiaquine, Artesunate-pyronaridine, OZ439/Ferroquine, Dihydroartemisinin-piperaquine

Outline agenda (cont'd)

DAY 2 morning – Plenary session

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

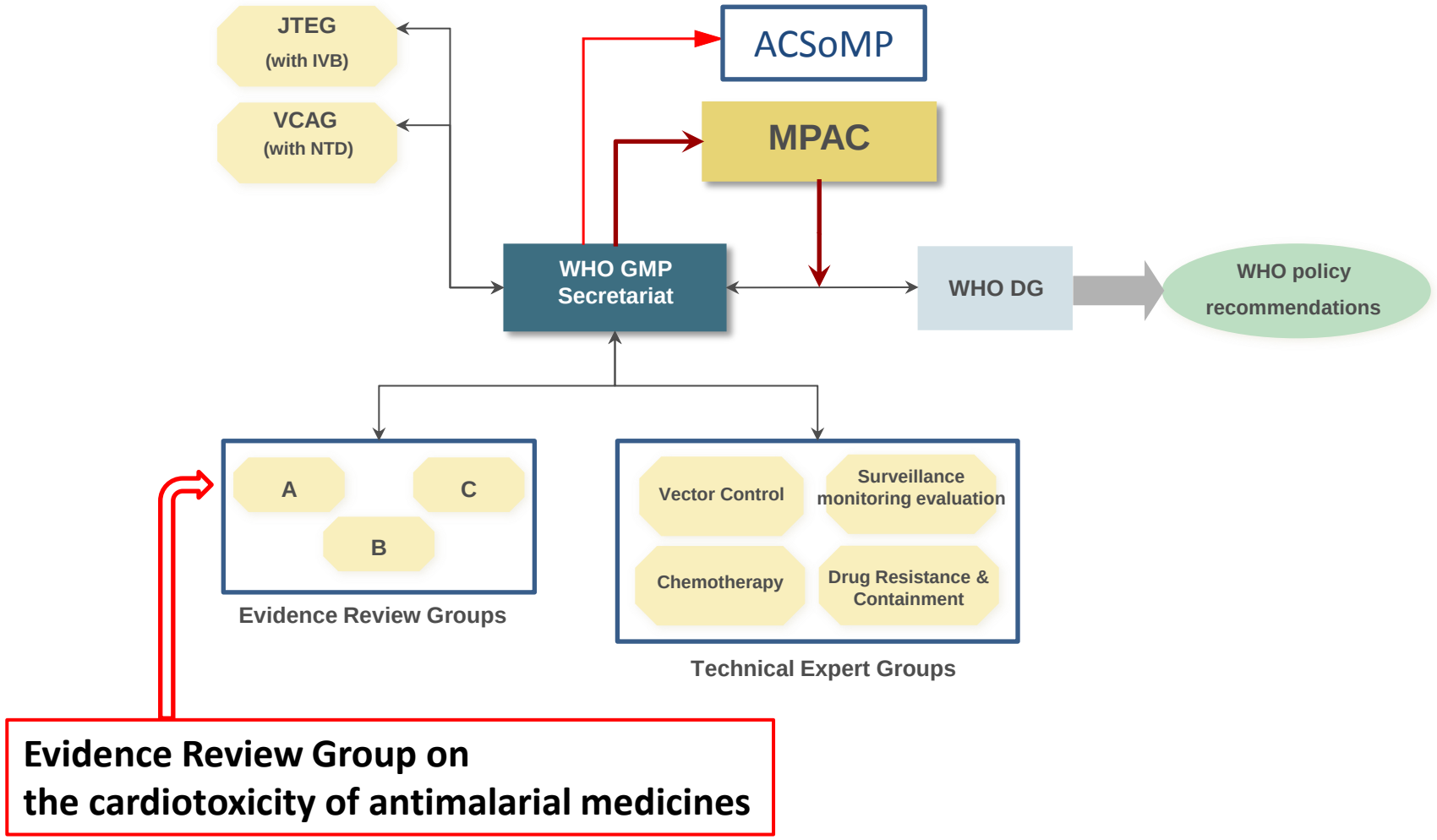
DAY 2 afternoon – Closed session for ERG Panel and WHO

- Development of draft recommendations

Questions for the ERG panel

1. What is the frequency of sudden death attributable to the cardiotoxicity of different antimalarial medicines ?
2. What is the frequency of life-threatening ventricular tachyarrhythmias and torsade de pointes (TdP) after treatment with antimalarials which prolong the QT interval?
3. Which factors increase the frequency of life-threatening ventricular tachy-arrhythmias after exposure to antimalarial medicines which induce QT prolongation?
4. Which strategies for malaria treatment (including preventive) can reduce the risk of life-threatening ventricular tachyarrhythmias after exposure to antimalarial medicines which induce QT prolongation?
5. Is the risk of cardiotoxicity after exposure to piperaquine containing medicines higher than that of chloroquine?
6. Is the risk of cardiotoxicity of piperaquine containing medicines higher in healthy volunteers compared to malaria patients?
7. What evidence sources and gaps can be identified, and what additional studies are recommended to inform the risk assessment for antimalarial cardiotoxicity?

WHO policy making process for malaria



Summary of findings and proposed recommendations

Questions for the ERG panel

1. What is the frequency of sudden death attributable to the cardiotoxicity of different antimalarial medicines ?
   - **Halofantrine** has been associated with >30 sudden deaths attributed to cardiotoxicity, considered an unacceptable risk.
   - **Dihydroartemisinin-piperaquine** and **artemether-lumefantrine** have been the most extensively studied antimalarial drugs. There have been no sudden deaths attributed to cardiotoxicity following artemether-lumefantrine. One possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported among ~200 000 individuals with close follow-up after treatment - consistent with risk of fatal cardiotoxicity associated with QT/QTc interval-prolonging medicines in current use.
   - Reported deaths following **chloroquine** and **hydroxychloroquine** have been associated with overdose or use in chronic indications other than the treatment of malaria.

Sudden unexplained deaths after DHA-PPQ

Study type	Subjects	Courses	Doses	Sudden unexplained deaths	Source(s)
MDA	154 762	~428 929	1 179 523	1*	Table 2
IPT & non-MDA repeated courses	14 014	~28 376	~85 128	0	Systematic review *(20)* & START-IPT (unpublished)
Case management	25 198	~25 198	~75 594	0	Table 4 & INESS *(21)*
Total	**193 974**	**482 503**	**1 340 245**	**1***	

*In all of these reviews, one sudden unexplained death following MDA was considered to be possibly drug-related.
~Derived from another denominator.

- This analysis suggests that the risk of sudden unexplained death following **DHA-piperaquine** is one in 193,974 individuals treated in studies with confirmed active follow-up over 3 days from starting drug treatment.

Pharmaceutical company safety databases

	Halofantrine (Halfan®)	AL (Coartem®/Riamet®)	DHA-PPQ (Eurartesim®)
Period	1988–October 2016	1998–October 2016	2011–October 2016
Sales figures† (doses)	23.2 million^	>840 million	2.8 million
Sudden unexplained or cardiac deaths	36	0	1

†Pharmaceutical company sales figures represent a proportion of the total sales of these antimalarials, which are mostly sold as generics (with the exception of halofantrine). ^Halfan® sales figures were available only up until 2012, while global safety database information was available to October 2016; the product was discontinued in April 2016, so it is unlikely that up-to-date sales figures would be much higher than those reported here.

- The Sigma Tau safety database yielded three cases of possible serious cardiovascular events following DHA-PPQ. These were reviewed by the ERG panel which considered the first case consistent with vasovagal syncope rather than TdP. The second and third cases were thought unlikely to be causally related to the drug in view of limited absorption in the very brief time from drug administration and after repeated vomiting respectively.

Questions for the ERG panel

2. What is the frequency of life-threatening ventricular tachyarrhythmias and torsade de pointes (TdP) after treatment with antimalarials which prolong the QT interval?
   - **Halofantrine** has been associated with dose- and concentration-dependent QTc interval prolongation at therapeutic doses in healthy volunteers and malaria patients; it has also been associated with conduction abnormalities, TdP, syncope and sudden death.
   - No episodes of TdP or life-threatening ventricular tachyarrhythmias have been documented following **dihydroartemisinin-piperaquine** or **artemether-lumefantrine**.
   - A QT/QTc interval >500ms has been associated with increased risk of TdP and sudden cardiac death. **DHA-piperaquine** has been associated with a QTc interval >500ms in 0.6% of individuals exposed, while **artemether-lumefantrine** has been associated with a QTc interval >500ms in 0.2–0.3% of individuals exposed.

Questions for the ERG panel

3. Which factors increase the frequency of life-threatening ventricular tachyarrhythmias after exposure to antimalarial medicines which induce QT prolongation?

- The general risk factors for TdP should also be considered risk factors for antimalarial medicines that prolong the QT/QTc interval, including:

i) concomitant medications that can induce QT/QTc interval prolongation (see http://crediblemeds.org) or potentiate the effects of QT/QTc interval-prolonging drugs,

ii) structural heart disease,

iii) genetic defects of cardiac ion channels,

iv) electrolyte abnormalities such as hypokalaemia,

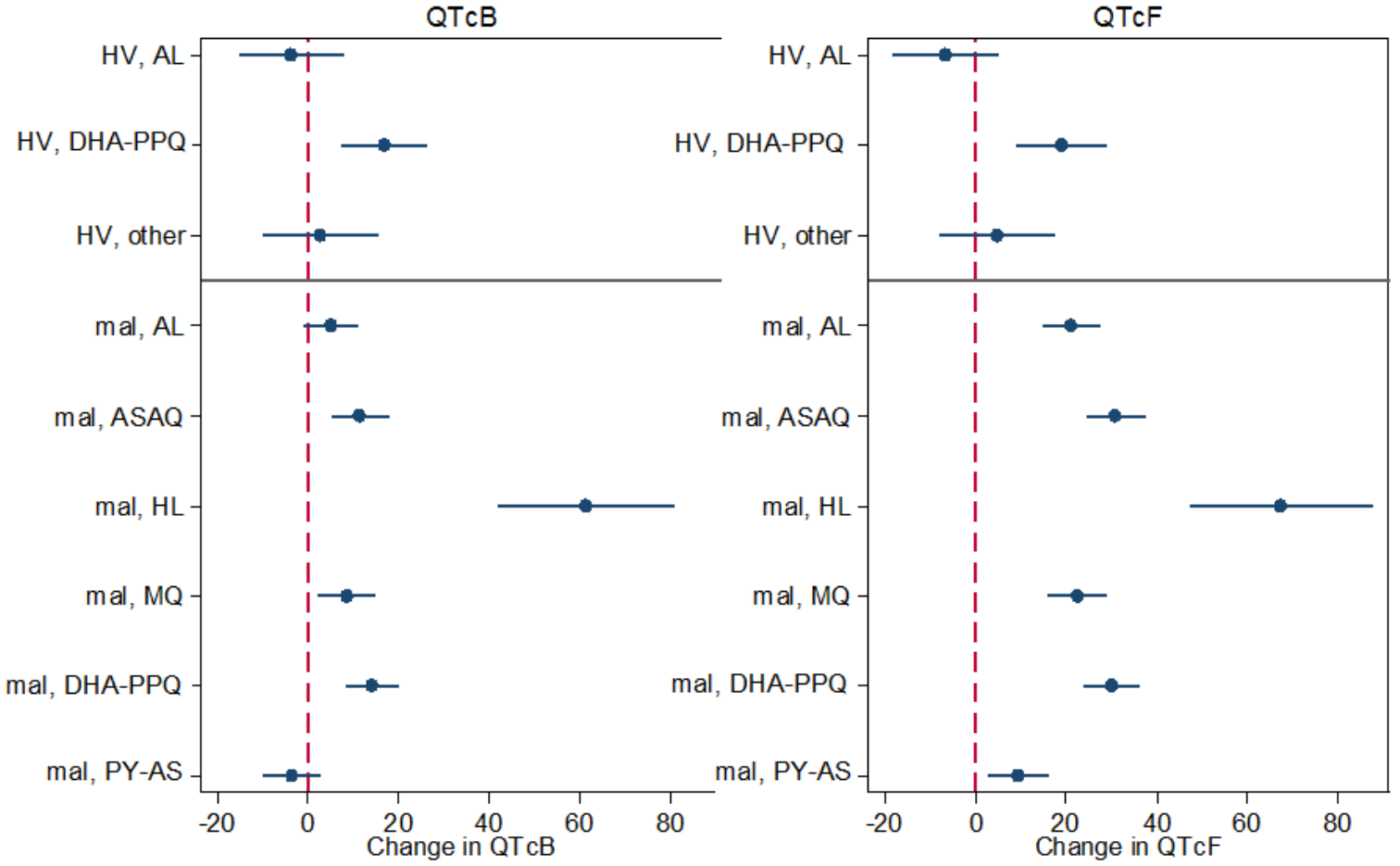
v) bradycardia

vi) hepatic impairment.

Questions for the ERG panel

4. Which strategies for malaria treatment (including preventive) can reduce the risk of life-threatening ventricular tachyarrhythmias after exposure to antimalarial medicines which induce QT prolongation?
    - No data are available to predict the risk of drug-induced TdP and life-threatening tachyarrhythmias in the general population and in specific population subgroups, or to quantify risks for individual antimalarials.
    - In individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmia, or who are already taking medicines that can prolong the QT/QTc interval, antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution. If possible, closer monitoring is advised when giving quinine, chloroquine, artesunate-amodiaquine or dihydroartemisinin-piperaquine to such individuals.

Change in QTc induced by antimalarials



HV = healthy volunteers, mal = patients with uncomplicated malaria.

AL = artemether-lumefantrine, DHA-PPQ = dihydroartemisinin-piperaquine, other = trimethoprim-sulfamethoxazole, ASAQ = artesunate-amodiaquine, HL = halofantrine, MQ = mefloquine / artesunate-mefloquine / artemether-mefloquine, PY-AS = pyronaridine-artesunate.

Effects of antimalarials on the ECG

- **Halofantrine** was associated with the greatest QTc interval prolongation of the antimalarial drugs studied.
- **Chloroquine** has been associated with a larger QTc interval prolongation than DHA-PPQ in healthy volunteers.
- **DHA-PPQ** and **ASAQ** have been associated with comparable degrees of QTc interval prolongation in malaria patients, although more data on amodiaquine are needed.
- QTc interval prolongation associated with **DHA-PPQ** has been found to be similar in both malaria patients and healthy subjects.
- **AL** has been associated with smaller QTc interval prolongation than **DHA-PPQ** in malaria patients and in healthy subjects.
- **Pyronaridine-artesunate** was associated with the smallest QTc interval prolongation of the antimalarials studied.

Questions for the ERG panel

5. Is the risk of cardiotoxicity after exposure to **piperaquine** containing medicines higher than that of **chloroquine**?
   - **No**. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, provides no evidence of a significant difference in the risk of cardiotoxicity following exposure to the currently recommended doses of piperaquine, chloroquine or amodiaquine.
6. Is the risk of cardiotoxicity of **piperaquine** containing medicines higher in healthy volunteers compared to malaria patients?
   - **No.** Review of pharmacovigilance and clinical data, along with preliminary results from PK/PD modelling, provides no evidence of a difference in the risk of cardiotoxicity of piperaquine-containing medicines in healthy volunteers compared to malaria patients.

Questions for the ERG panel

7. What evidence sources and gaps can be identified, and what additional studies are recommended to inform the risk assessment for antimalarial cardiotoxicity

- Exploration of alternative dosing strategies to further minimize the cardiotoxicity risk associated with antimalarial medicines, through field trials and PK/PD modelling, including:
  - Age-based dosing in children
  - Weekly drug administration in MDA
- Identification of genetic polymorphisms and other pre-existing conditions that may contribute to the risk of repolarization-related cardiotoxicity, through:
  - Further investigation of individual outliers in antimalarial drug safety studies
  - Further investigation of special risk groups such as malnourished children
  - Pooling data from potential trial participants with a QTc interval >450ms at screening

Questions for the ERG panel

7. What evidence sources and gaps …. (cont'd)

- Direct comparison of the cardiotoxicity risk of antimalarial drugs in different populations, through:
  - Pooled PK/PD and statistical analyses of individual patient data on QTc interval prolongation
  - Further nested PK/PD studies, especially in populations exposed to MDA
  - Preclinical in vitro and in vivo assays conducted by independent laboratories
  - More evidence is needed with respect to chloroquine, amodiaquine and primaquine.
- Centralization and standardization of the format of reporting adverse events following antimalarial medicines, particularly deaths, in order to improve signal detection for cardiotoxicity, including:
  - Spontaneous reports to international and national pharmacovigilance centres
  - Serious adverse event and loss to follow-up reporting from clinical trials
  - Active pharmacovigilance strategies in populations exposed to MDA
- Harmonization of ECG measurement methodologies in antimalarial cardiotoxicity safety studies.

Conclusions and draft recommendations

1. Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, chloroquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine, have been associated with a low risk of cardiotoxicity.

2. Drug-induced QT/QTc interval prolongation is a surrogate indicator for increased risk of drug-induced torsade de pointes (TdP), a potentially lethal polymorphic ventricular tachycardia. Risk factors for drug-induced QT/QTc prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels. Antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution in individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmias, or who are already taking medicines that can prolong the QT/QTc interval

Conclusions and draft recommendations

3. Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most intensively studied antimalarial drugs. No sudden deaths have been attributed to cardiotoxicity following artemether-lumefantrine. However, among ~200 000 treated individuals with close follow-up, one possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported. This finding is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc-prolonging medicines in current use.

4. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, reveals no evidence of a significant difference in the risks of cardiotoxicity following exposure to piperaquine, chloroquine or amodiaquine at the current recommended doses. The risks of cardiotoxicity of piperaquine-containing medicines are probably similar for healthy volunteers and malaria patients.

Conclusions and draft recommendations

5. Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk. Further studies are needed to identify genetic polymorphisms and other pre-existing conditions that may contribute to the risk of drug-induced cardiotoxicity. More evidence on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine is needed.

Malaria surveillance, monitoring and evaluation manual

Abdisalan M Noor, Team Leader, Surveillance

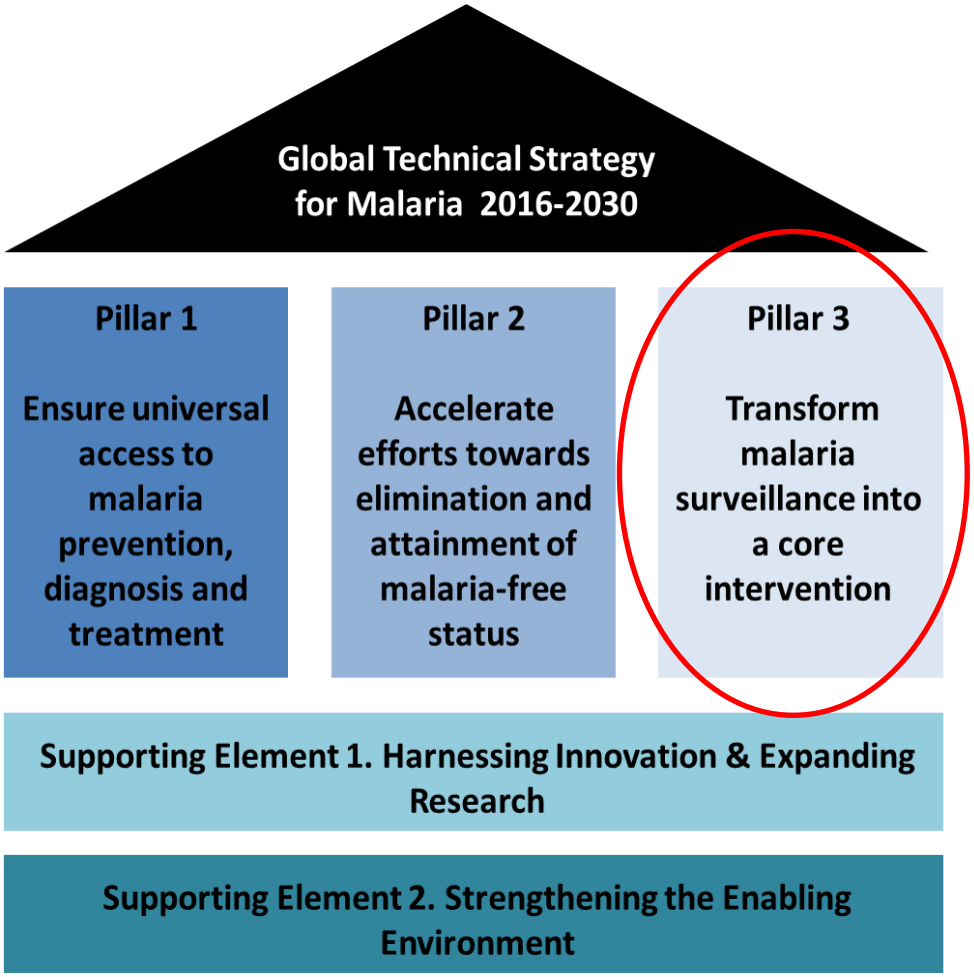
Malaria Policy Advisory Committee (MPAC) meeting

22-24 March 2017, Geneva, Switzerland

Global **Malaria** Programme

World Health Organization

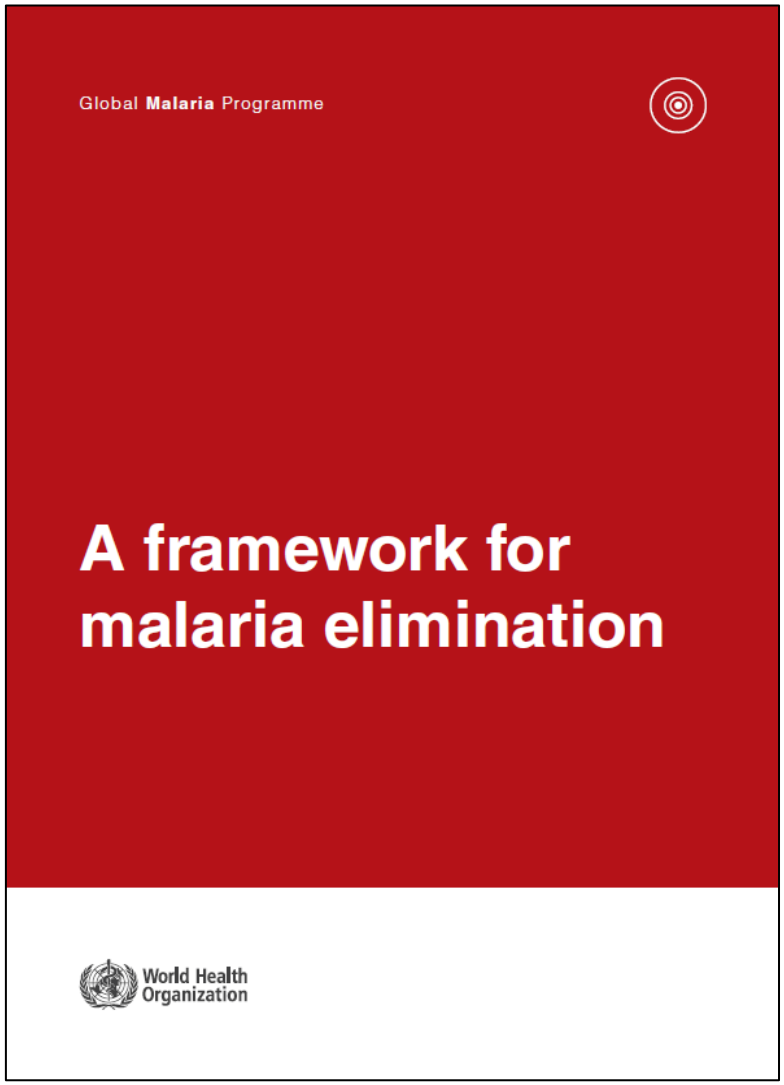
Global Technical Strategy for Malaria 2016-30



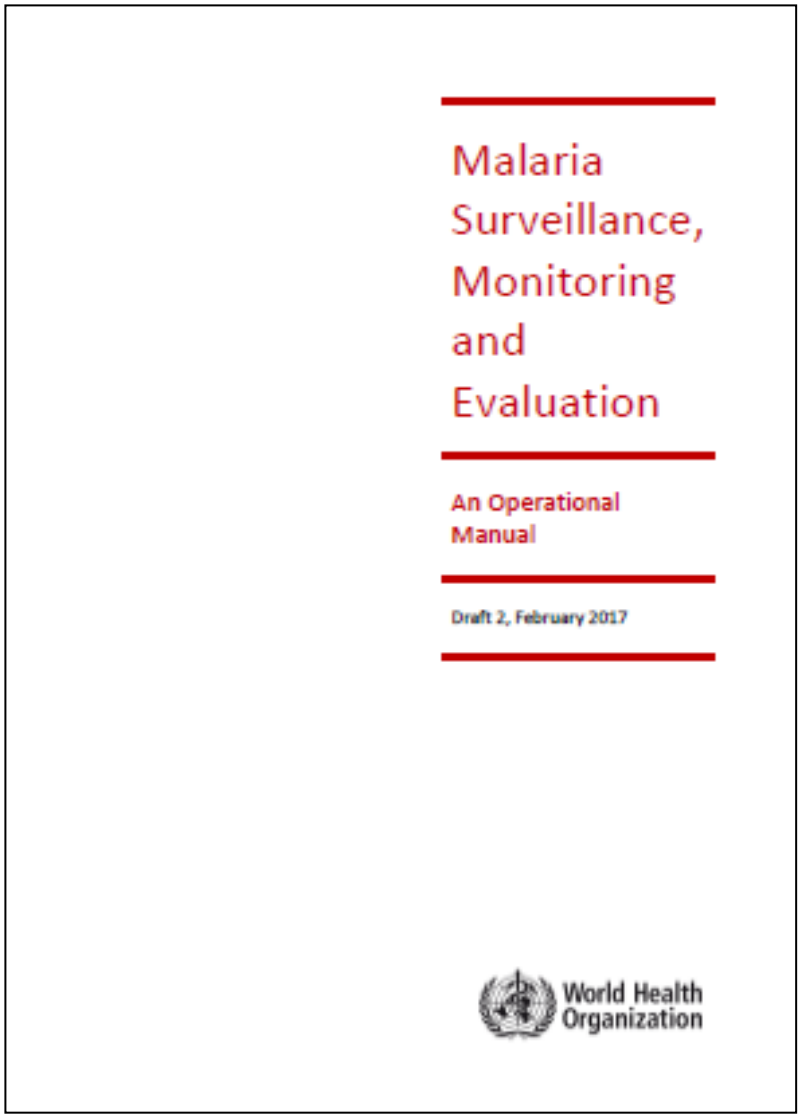
"Irrespective of where countries are on the path to elimination, surveillance of malaria should be upgraded to a core intervention in national and subnational malaria strategies."

Global Technical Strategy for malaria 2016-2030

A framework for malaria elimination



Updated surveillance manual



1. Guidance from MPAC
2. Online approval in June or July 2017

What is new?

- the 2012 Control and Elimination operation manuals are combined into one document
- the revised manual is aligned with both the GTS 2016-2030 and the Elimination Framework 2017
- the case and foci investigation forms will be automated and a section on foci mapping is included

What is new?

- new sections on surveillance in the private and community health sectors and migrant and mobile populations
- monitoring and evaluation of:
  - national programmes
  - the GTS
  - surveillance systems

Chapter 1: Surveillance on the pathway to malaria elimination

Malaria surveillance across the continuum

Pillar 3 of the GTS 2016-2030

Transform Malaria Surveillance into a Core Intervention

	High	Moderate	Low	Very Low	Zero	Maintaining Zero
	≥35% PR or ~450 per 1000 API	10 – 35% PR or 250-450 per 1000 API	1-10% PR or 100-250 per 1000 API	>0 but <1% PR or <100 per 1000 API	No transmission	
Case detection	Passive case detection				Passive + Active case detection	
Recording	Outpatient and inpatient registers				Individual patient forms	
Reporting frequency	Monthly		Weekly		Real Time	
Resolution of reported data	Aggregate case by age, sex		Aggregate or line listing by age, sex		Case reports with case classification	
Data use: health facility	Data analysed and displayed weekly				Data analysed and displayed in real time	
Data use: intermediate levels	Data analysed and displayed monthly		Data analysed and displayed weekly			
Data use: national	Data analysed and displayed monthly or quarterly		Data analysed and displayed monthly		Data analysed and displayed weekly	
Response time	Monthly		Weekly		Case investigation within 48 hours, foci investigation within a week	
Feedback frequency to lower level	Annually	Quarterly	Monthly		Every two weeks	
Surveillance system monitoring	Annually	Quarterly	Monthly		Every two weeks	

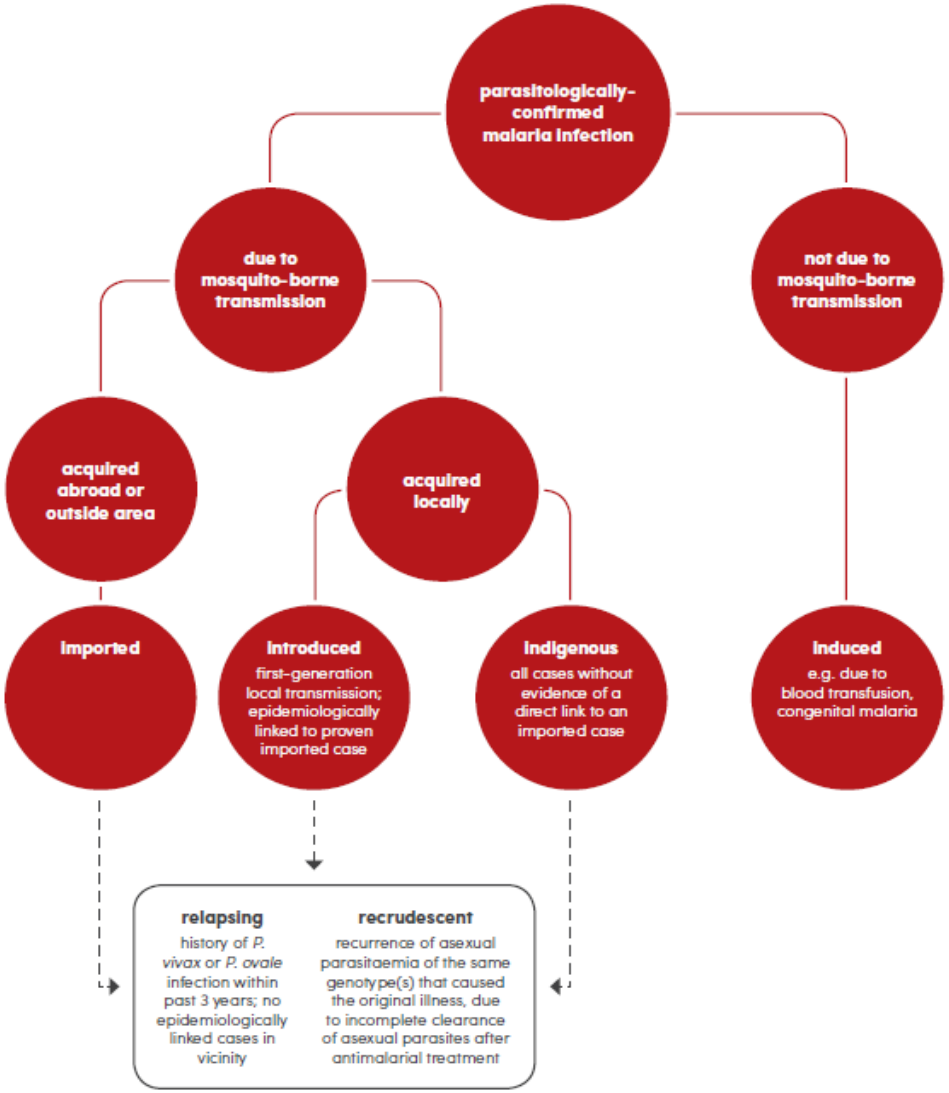
Core principles of malaria surveillance

1. Integration of surveillance systems with HIS
2. Accurate diagnosis of malaria
3. Alignment of SoPs with WHO recommendation & regulation to make malaria notifiable
4. Stratified surveillance for heterogeneous epidemiology
5. Investments in surveillance prior to transition of epidemiology
6. Near real time reporting during elimination
7. Empowerment of frontline staff
8. Linking surveillance to response
9. Surveillance in all sectors (private, community, MMPs etc)
10. Continued efforts post elimination
11. Surveillance and innovation
12. Monitor the surveillance system's performance

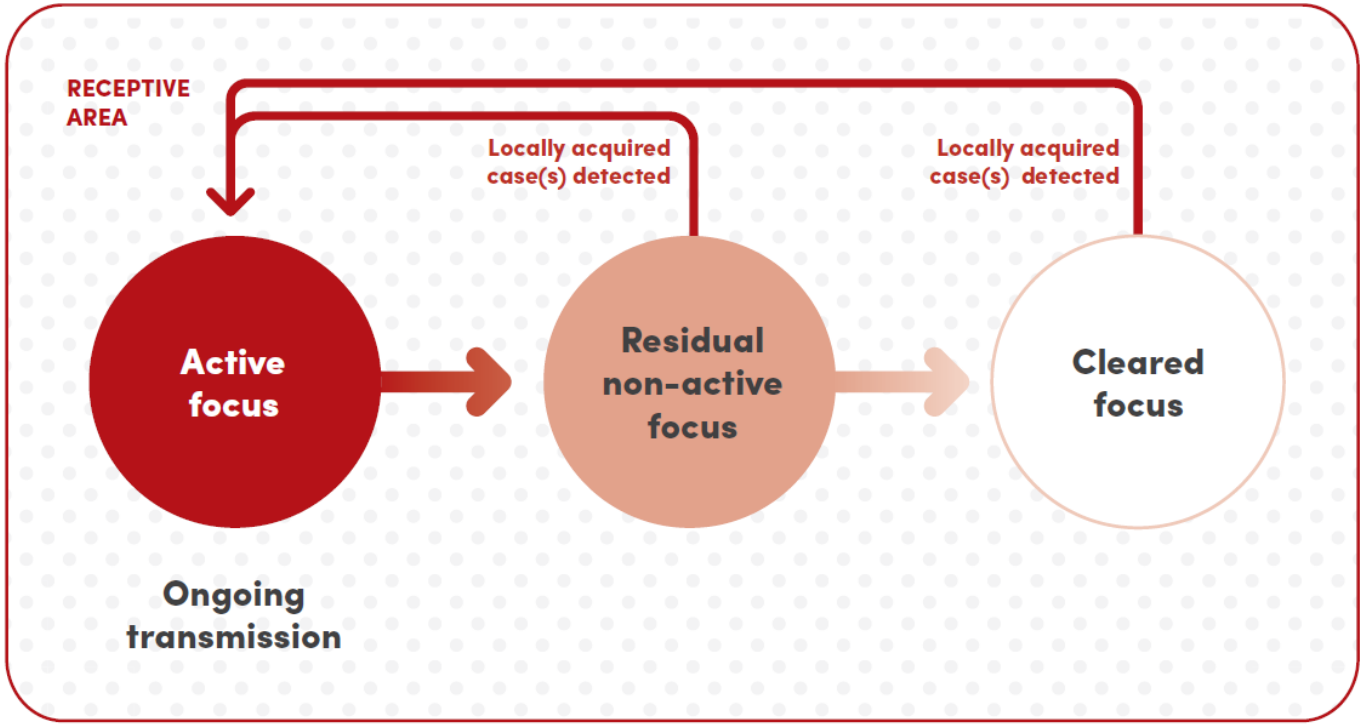
Chapter 2: Concepts and practice of malaria surveillance systems

1. Case definitions
2. Case detection
3. Case investigation
4. Case classification
5. Foci investigation and mapping
6. Foci classification
7. Foci response

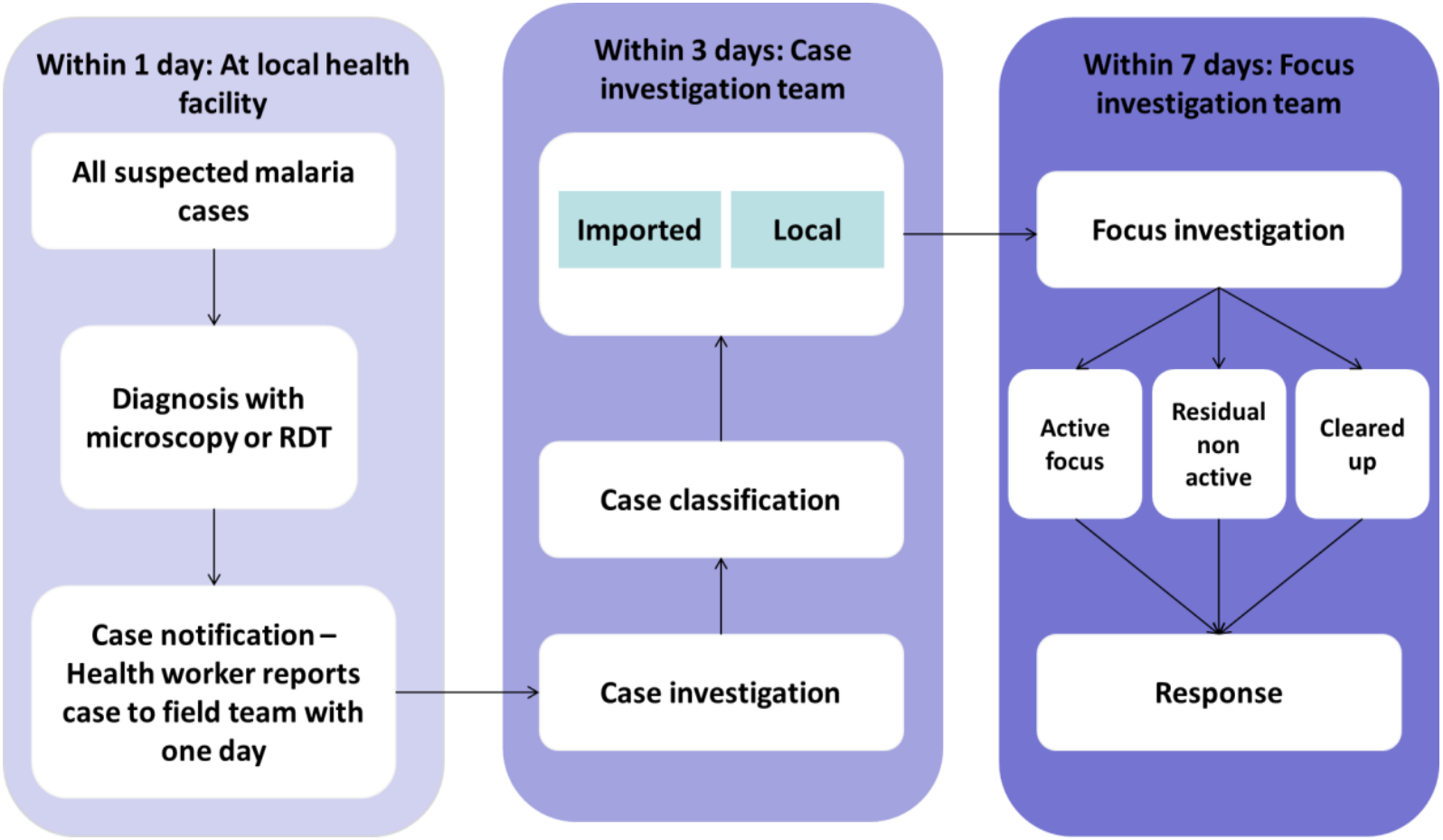
Case classification



Foci classification

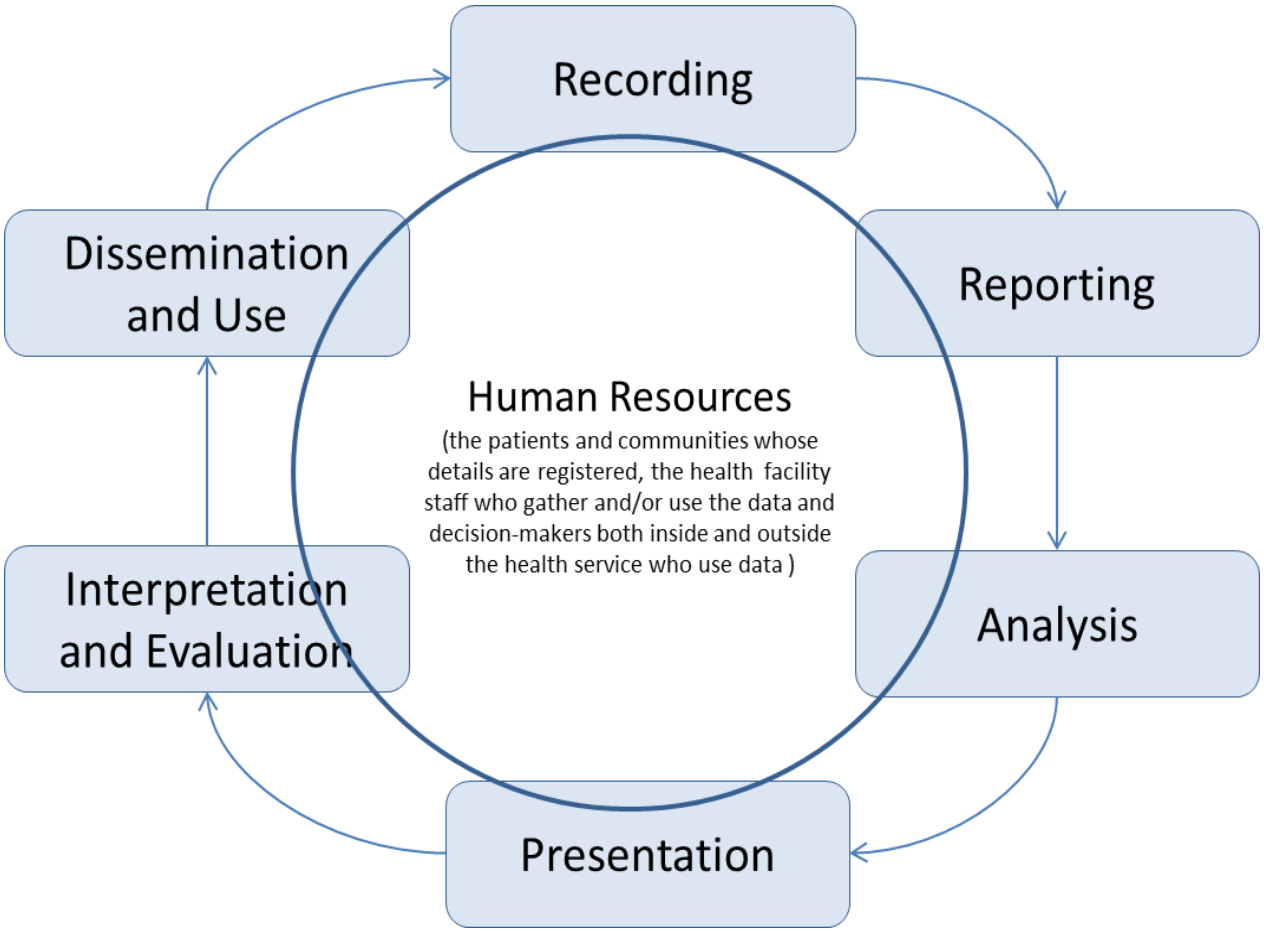


Active case detection process



Chapter 3 Establishing surveillance systems

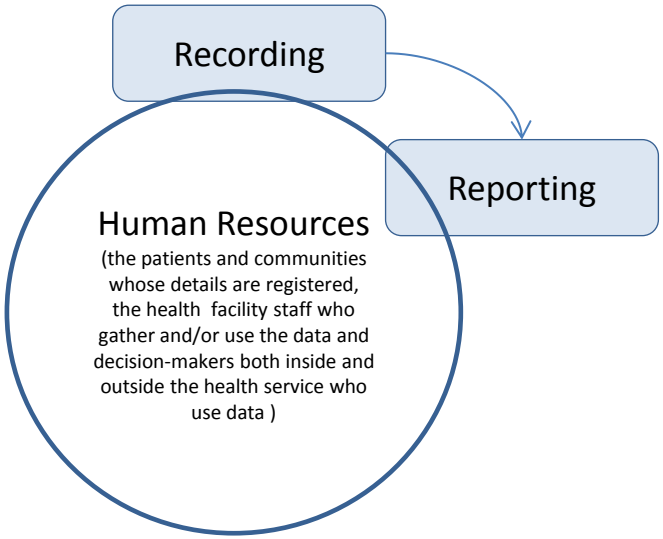
Health information cycle



Health information cycle

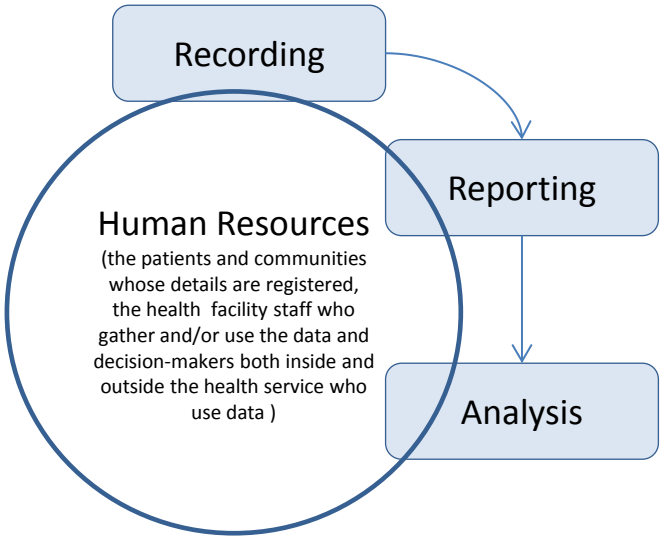
- clearly defined essential indicators
- diagnosis
- system for data recording - Patient and laboratory registers/forms/cards, tally sheets, pens, computers, databases software, printers
- training materials and SoPs

Health information cycle



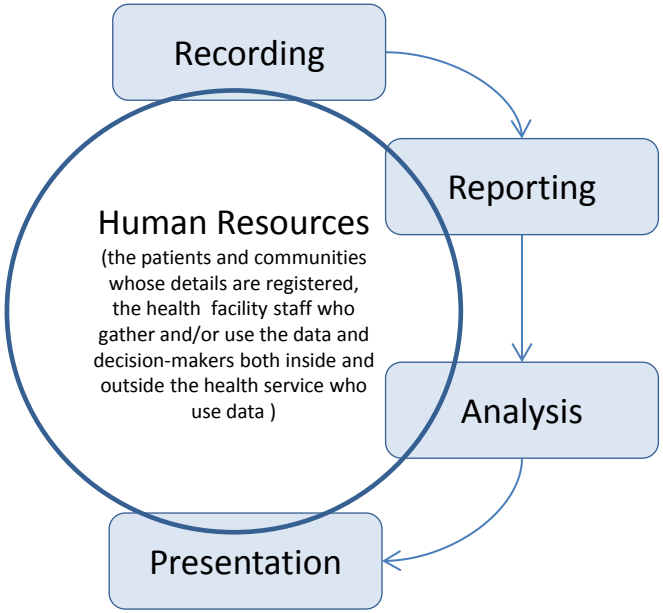
- data compilation
- data quality and completeness verification
- data transmission
- data archiving
- system manuals and SoPs

Health information cycle



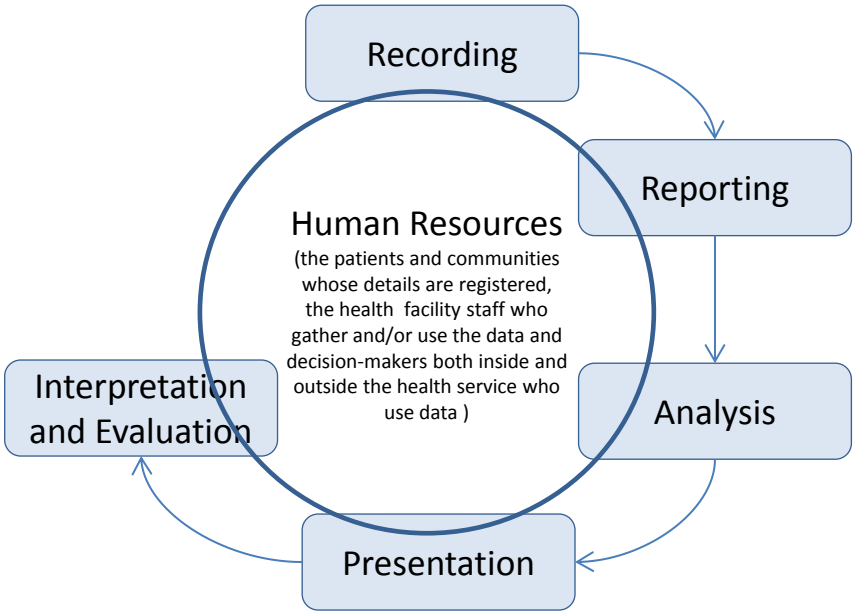
- relevant analytical skills and data quality checks
- hardware and software
- standard analytical plan and expected products – e.g. charts, surveillance bulletin etc.

Health information cycle



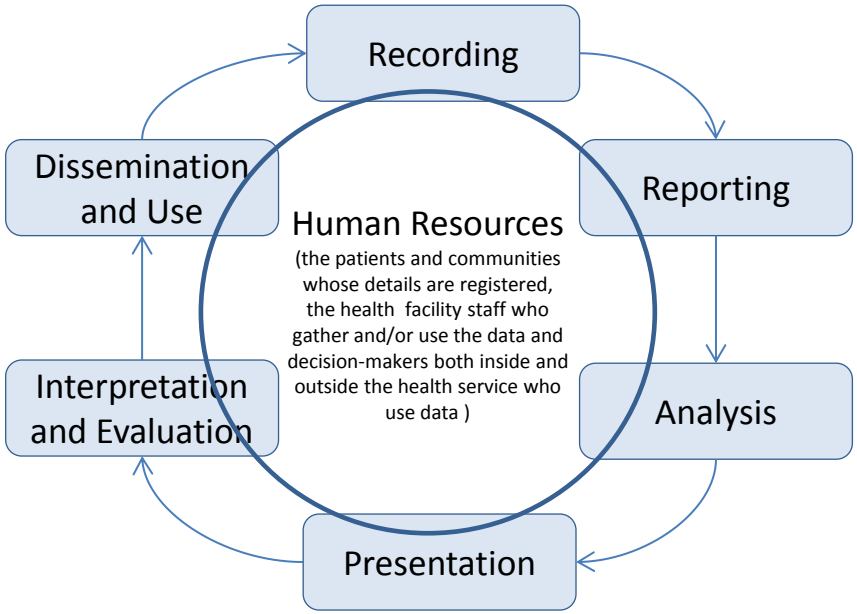
- hardware and software for data display
- agreed format for data presentation targeted different audiences
- communication – meetings etc

Health information cycle



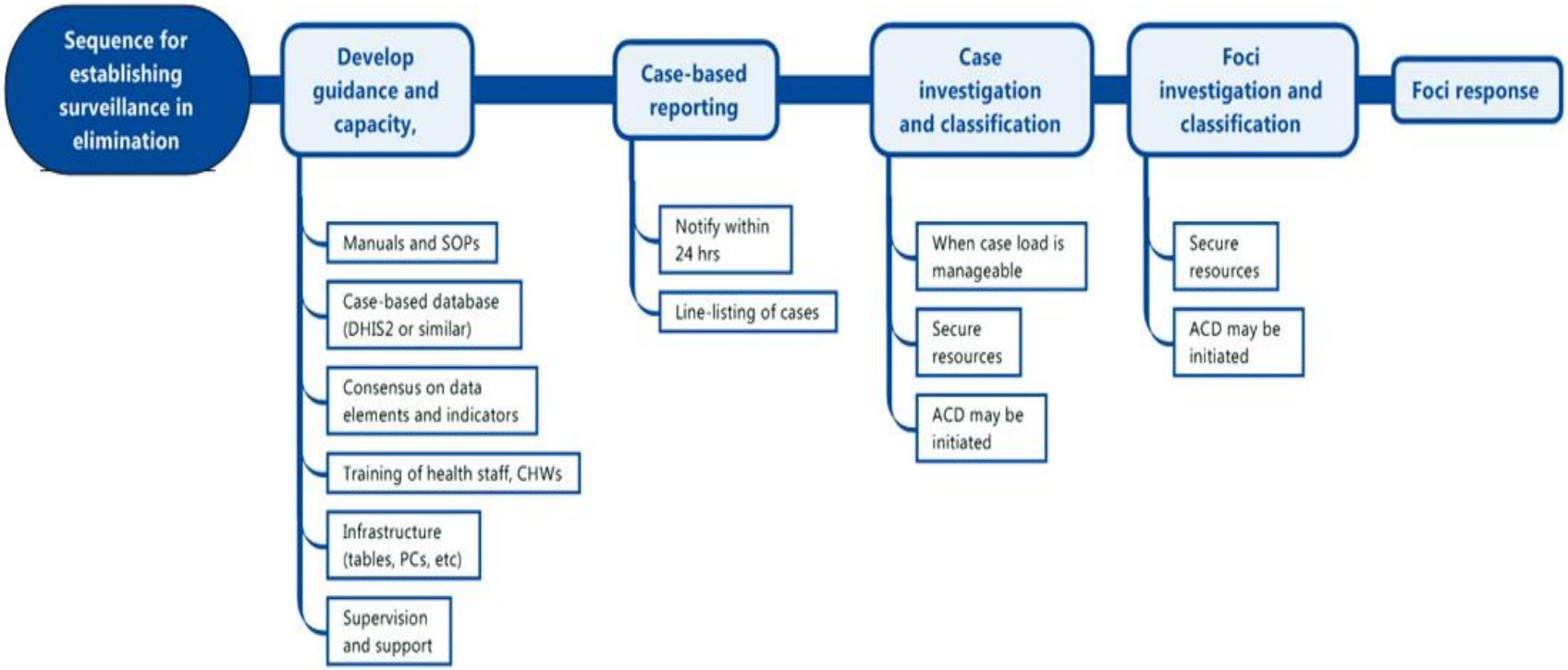
- completeness of data and reporting frequencies
- data quality checks
- system performance and bottlenecks
- performance of staff tasked with managing the system
- assessment of trends of key indicators

Health information cycle



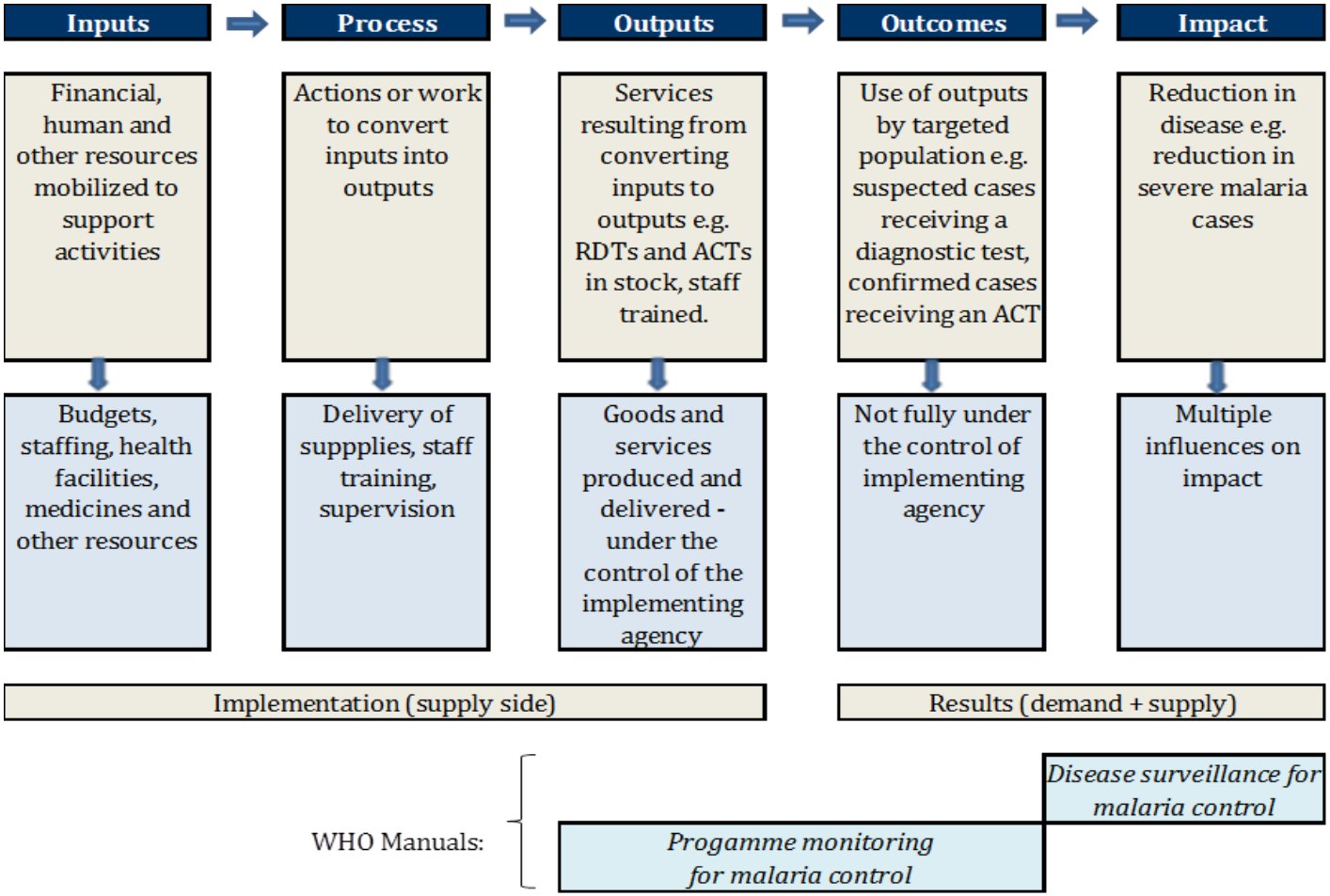
- develop mechanisms of dissemination of data to stakeholders
- use data for decision making at country level
- use data for quantification and forecasting resource needs
- use data to respond to epidemics and other threats
- tracking progress towards elimination
- supervision and feedback

Surveillance for elimination



Chapter 4: Use of surveillance, surveys and other data for monitoring and evaluation of national programmes and the GTS

Monitoring and evaluation process



SME indicators

Indicator		Indicator	Applicability of Indicator: Transmission intensity: High transmission	Transmission intensity: Low transmission	Transmission intensity: Elimination/ prevention of re-establishment	Geography: Sub-Saharan Africa	Geography: Outside sub-Saharan Africa	Level: International	Level: National	Level: Sub-national	Data source: Routine reporting system	Data source: Health facility survey	Data source: Household survey
Inputs													
Financing	1.1	Malaria expenditure per capita for malaria control and elimination	●	●	●	●	●	●	●	●	●		
	1.2	Funding for malaria relevant research	●	●	●	●	●	o	o		●		
	1.3	Number of top-10 registered corporations that invest in malaria	●			●	●		●		●		
Outcome													
Vector control	2.1	Proportion of population at risk sleeping under an insecticide-treated net (ITN) or living in house sprayed by IRS in the previous 12 months	●	o		●	●	●	●		©		©
	2.2	Proportion of population at risk that slept under an ITN the previous night	●	o		●	●	o	●				●
	2.3	Proportion of population with access to an ITN within their household	●	o		●	●	o	●				●
	2.4	Proportion of households with at least one ITN for every two people	●	o		●	●	o	●				●
	2.5	Proportion of households with at least one ITN	●	o		●	●	o	●				●
	2.6	Proportion of available ITNs used the previous night	●	o		●	●	o	●				●
	2.7	Proportion of population at risk potentially covered by ITNs distributed	●	o		●	●		●	●	●		
	2.8	Proportion of targeted risk group receiving ITNs	●	●	●	●	●	o	●	●	●		
	2.9	Proportion of population at risk protected by indoor residual spraying	●	o		●	●	o	●	●	●		
	2.10	Proportion of targeted risk group receiving IRS	●	●	●	●	●		●	●	●		

● Indicator highly relevant to setting o Indicator potentially relevant to setting © Requires data from both routine systems and household survey

SME indicators

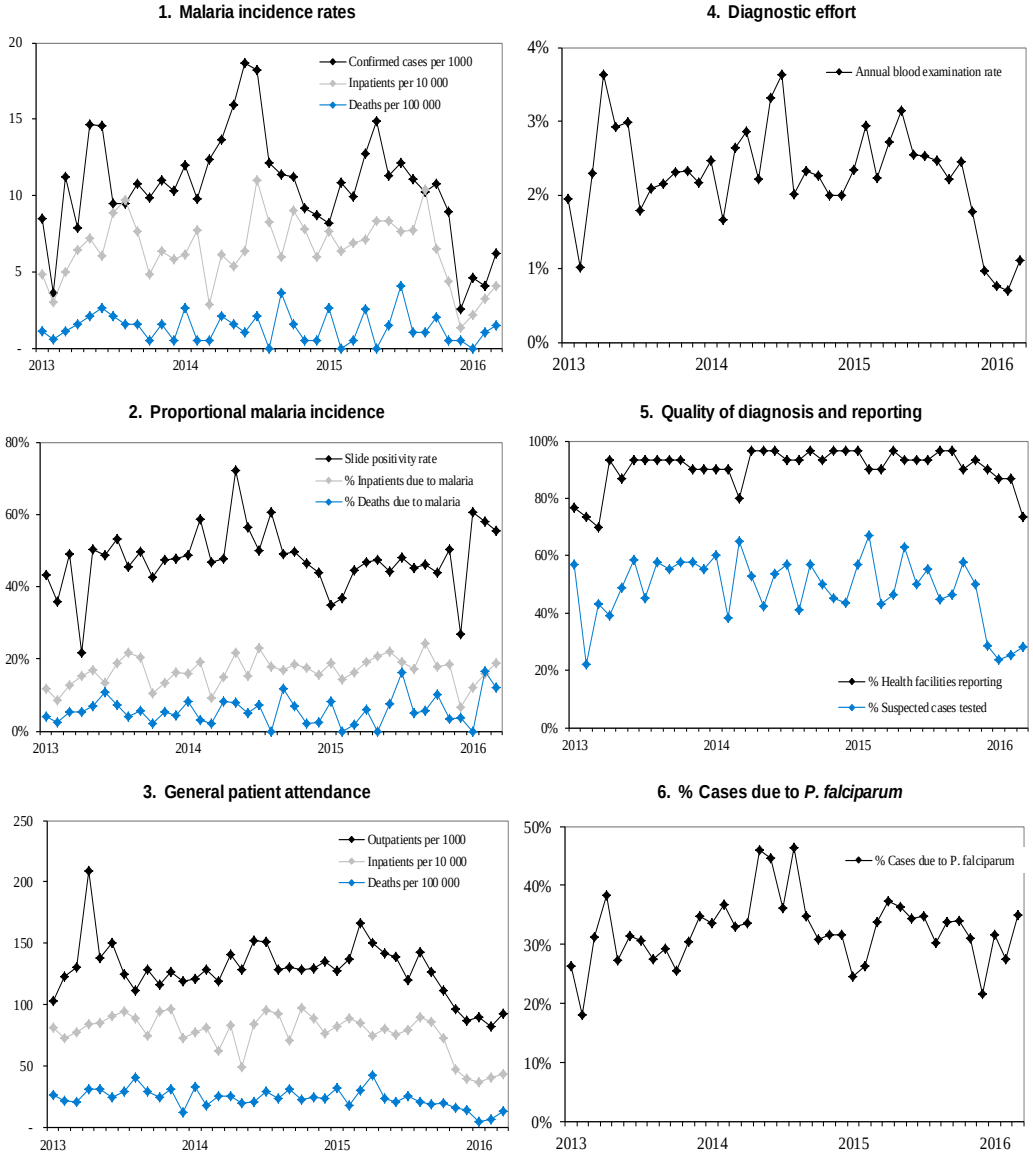
Indicator		Indicator	Applicability of Indicator: Transmission intensity: High transmission	Transmission intensity: Low transmission	Transmission intensity: Elimination/ prevention of re-establishment	Geography: Sub-Saharan Africa	Geography: Outside sub-Saharan Africa	Level: International	Level: National	Level: Sub-national	Data source: Routine reporting system	Data source: Health facility survey	Data source: Household survey
Inputs													
Chemoprevention	3.1	Proportion of pregnant women who received ≥3 doses of intermittent preventive therapy (IPTp)	●			●		●	●	●	●		●
	3.2	Proportion of pregnant women who received 2 doses of IPTp	●			●		o	●	●	●		●
	3.3	Proportion of pregnant women who received 1 dose of IPTp	●			●		o	●	●	●		●
	3.4	Proportion of pregnant women who attended antenatal care (ANC) at least once	●			●		o	●	●	●		●
	3.5	Proportion of children aged 3–59 months who received the full number of courses of SMC per transmission season	●			●		●	●	●	●		
Case detection	4.1	Proportion of children under 5 with fever in the previous 2 weeks for whom advice or treatment was sought	●	o		●	o	●	●				●
	4.2	Proportion of detected cases contacting health services within 48 hours of developing symptoms			●	●	●		●	●	●		
Diagnostic testing	5.1	Proportion of patients with suspected malaria who received a parasitological test	●	o		●	●	●	●	●	●	●	
	5.2	Proportion of children under 5 with fever in the previous 2 weeks who had a finger or heel stick	●			●	o	o	●				●
	5.3	Proportion of health facilities without stockouts of key commodities for diagnostic testing	●	o		●	●		●	●	●	●	
Treatment	6.1	Proportion of patients with confirmed malaria who received first-line antimalarial treatment according to national policy	●	●	●	●	●	●	●	●	●	●	
	6.2	Proportion of treatments with ACTs (or other appropriate treatment according to national policy) among febrile children <5	●	o		●	o	o	●		●	●	●
	6.3	Proportion of *P. vivax* and *P. ovale* patients who received radical cure treatment	●	●	●	o	●	o	●	●	●	●	
	6.4	Proportion of health facility months without stockouts of first-line treatments	●	o		●	●		●	●	●	●	

SME indicators

Surveillance	7.1	Proportion of malaria cases detected by surveillance systems	●	●	●		●	●	●	●			©	©
	7.2	Proportion of expected health facility reports received	●	●	●		●	●	o	●	●		●	
	7.3	Annual blood examination rate	●	●	●		●	●		●	●		●	
	7.4	Proportion of cases investigated and classified			●		●	●		●	●		●	
	7.5	Proportion of foci investigated and classified			●		●	●		●	●		●	
	7.6	Percentage of case reports received <24 hours after detection			●		●	●		●	●		●	
Impact														
Prevalence	8.1	Parasite prevalence: proportion of population with evidence of infection with malaria parasites	●	o			●	o	●	●				●
Incidence	9.1	Malaria case incidence: number of confirmed malaria cases per 1000 persons per year	●	●	●		●	●	●	●	●		●	
	9.2	Malaria admission rate: number of malaria admissions per 10 000 persons per year	●	o	o		●	●		●	●		●	
	9.3	Malaria test positivity rate	●	o			●	●		●	●		●	
	9.4	Proportion of admissions due to malaria	●	o			●	o		●	●		●	
	9.5	Number of foci by classification			●		●	●		●	●		●	
Mortality	10.1	Malaria mortality rate: number of malaria deaths per 100 000 persons per year	●	o	o		●	●	●	●	●		●	
	10.2	Proportion of inpatient deaths due to malaria	●	o			●	o		●	●		●	
Elimination	11.1	Number of areas/ countries that have newly eliminated malaria since 2015			●		●	●	●	●			●	
Prevention of reestablishment	12.1	Number of areas/ countries that were malaria-free in 2015 in which malaria has been re-established			●		●	●	●	●			●	

● Indicator highly relevant to setting o Indicator potentially relevant to setting © Requires data from both routine systems and household survey

SME indicators



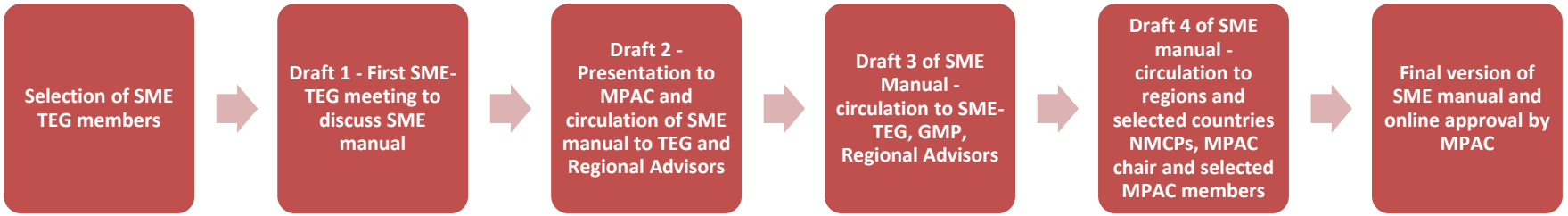
Pending or incomplete sections

1. Surveillance of *Plasmodium vivax*
2. Entomological surveillance in burden reduction and elimination
3. Routine information systems high burden countries
4. Improved approaches to data use – electronic tutorials, forms, annexes
5. Mapped examples for foci mapping
6. Surveillance systems assessments - electronic check lists and a sample questionnaire
7. Accompanying DHIS 2 modules (burden reduction and elimination)
8. Expanded section on epidemics

SM-TEG members

Name	Nationality
1. Adam Bennett	USA
2. Arantxa Roca-Feltrer (Chair)	Spain
3. Arnaud Le Manech	France
4. Chris Drakeley (co-Chair)	UK
5. Erin Eckert	USA
6. Jian-wei Xu	China
7. John A. Painter	USA
8. Kes Herdiana	Indonesia
9. Khalid Abdelmutalab Elmardi	Sudan
10. Laurence Slutsker - MPAC	USA
11. Ndiop Medoune	Senegal
12. Paola Marchesini	Brazil
13. Saute Franscisco	Mozambique

SME Manual revision - process



Malaria Policy Advisory Committee Meeting
22–24 March 2017, Geneva, Switzerland
Background document for Session 3

World Health Organization

Development of a Guideline for malaria vector control

March 2017, Geneva, Switzerland

Introduction

To guide the implementation of malaria vector control, WHO/GMP has 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 for 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 in order to offer an analysis of the current evidence related to malaria vector control. A transparent and explicit process using the available evidence base will ensure the high quality of the Guideline. The analysis will inform and guide technical decisions, and provide a framework with which WHO Member States can develop specific malaria vector control guidelines.

The detailed objectives, target audience, scope and development processes of the Guideline were presented and endorsed at the last MPAC meeting (September 2016). The aim of this pre-read is to provide MPAC with an update on any progress made and a revised timeline for the development of the Guideline. First, however, the following section establishes the context by summarizing the objectives and scope of the Guideline.

Objectives and scope 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.

The Guideline will address the following components or topics:

- Main vector control interventions: indoor residual insecticide spraying (IRS) and insecticide-treated nets (ITNs), including long-lasting insecticide-treated nets (LLINs);
- Supplementary interventions: larval source management (LSM), space spraying, personal protection such as repellents, use of protective clothing, and household improvements, e.g., the use of door and window screens.

WHO/HTM/GMP/MPAC/2017.3

Updates since the last MPAC meeting

1. **Approval by the GRC**: The WHO Guidelines Review Committee (GRC) approved the initial guideline development proposal in November 2016.
2. **Systematic reviews commissioned**: The Cochrane Infectious Disease Group at the Liverpool School of Tropical Medicine was contacted; they will conduct reviews, update existing reviews as necessary, and provide GRADE tables summarizing the evidence.

Review process and timelines

The overall timeframe for the development of the Guideline has been modified on the basis of the projected timelines for the evidence review process and the production of the GRADE tables. The revised timeline is presented below:

Timeline for the development of the vector control Guideline

June/16	Establishment of a WHO Guideline Steering Group (GSG). This is an in-house WHO 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 GSG to discuss the scope of the Guideline and to formulate PICO questions
Aug–Nov/16	Draft of the Guideline proposal and submission to the Guidelines Review Committee (GRC)
Dec–Jan/16	Identification of evidence needs and commission of systematic reviews
Feb–Sept/17	Development of GRADE tables and summary tables
Mar/17	Meeting of the Guidelines Development Group (GDG) to discuss the scope of the Guideline, and to review and discuss the PICO questions (VCTEG meeting)
Apr/17	External electronic consultations, as needed
Oct/17	Formulation of recommendations based on the available evidence, systematic reviews and GRADE tables (VCTEG meeting)
Mar–Oct/17	Development of the draft Guideline
Nov–Dec/17	Peer review (external review group) and editing
Dec/17	Submission to the WHO GRC
Dec/17	Revision based on GRC comments, and seeking of final departmental and WHO approvals

Guideline for malaria vector control

MPAC 22–24 March, 2017

Entomology and Vector Control Unit

Global **Malaria** Programme

World Health Organization

Objectives of the Guidelines

- 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.

Scope: Malaria vector control interventions

- Core Interventions
  - Indoor residual spraying (IRS)
  - Insecticide Treated Nets (ITNs, LLINs)
- Supplementary Interventions
  - Larval Source Management (LSM)
  - Others:
- Scaling-back vector control
- Settings and programmatic factors for selection of vector control interventions

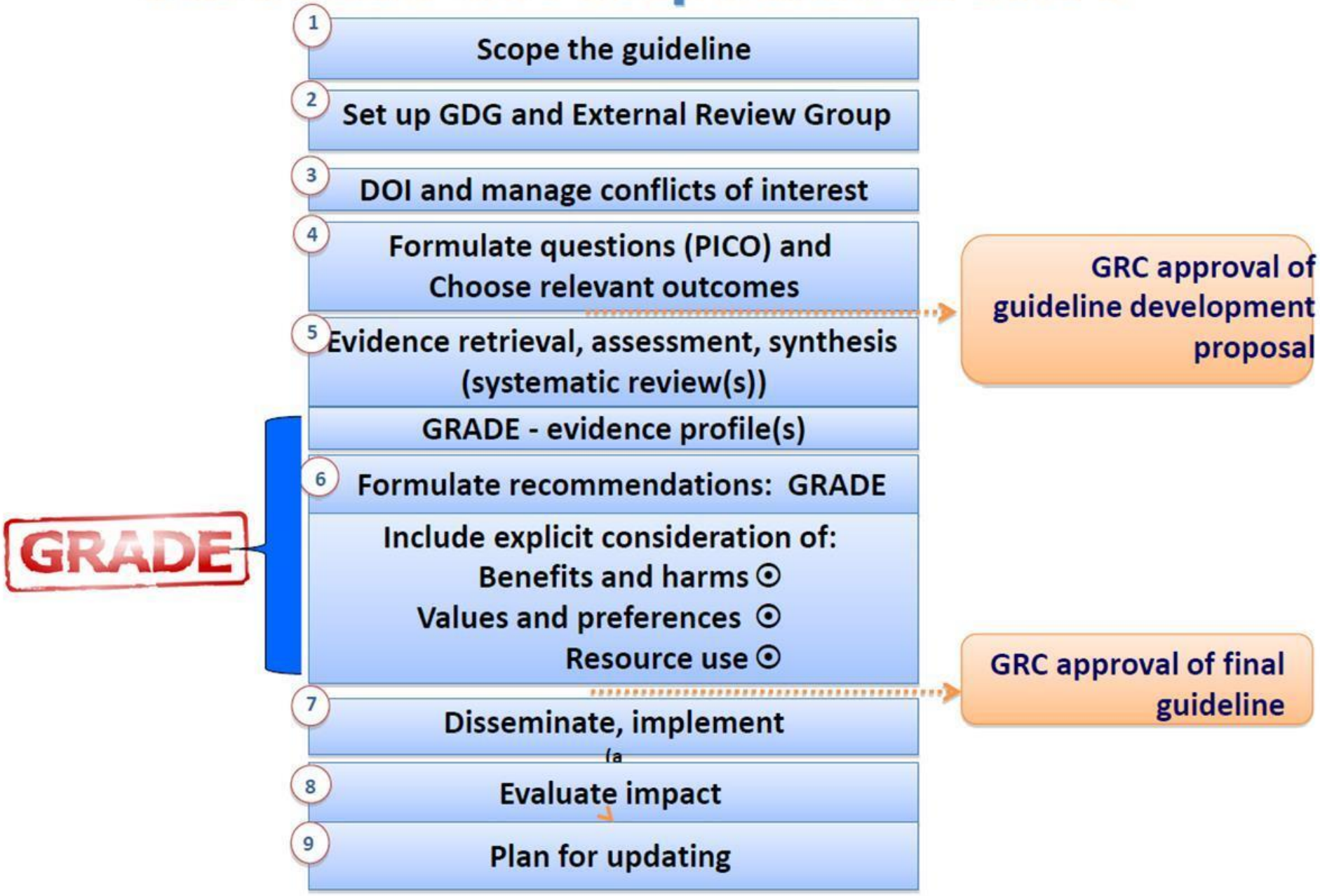
Current status of the Guideline development

- Proposal was submitted to the GRC after MPAC, October 2016
- Reviewed, responses were sent back to the GRC, and the proposal was approved.
- Guideline Developing Group was convened (VCTEG) to reach consensus on the PICO questions and Outcomes. 13–15 March, 2017
- The Cochrane Infectious Diseases Group (CIDG) at the Liverpool School of Tropical Medicine was commissioned for the systematic reviews and GRADE tables.

Working group discussion (March 2017)

- Objectives:
  - To agree on the PICO questions and outcomes, for each intervention.
- Procedure:
  - Review and revise the draft key questions and outcomes. Prioritize key questions.
  - Identify key outcomes that need to be considered in the Guideline, for each question or intervention. See those already selected and identify any other outcomes that have not been listed. Generally no more than 7 outcomes considered important or critical to the formulation of recommendations should be selected by question.
  - For each question rank the outcomes in order of priority on a scale of 1 – 9, where 7 – 9 rates the outcome as critical for a decision, 4 – 6 rates as important and 1 – 3 rates them as unimportant.
  - Deliverable: Consensus of high priority key questions and important and critical outcomes.

Guideline development at WHO



Timeline

DATE	ACTIVITY
June, 2016	Establishment of the Guideline Steering Group (GSG)
Jul-Aug, 2016	Defining the scope of the Guideline and PICO questions by the GSG
Sept - Oct, 2016	Draft the Guideline proposal and submission to the GRC
Oct – Nov, 2016	Identification of evidence needs and commission systematic reviews
March, 2017	Agree on PICO key questions and rank outcomes
March – Sept, 2017	**Systematic reviews and GRADE tables**
October, 2017	**Panel meeting for formulation of recommendations (VCTEG)**
April - Nov, 2017	**Development of the draft Guideline**
April- Nov, 2017	**External electronic consultations as neededd**
Dec, 2017	**Peer review and editing**
Jan, 2018	**Submission to the GRC**
Feb, 2018	**Revision based on GRC comments and seeking of final departmental and WHO approval.**

Thank you

Outcomes from the Evidence Review Group on *Plasmodium knowlesi*

Malaria Policy Advisory Committee
Geneva, Switzerland

Dr. Rabi Abeyasinghe,
Coordinator MVP Unit, WPRO
22 March 2017

Outline

- Why an ERG on *Plasmodium knowlesi*
- Members of the ERG
- WHO Consultation on *P. knowlesi* (2011)
- Brief history and current situation
- Transmission, hosts and vectors
- Diagnosis, clinical and treatment
- Human-vector-human transmission, is it taking place?
- Research priorities

Why an ERG on *Plasmodium knowlesi*?

The MPAC meeting of September 2015 recommended the constitution of an ERG to address the following knowledge gaps;

- The epidemiological distribution of *P. knowlesi* infection in humans including common clinical outcomes, the range and distribution of the primary hosts and vectors.
- The most effective methods of control and prevention including diagnostics and treatment and the potential impact on the success of malaria elimination programmes.
- The plausibility of human-vector-human transmission and potential future changes that may influence the levels of exposure to *P. knowlesi*.
- Operational research priorities to limit *P. knowlesi* transmission to humans
- Scope to be expanded to include other primate malarias

Evidence Review Group

Members

- Dr Rohani Ahmed
- Dr Nicholas Mark Anstey
- Dr John Kevin Baird
- Dr Christopher Drakeley
- Dr Jenarun Bin Jelip
- Dr Yee Ling Lau
- Dr Asmad Matusop
- Dr Kamini Mendis
- Dr Rose Nani Mudin
- Dr Ummi Shamsudin
- Dr Ruben Sunil Kumar Sharma
- Prof Balbir Singh
- Dr Lokman Hakim Bin Sulaiman
- Professor Indra Vythilingam
- Professor Nicholas John White
- Dr Timothy William

Secretariat

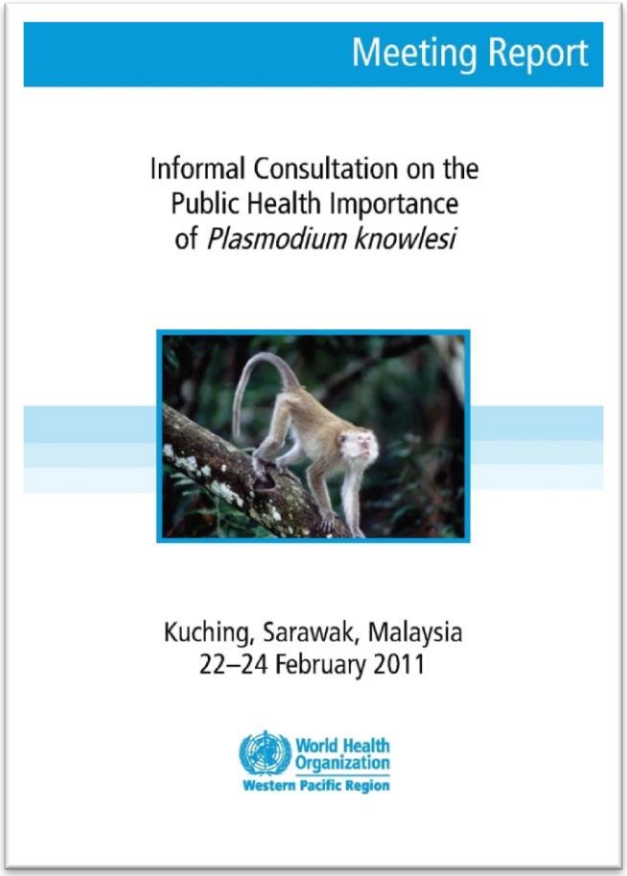
- Dr Andrea Bosman
- Dr Rabindra Abeyasinghe
- Ms Glenda Gonzales

Presenters

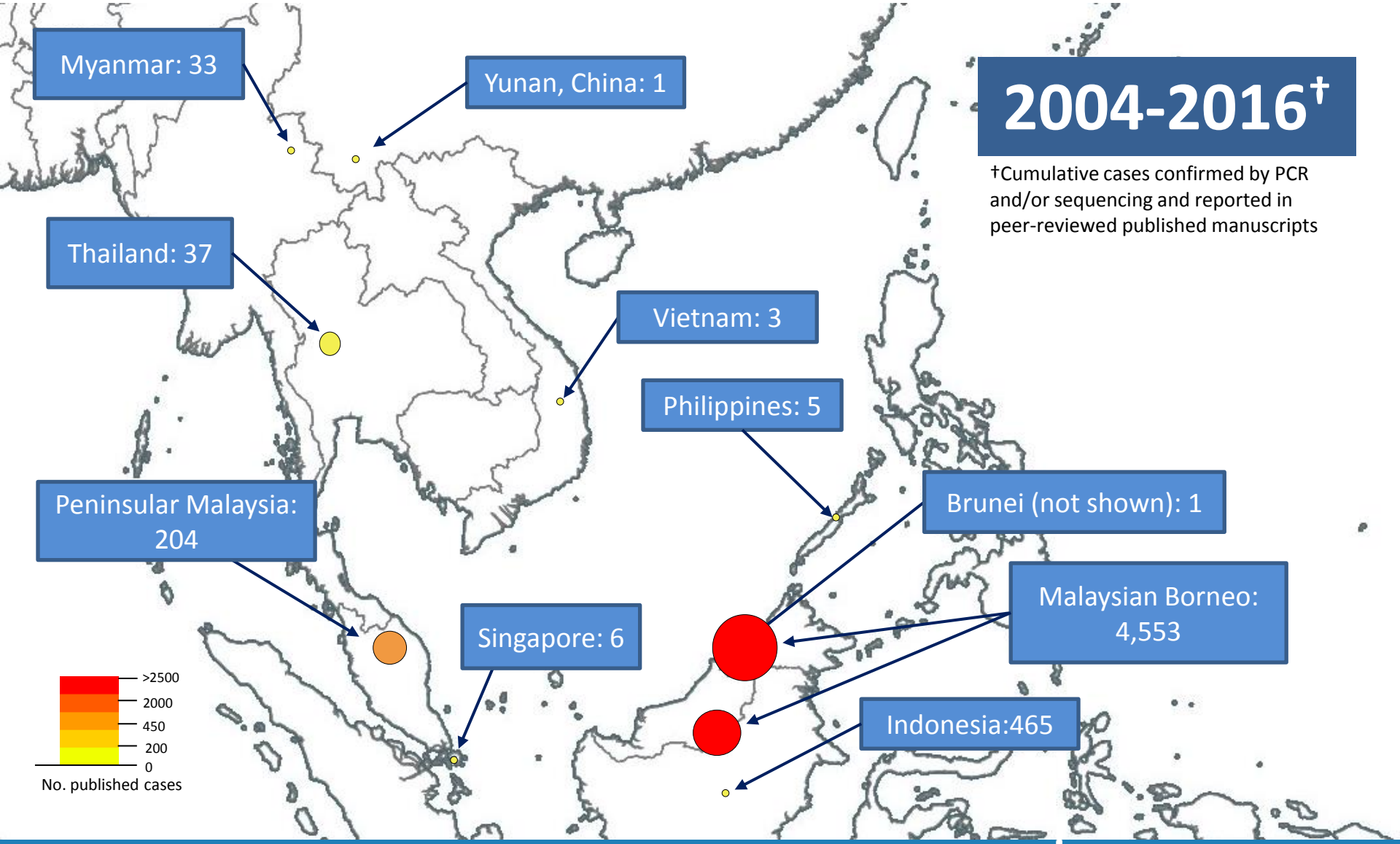
- Dr Rohani Ahmed
- Dr Nicholas Mark Anstey
- Dr John Kevin Baird
- Dr Christopher Drakeley
- Dr Jenarun Bin Jelip
- Dr Yee Ling Lau
- Dr Asmad Matusop
- Dr Rose Nani Mudin
- Dr Ruben Sunil Kumar Sharma
- Prof Balbir Singh
- Professor Indra Vythilingam
- Dr Timothy William

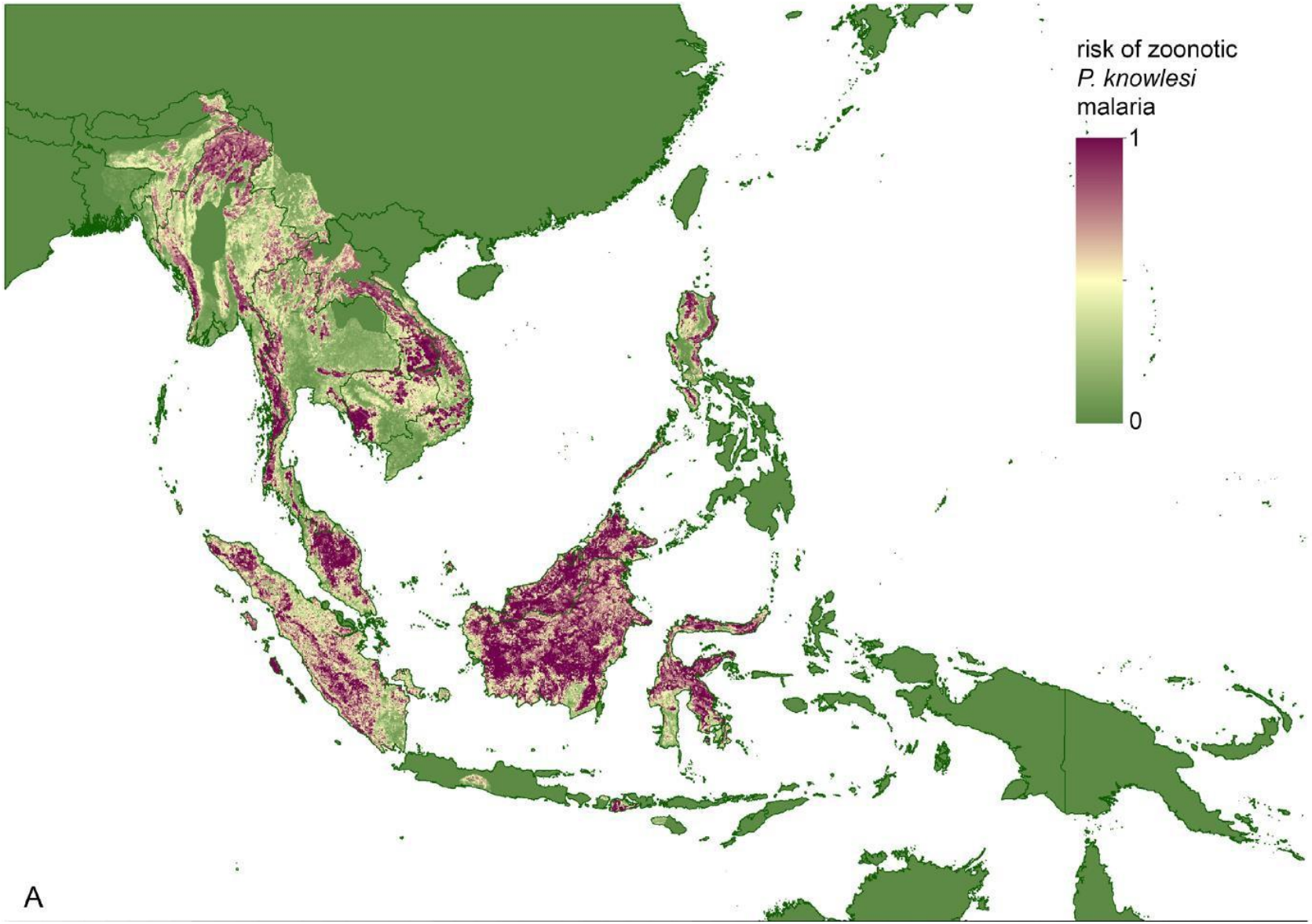
WHO Informal Consultation on the Public Health Importance of *P. knowlesi*

- 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



Current situation and distribution





Citation: Shearer FM, Huang Z, Weiss DJ, Wiebe A, Gibson HS, Battle KE, et al. (2016) Estimating Geographical Variation in the Risk of Zoonotic *Plasmodium knowlesi* Infection in Countries Eliminating Malaria. PLoS Negl Trop Dis 10(8): e0004915. doi:10.1371/journal.pntd.0004915

PLOS | NEGLECTED TROPICAL DISEASES

Estimating Geographical Variation in the Risk of Zoonotic *Plasmodium knowlesi* Infection in Countries Eliminating Malaria

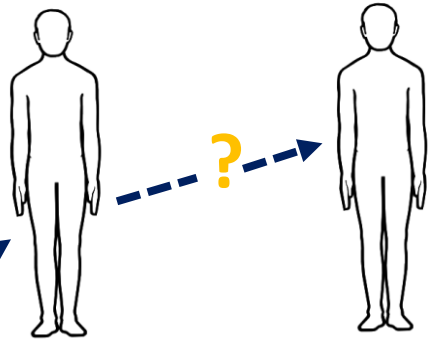
World Health Organization 2016

Transmission and factors for zoonotic infections

HOST

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

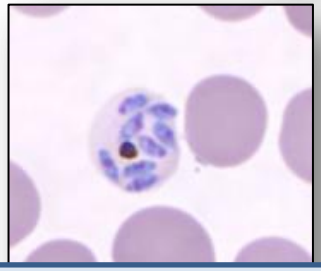
SOCIAL
Employment
Migration
Others



Humans:
Zoonotic infections

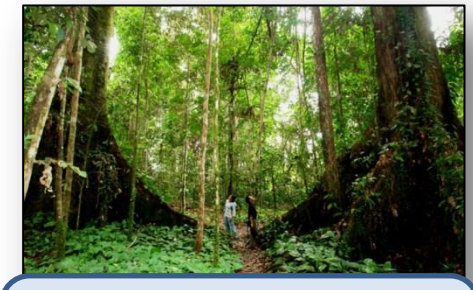
VECTOR

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



MALARIA

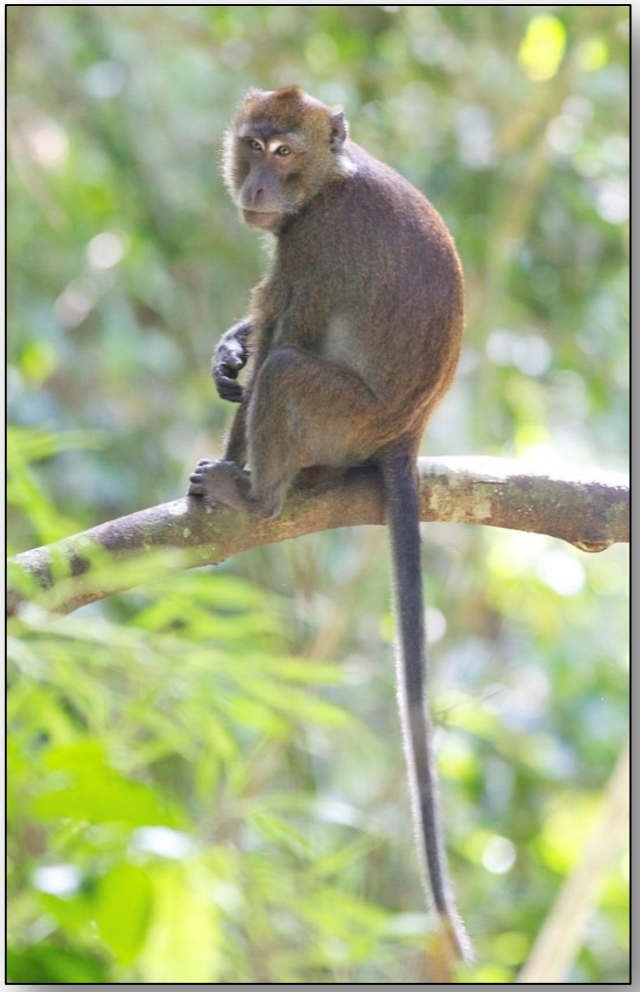
Plasmodium knowlesi



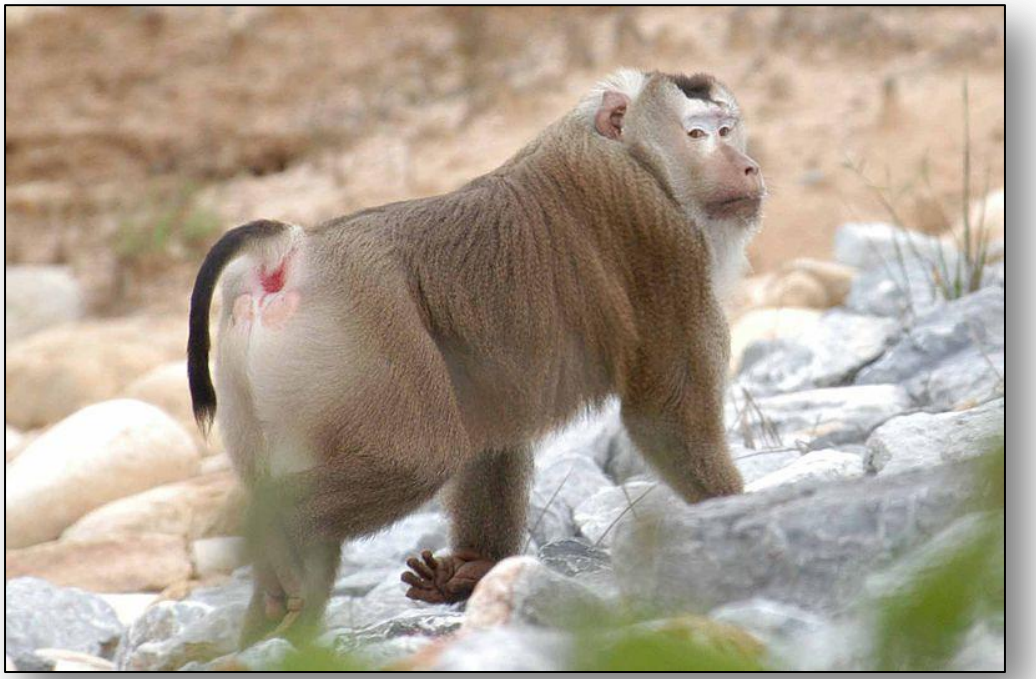
ENVIRONMENT

Dense jungle and forest fringe areas

Natural hosts in Sarawak, Malaysian Borneo



Macaca fascicularis
Long-tailed macaque

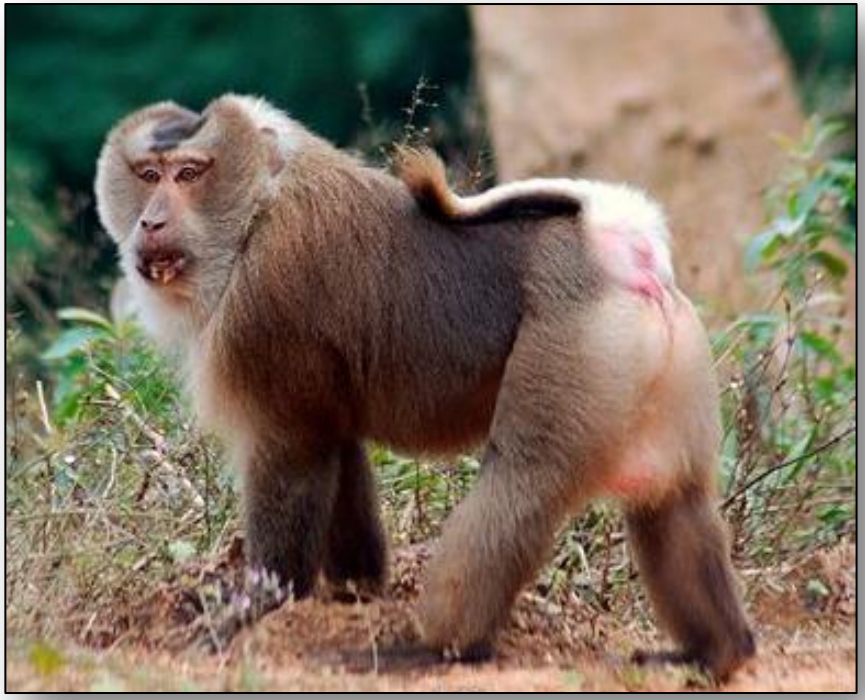


Macaca nemestrina
Pig-tailed macaque

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

Vector habitat

Slow running streams

Animal foot paths

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

Vector habitat

Stagnant water

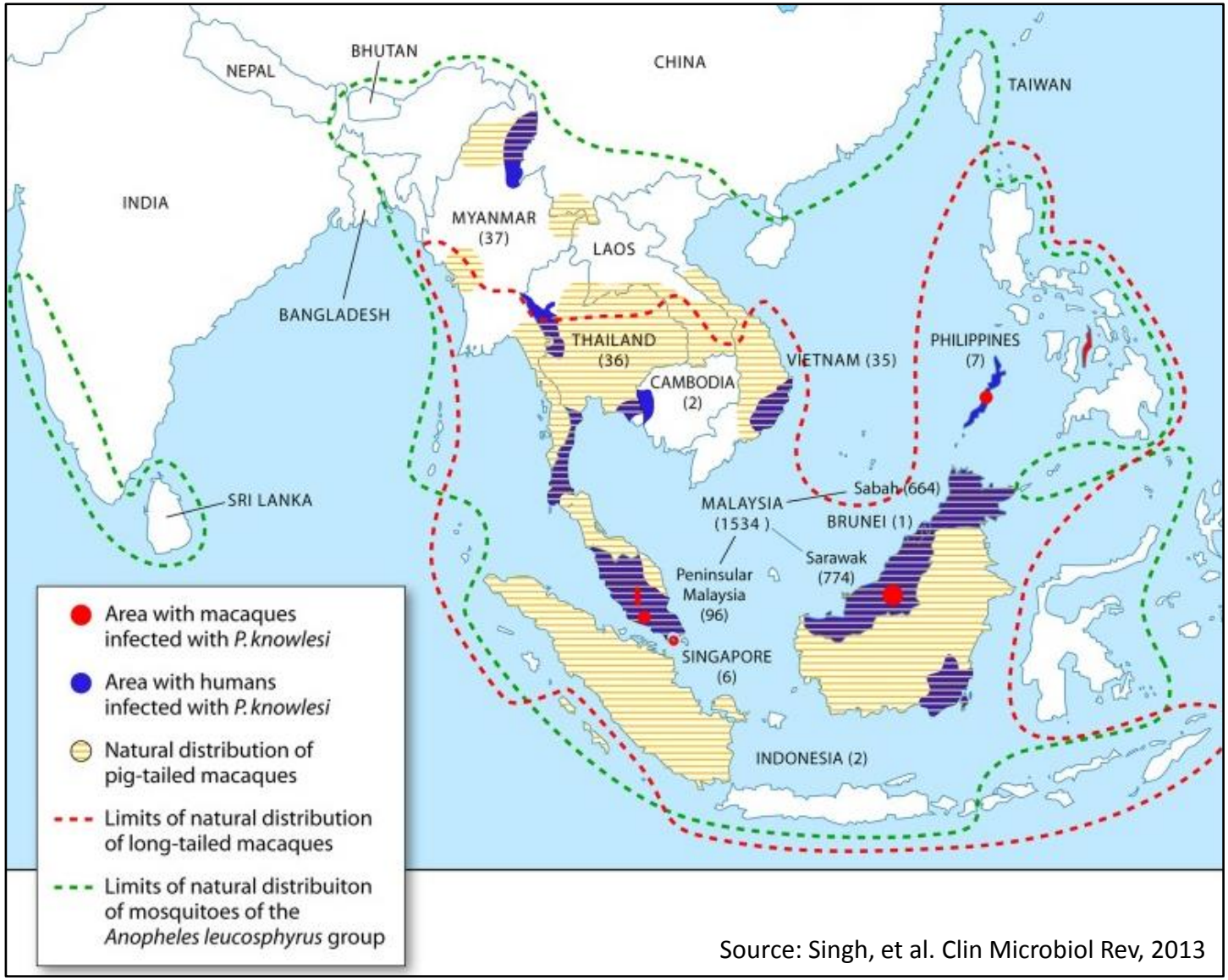
Ground pools

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

Larval sampling

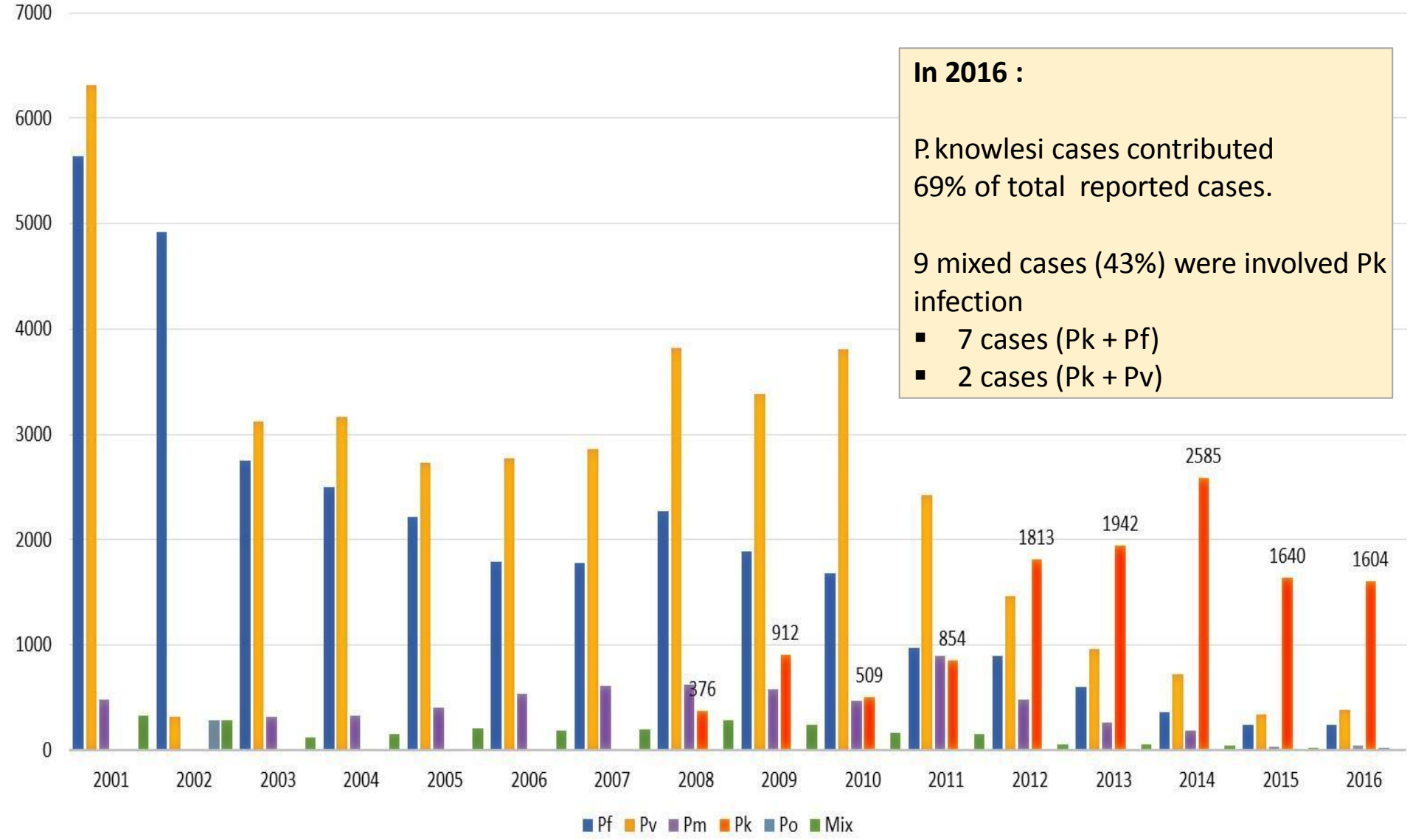
Source: EntoPest Unit of Sabah Health Department, Malaysia, 2016

Host and vector range



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

DISTRIBUTION OF MALARIA CASES BY SPECIES (2001-2016)



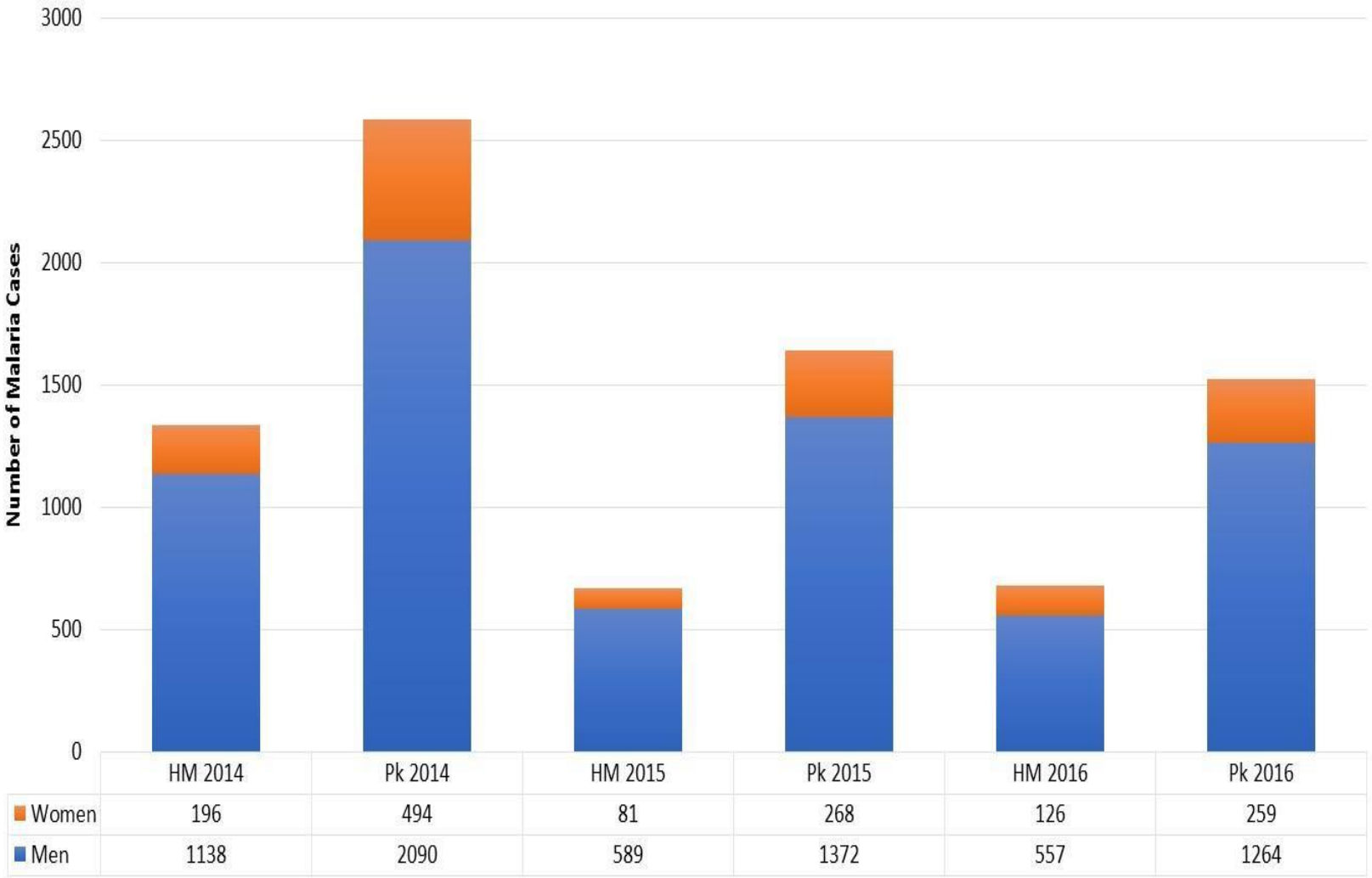
In 2016 :

P. knowlesi cases contributed 69% of total reported cases.

9 mixed cases (43%) were involved Pk infection

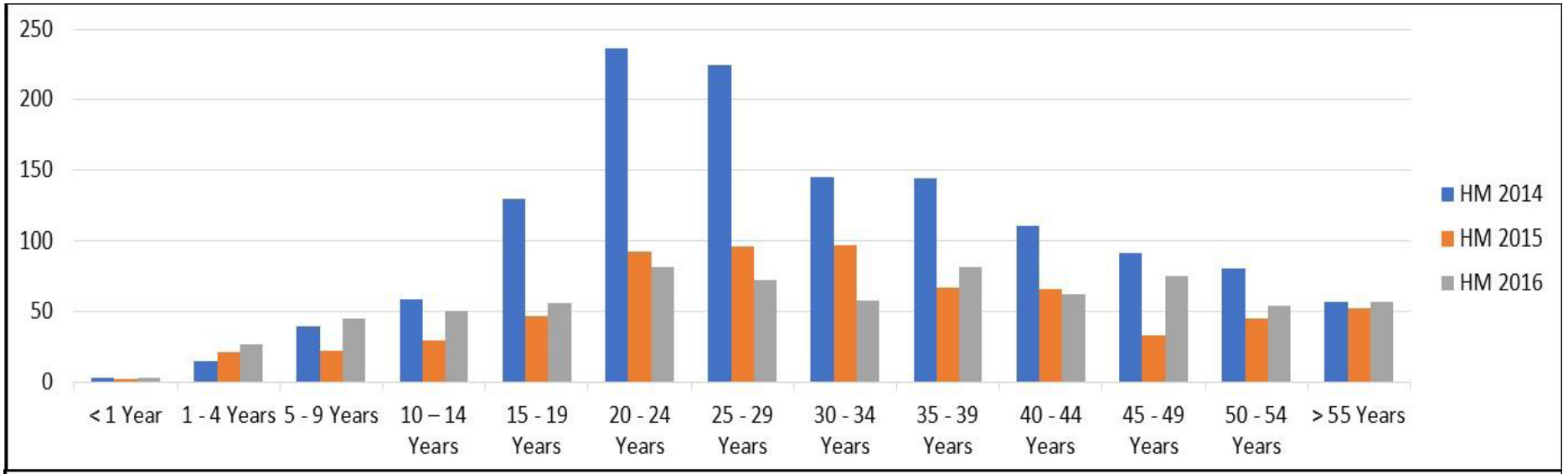
- 7 cases (Pk + Pf)
- 2 cases (Pk + Pv)

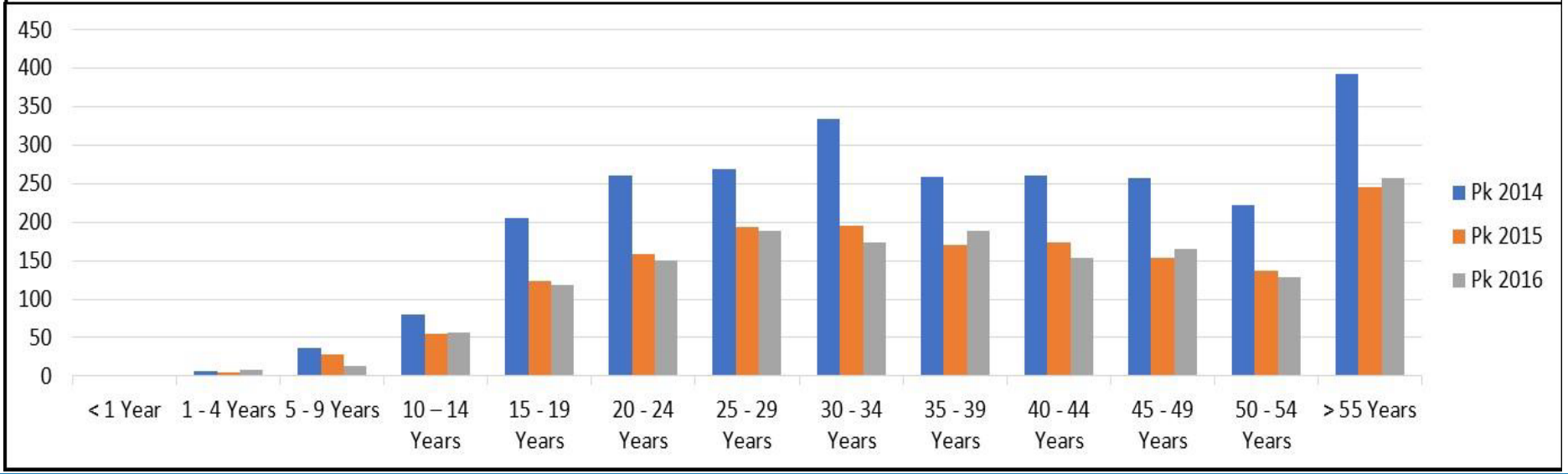
DISTRIBUTION OF HUMAN MALARIA AND P.KNOWLESI CASES BY GENDER in MALAYSIA 2014-2016



	HM 2014	Pk 2014	HM 2015	Pk 2015	HM 2016	Pk 2016
Women	196	494	81	268	126	259
Men	1138	2090	589	1372	557	1264

DISTRIBUTION OF HUMAN MALARIA AND P.KNOWLESI CASES BY AGE GROUP IN MALAYSIA (2014-2016)





Source: Vector Borne Disease Sector, Disease Control Division, MOH

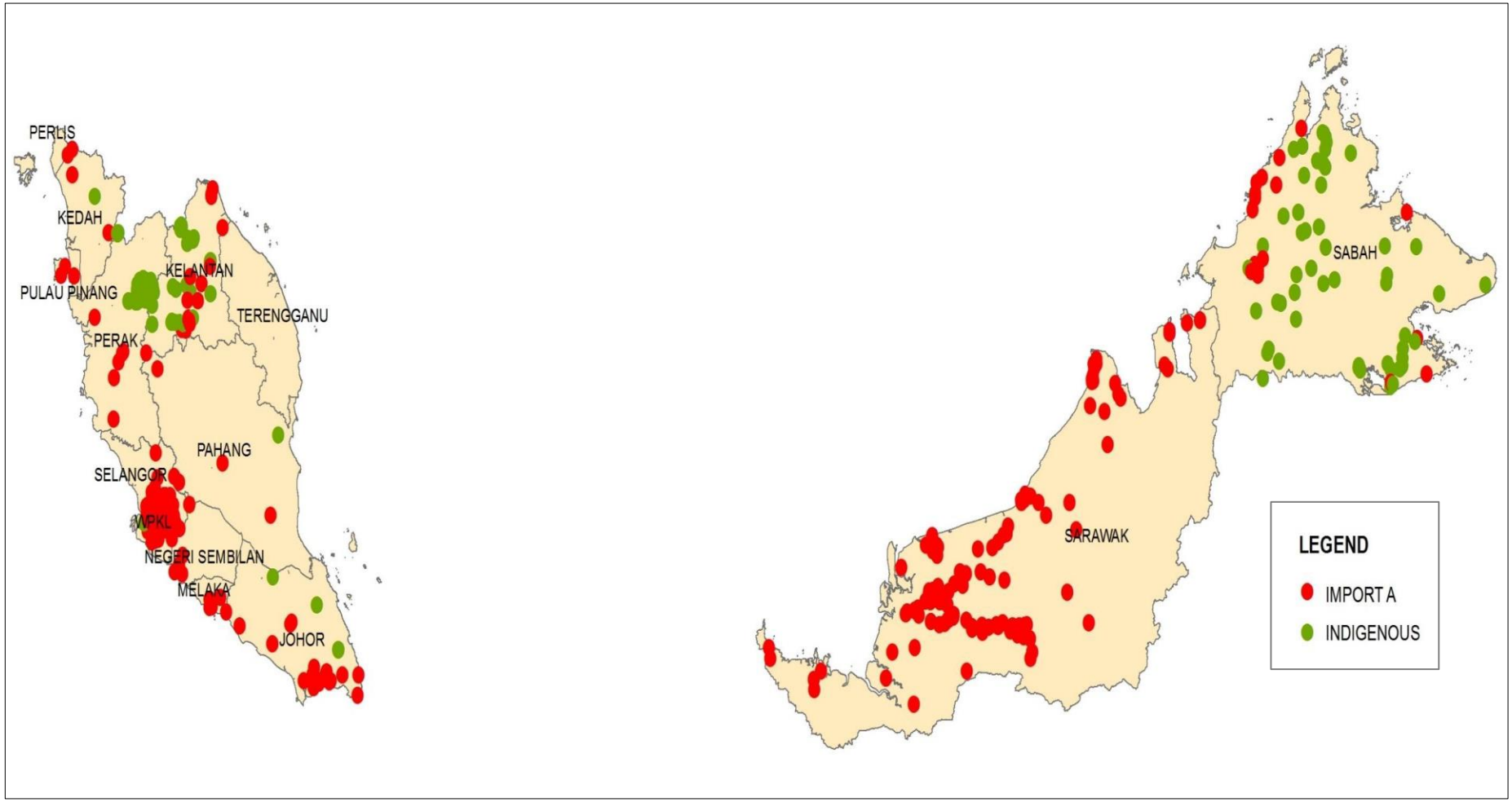
DISTRIBUTION OF *HUMAN MALARIA* CASES BY INFECTION STATUS (SPORADIC/CLUSTER) IN MALAYSIA 2016

	PERLIS	KEDAH	P.PINANG	PERAK	SELANGOR	WPKL	N.SEMBILAN	MELAKA	JOHOR	PAHANG	TERENGGANU	KELANTAN	SARAWAK	SABAH	WP LABUAN
CLUSTER	0	0	0	3	2	0	1	0	2	0	0	10	28	7	0
SPORADIC	1	5	3	6	72	14	5	6	18	7	0	27	146	78	0

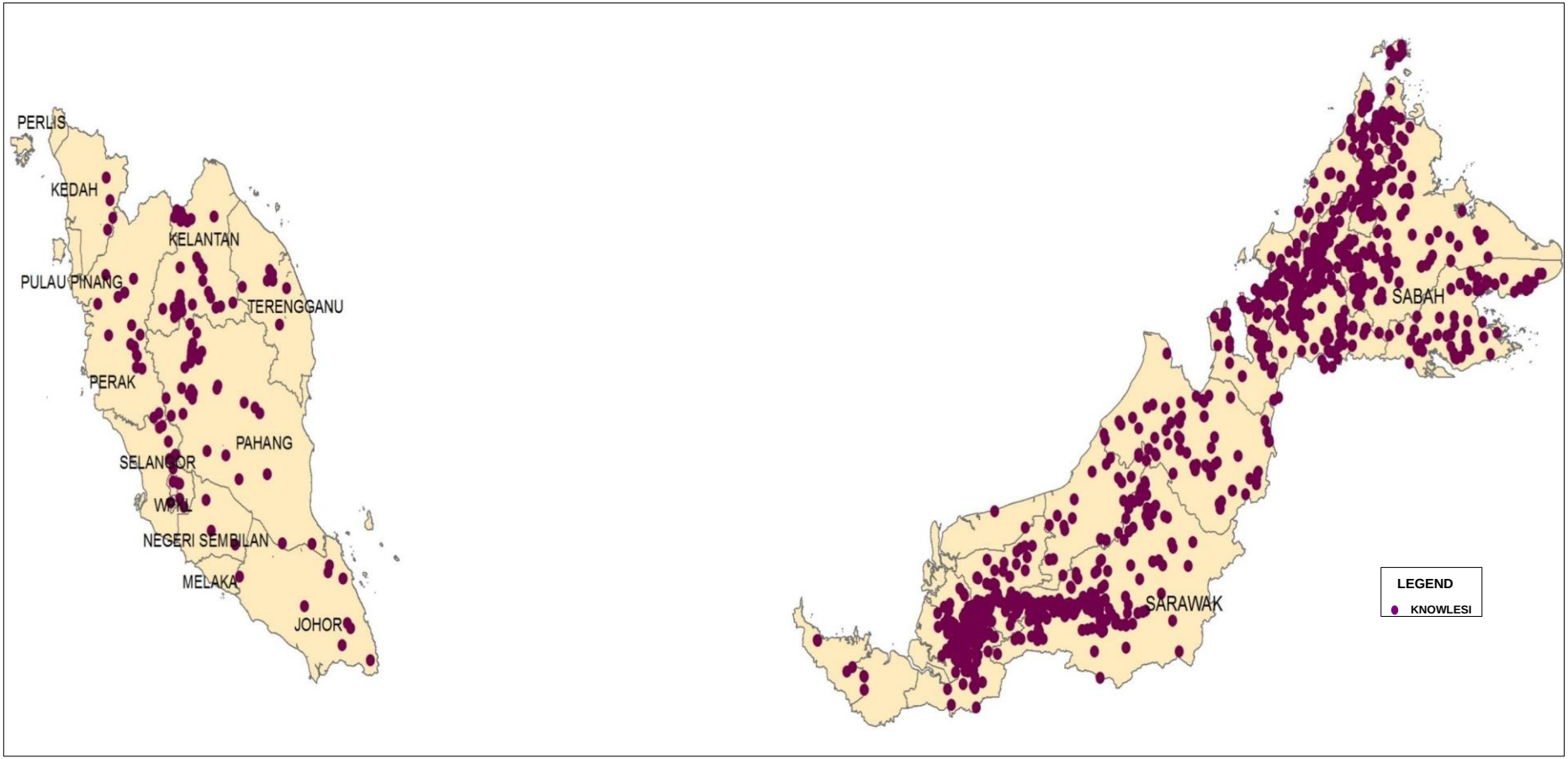
DISTRIBUTION OF *ZOONOTIC MALARIA* CASES BY INFECTION STATUS

	PERLIS	KEDAH	P.PINANG	PERAK	SELANGOR	WPKL	N.SEMBILAN	MELAKA	JOHOR	PAHANG	TERENGGANU	KELANTAN	SARAWAK	SABAH	WP LABUAN
CLUSTER	0	0	0	3	1	0	0	0	1	1	0	2	93	68	0
SPORADIC	0	4	0	21	11	1	3	0	10	30	8	30	591	479	0

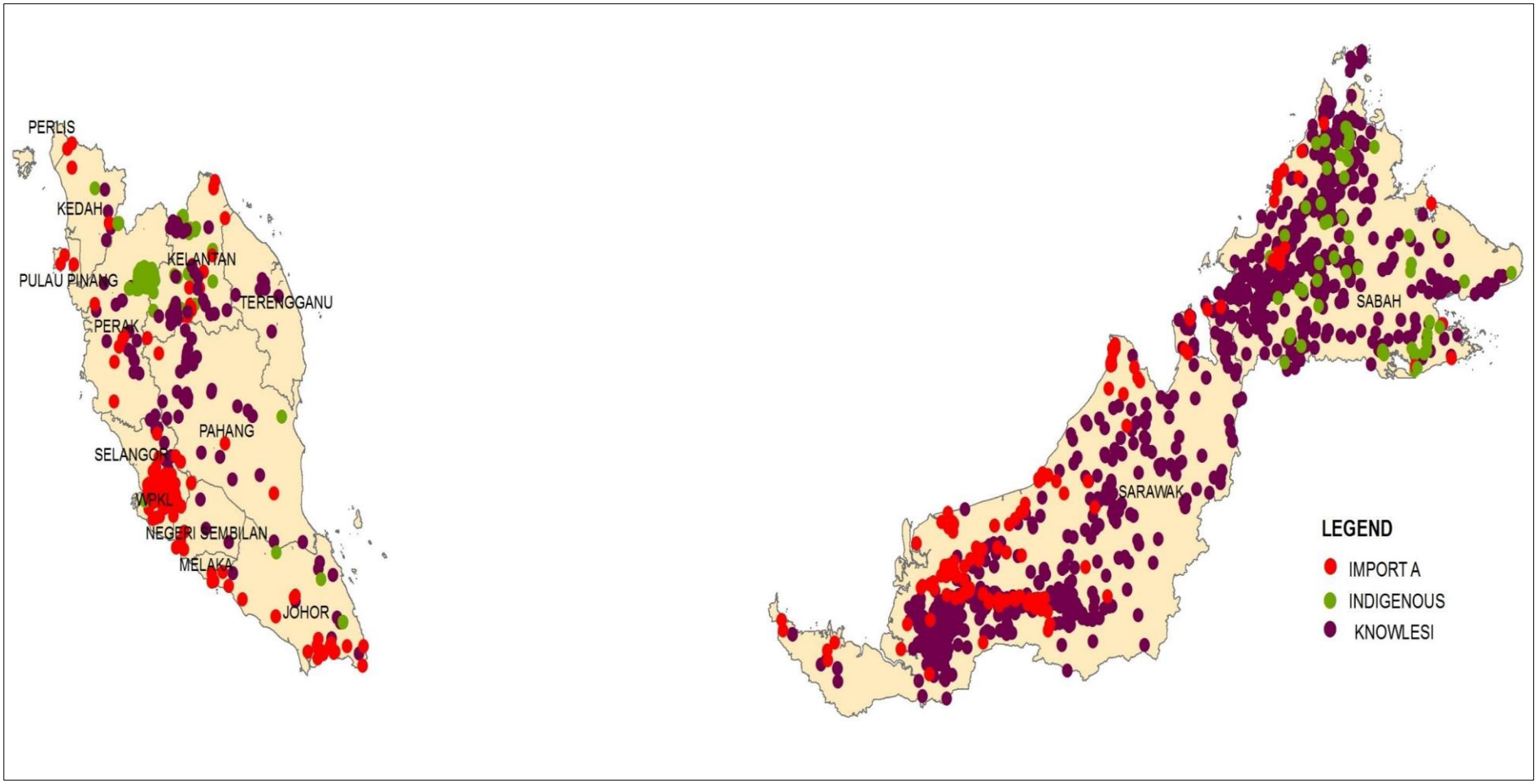
SPATIAL DISTRIBUTION OF HUMAN MALARIA CASES IN MALAYSIA (2016)



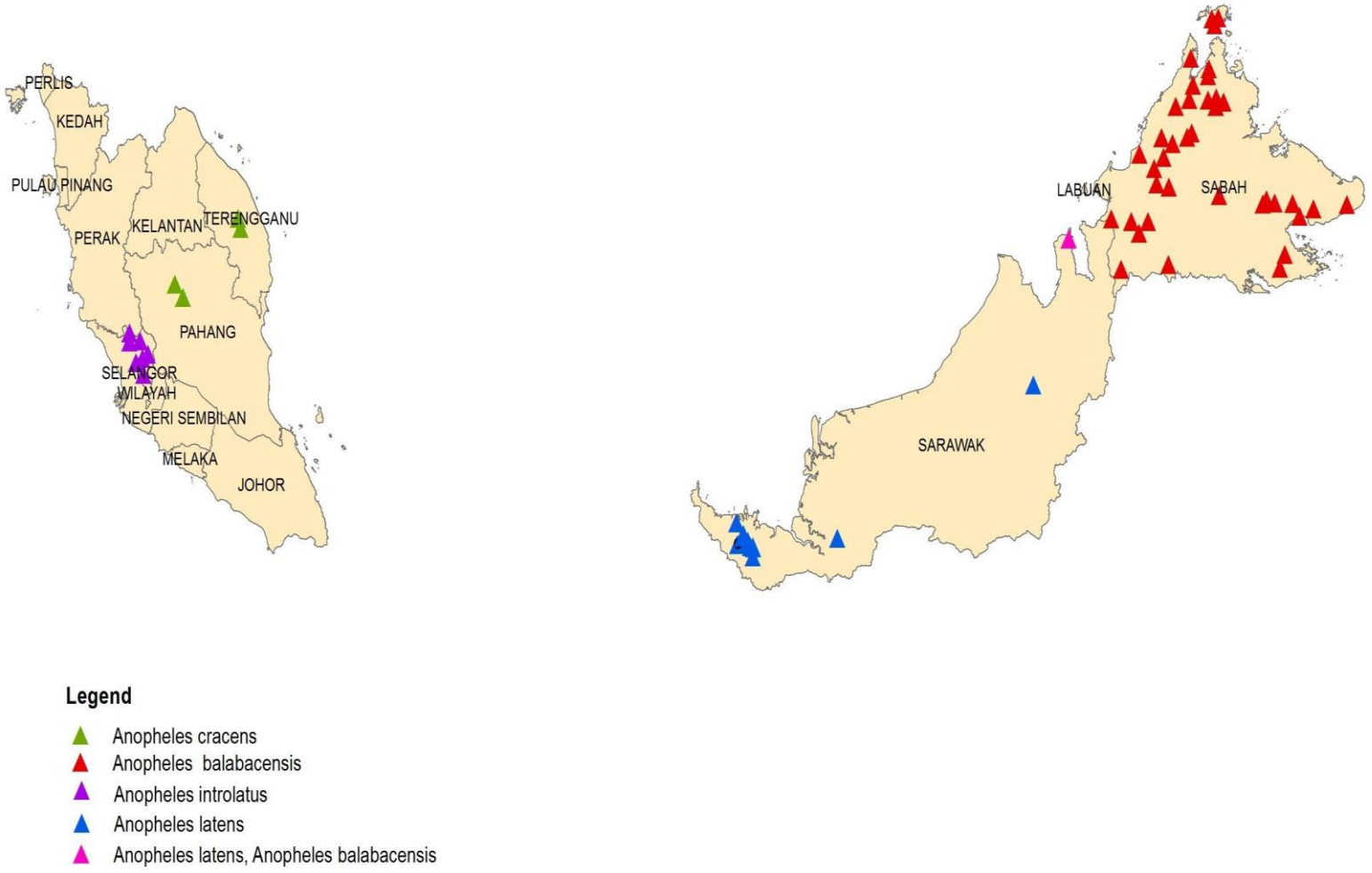
SPATIAL DISTRIBUTION OF ZOONOTIC MALARIA CASES IN MALAYSIA (2016)



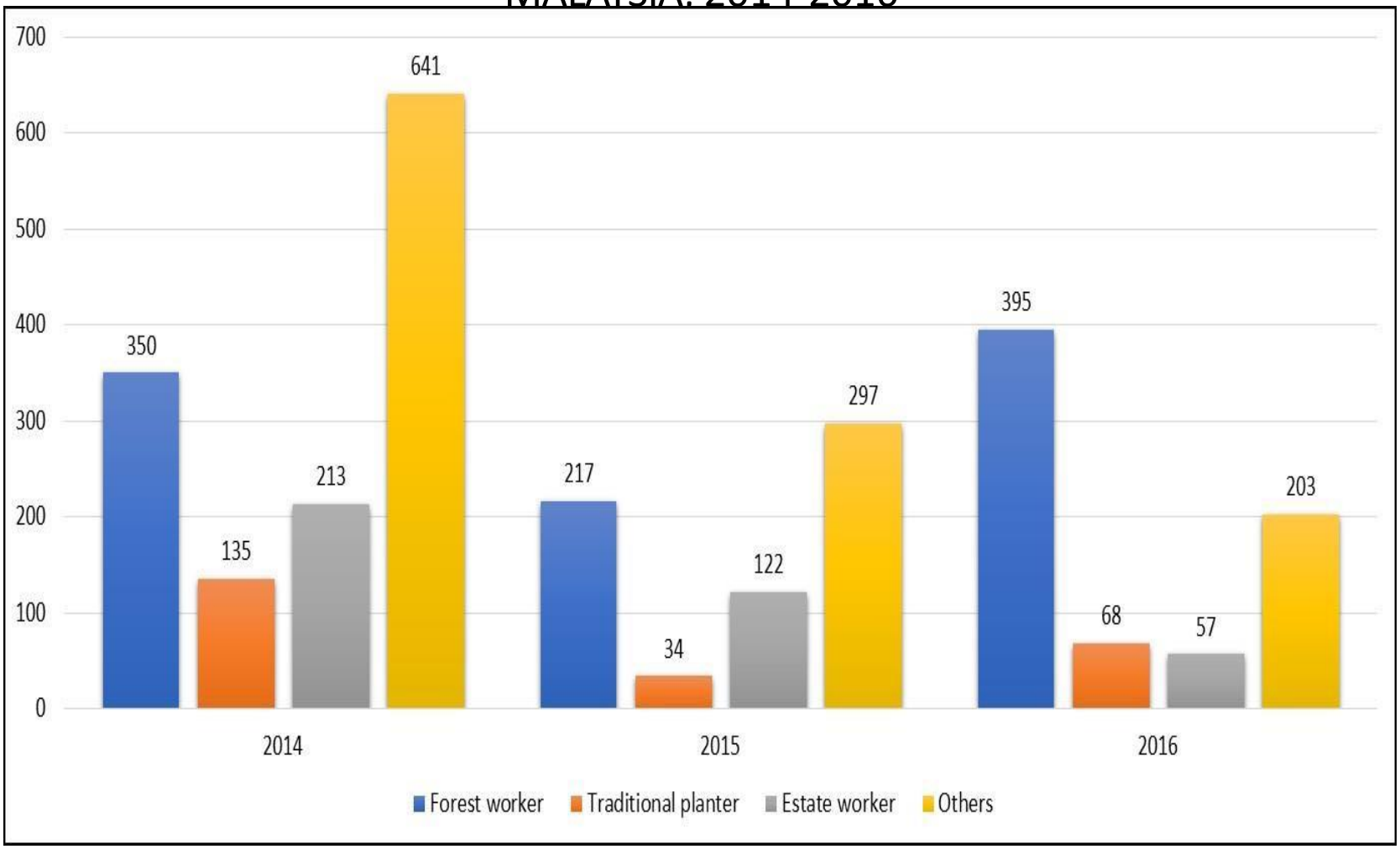
SPATIAL DISTRIBUTION OF HUMAN MALARIA & ZOONOTIC MALARIA CASES IN MALAYSIA (2016)



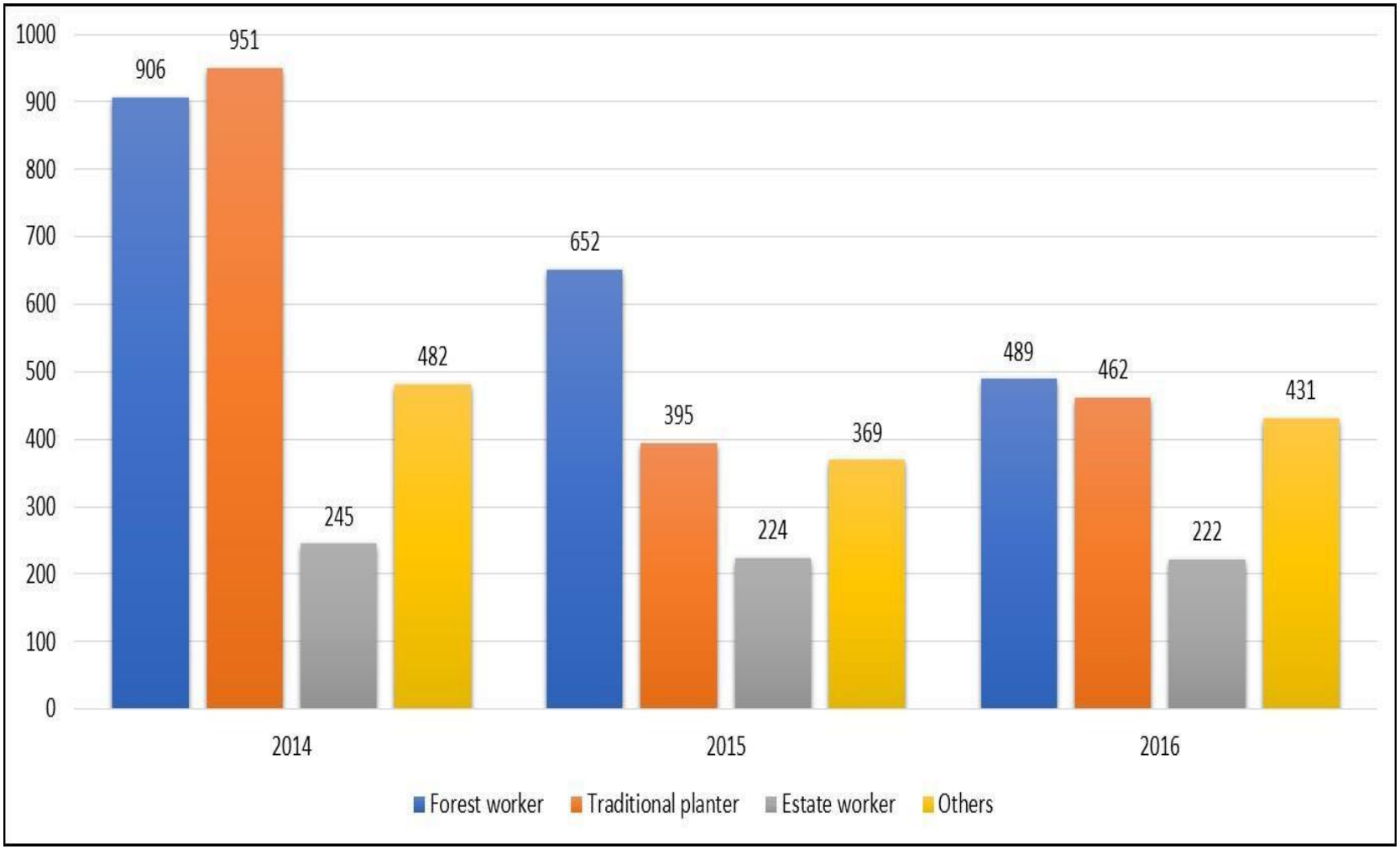
SPATIAL DISTRIBUTION OF VECTOR SPECIES FOR ZOONOTIC



DISTRIBUTION OF HUMAN MALARIA CASES BY OCCUPATION IN MALAYSIA, 2014-2016

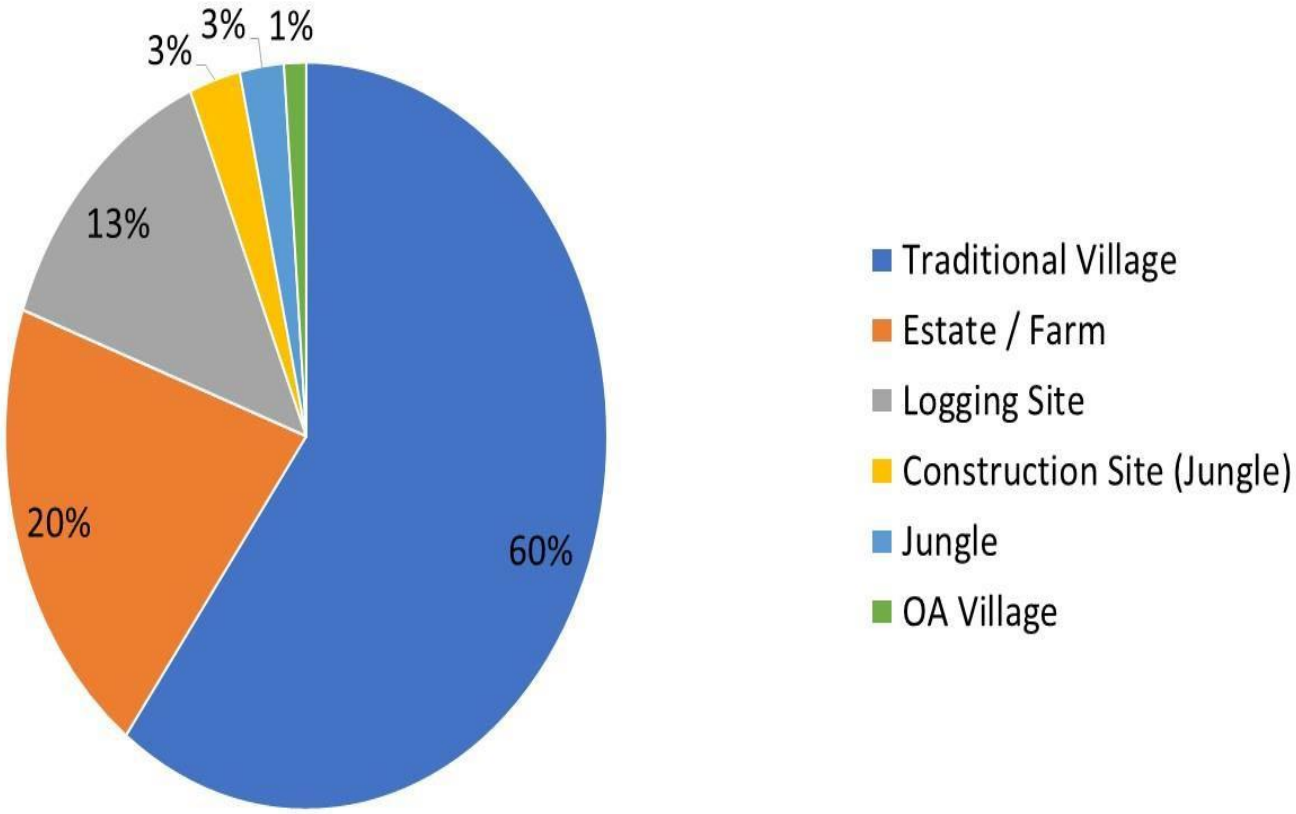


DISTRIBUTION OF ZOONOTIC MALARIA CASES BY OCCUPATION IN MALAYSIA, 2014-2016



Source: Vector Borne Disease Sector, Disease Control Division, MOH

DISTRIBUTION OF *ZOONOTIC MALARIA* CASES BY LOCALITY STATUS IN 2016



Source: Vector Borne Disease Sector, Disease Control Division, MOH

First successful survey in Indonesia

Contribution of *Plasmodium knowlesi* to multi-species human malaria infections in North Sumatera, Indonesia

Inke ND Lubis[1,2], Hendri Wijaya[2], Munar Lubis[2], Chairuddin P Lubis[2], Paul CS Divis[3,4], Khalid B Beshir[1], Colin J Sutherland[1]

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Sumatra results

Table 1. Comparison of two PCR assays for *P. knowlesi* cases detection

	18 ssu rRNA assay	SICAvar assay
Total *P. knowlesi* cases	76	377
P. knowlesi mono infection	42 (55.3%)	215 (57.0%)
P. knowlesi + *P. vivax*	16 (21.1%)	65 (17. 2%)
P. knowlesi +other *Plasmodium* spp. infe ctions	18 (23.7%)	97 (25.7%)
Cases positive by both assays	10	
Total *P. knowlesi* cases detected with any assay	443	
P. knowlesi mono infection	254/443 (57.34%)	

Relative frequencies (percentages) read vertically.

Evidence from Aceh, Indonesia

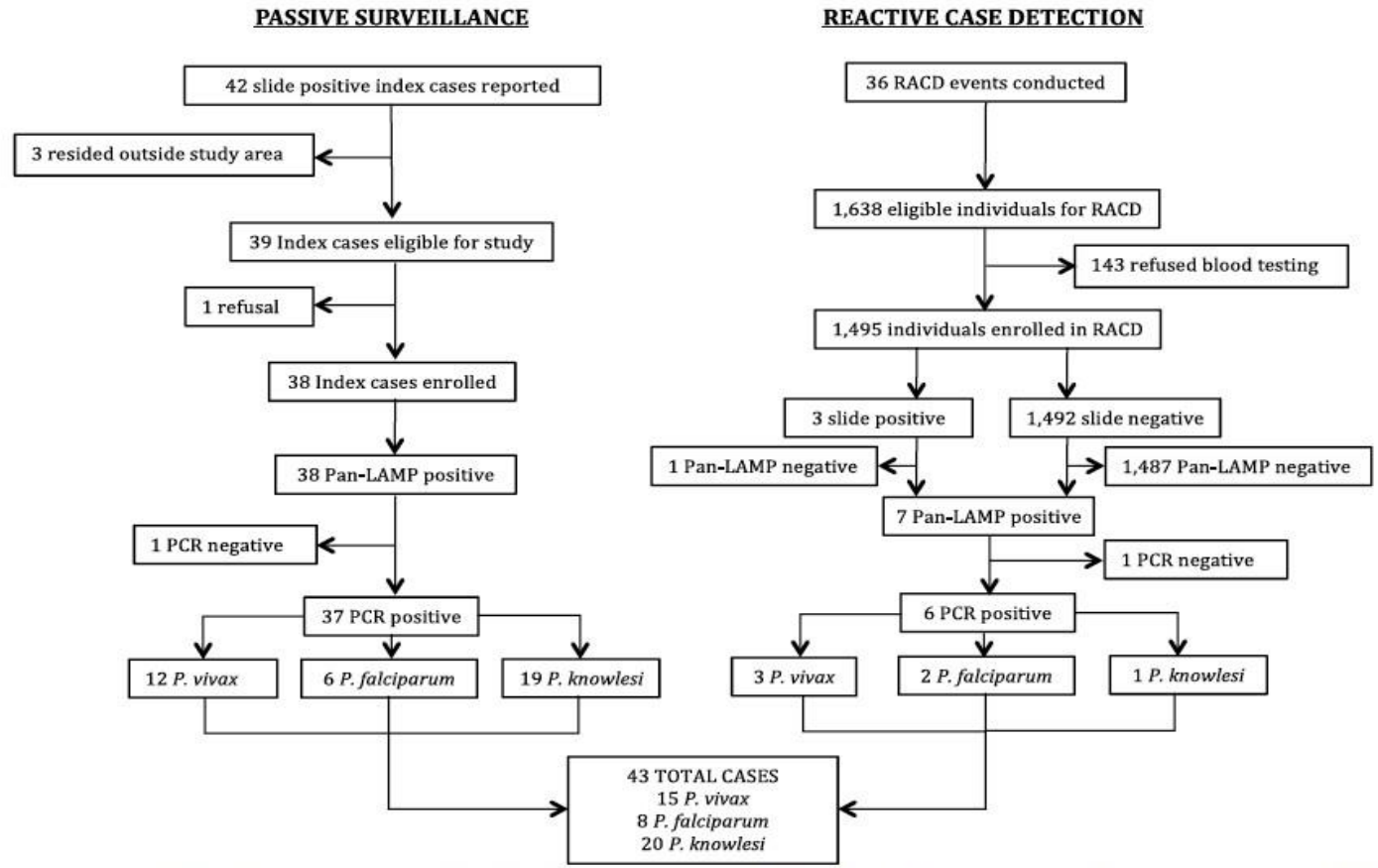


Fig. 2 Study recruitment and laboratory testing results 38 index cases were enrolled through passive surveillance and triggered 36 RACD events. One RACD event covered three contemporaneous indexes cases from the same household. In passive surveillance, 37 cases were confirmed by PCR and by RACD, there were six PCR-confirmed cases, resulting in a total of 43 cases. *Pan-LAMP* Pan-loop-mediated isothermal amplification

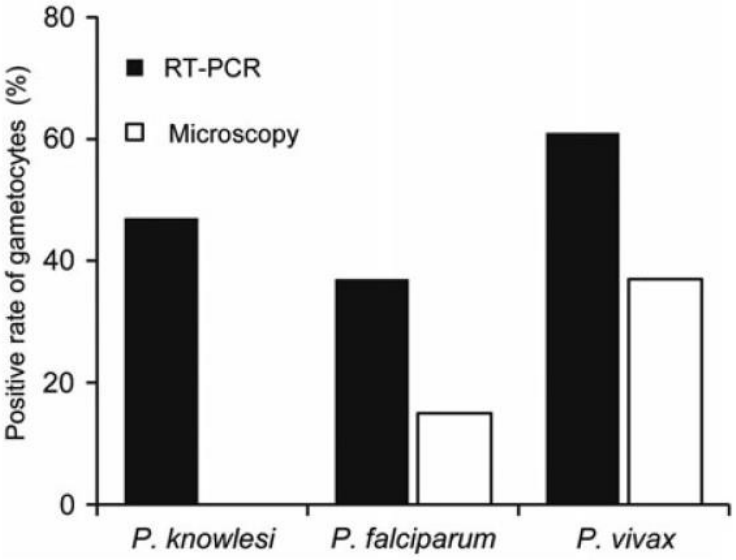


Fig. 2. Gametocyte positivity rate in patients infected with *Plasmodium knowlesi*, *Plasmodium falciparum* and *Plasmodium vivax*. *pks25*, *pvs25* and *pfg377* mRNA expression by RT–PCR.

Data from Vietnam

Plasmodium knowlesi infected about 25% of confirmed malaria cases, and nearly half of those were gametocytemic

Plasmodium knowlesi occurred in 33 of 70 *An. dirus* carrying malaria.

Table 2. Number of salivary glands of *Anopheles dirus* mosquitoes infected with parasites collected in different sites in the forest near Khanh Phu, Vietnam

	No. of PCR positive salivary glands		No. of examined for gametocyte DNA	
	Forest fringe	In the forest	Forest fringe	In the forest
Pf	4	17	4	17
Pv	2	10	1	3
Pm	0	0	0	0
Pk	2	8	0	0
Pf + Pv + Pk	0	7	0	7
Pf + Pk	1	0	1	0
Pv + Pk	1	14	1	8
Pf + Pv	1	0	1	0
Pf + Pm	0	3	0	3
Total	11	59	8	38

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

RDTs for detection of knowlesi malaria

RDT	Sensitivity	Sensitivity (<1,000 p/ µl)
OptiMal-IT	72%	45%
	32%	-
FirstResponse	74%	25%
CareStart	42%	-
Paramax-3	35%	-
Binax NOW	26%	0%
ParaHIT	23%	-

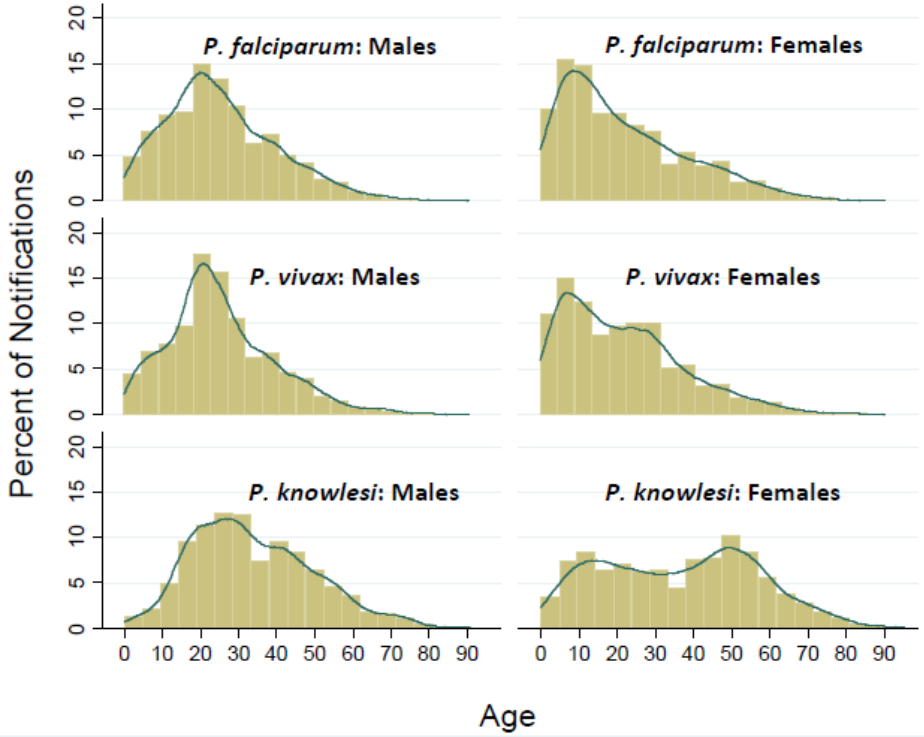
Barber *et al* (2013) J Clin Microbiol; Foster *et al* (2014) Mal J; Grigg *et al* (2014) J Clin Microbiol

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
  - Relatively high parasitemia (lower than for falciparum) is associated with severe *P. knowlesi* malaria
  - Patients having parasitemia >15,000 parasites/ul should be treated urgently and closely monitored until parasitemia is controlled, especially if > 45 years.

Age distribution and gender: Sabah MOH *P. knowlesi* notification data 2007 - 2014

Source: Menzies School of Health Research



- Patients with Pk older than those with Pf and Pv (median 32, 23, 24 yrs)
- 80% male

  (in children, 64% male)
- Females with Pk older than males: 38 vs. 31 yrs (45 yrs vs. 34 yrs in adults)
- Bimodal age distribution among females with peaks at 12 and 52 years

Who is at risk of severe disease and death from *P. knowlesi*?

Source: Menzies School of Health Research

- Parasitaemia and disease severity increase with age (Daneshvar *CID*, 2009, Barber, *CID*, 2013).
- Severe Pk not yet reported in children <12 yrs.
- Sabah MOH notifications 2010-2014: 0% mortality in 373 children (Rajahram, *EID*, 2016)
- Youngest reported death 31 years (range 31-84)
- Gender: females 19% of 4217 Sabah *P. knowlesi* notifications, but 46% of fatal knowlesi cases. Not significant after controlling for age. (Rajahram *et al, EID*, 2016)
- Larger cohorts: **Age** and **parasitaemia** are independently associated with severe disease (Sabah District data (Grigg et al, n=481; under review and Sabah Tertiary data (Barber et al, n=146; under review)

Parasites outside Malaysia benign?

- *"What we see in Vietnam, at least the work I've been involved in, seems very different to* the picture in Malaysia - all infections are pretty much asymptomatic, sub-microscopic a lot of the time, and very often in mixed species infections... I think other studies from Mekong have showed the same thing now too. I wonder if the Pk strains in this region my not be particularly well adapted to humans for some reason, and only cause very low level, and transient infection."

- Richard Culleton, 24 Feb 2017

It may be that *P. knowlesi* outside of Malaysian Borneo is different, more often causing low-grade asymptomatic carriage rather than aggressive and symptomatic infections.

Knowlesi malaria – is human-vector-human transmission happening?

Key Axiom: *Absence of evidence is not evidence of absence*

- No outbreak of *P. knowlesi* was reported in areas without presence of macaques.
- Genetic analysis of strains in macaques and human infections of *P. knowlesi* showed
  - same lineage – but it would take a very long time – several decades to centuries for a change to occur
  - absence of dhfr mutations in spite high SP pressure in humans
- Two largescale case control studies in Malaysia failed to show the presence of submicroscopic infections of P. knowlesi in humans. The indonesian study did detect asymptomatic infections
- One published study from Vietnam reported the presence of sporozoites of both *P. vivax* and *P. knowlesi* in the same mosquitoes. One conducted in Malaysia too, but results of this were not presented, nor details on the PCR methodology used.

Conclusion - is human-vector-human transmission happening

- Human *P.knowlesi* is still largely a zoonosis

- But all indications are that human to human transmission can take place, and probably **is** taking place in some situations, although not very efficiently yet. But this could change with time and with parasite adaptation

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

Treatment of uncomplicated knowlesi malaria

Artemether-lumefantrine vs chloroquine RCT (CAN KNOW study)
(Grigg et al. unpublished)

Rationale: no efficacy data for A-L despite being used in Malaysia, likely better safety profile compared to ASMQ

- A-L (n=58); CQ (n=65)
- No treatment failure in either arm by day 42
- Better early therapeutic response with A-L
  - PCT median 18 vs. 24 h; p=0.021
  - PCT_{50} 7.2 h vs. 8.2 h
  - PCT_{90} 13.7 h vs. 15.6 h
  - Microscopy negative at 24 h: 76% vs. 60%
  - Microscopy negative at 48 h: both 100%
- ↓ risk of anaemia at day 28 with A-L: 66% vs. 81%
- No difference in adverse events or SAEs between groups

Recommendation: ACT is preferred over CQ for treatment of uncomplicated *P. knowlesi* (irrespective of the presence of chloroquine-susceptible *P. vivax* in co-endemic areas)

Research Priorities

- **Evidence for human-to-human transmission**
  - Presence of mixed infections of *P.knowlesi* with human malaria species (*P.falciparum, P.vivax, P.malariae*) in the mosquito vectors
  - Vector host preferences and feeding habits – High human blood index in human *P.knowlesi* vectors
  - Laboratory studies and parasite genomics
- **Laboratory diagnosis**
  - Development of new rapid diagnostic tests for *P.knowlesi*
  - Development of high throughput tests (LAMP) for *P.knowlesi*
  - Selection of serological markers to assess human *P.knowlesi* transmission intensities
  - Development of a quantitative PCR (eg., to determine what proportion of the population is infected with *P.knowlesi).*
- **Entomology**
  - Mapping vectors of *P.knowlesi* and overlay on human *P.knowlesi* incidence/prevalence maps, and those of environmental risk factors
- **Clinical management**

Thank you.

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Dr Kamini Mendis
Ms Glenda Gonzales

References

Napier, L.E. and H.G.M. Campbell, *Observations on a Plasmodium infection with causes haemoglobinuria in certain species of monkeys*. Indian Med. Gaz, 1932. **67**: p. 151-60.

Knowles, R. andB.M. Das Gupta, *A study of monkey-malaria and its experimental transmission to man.* Indian Med. Gaz., 1932. **67**: p. 301-20.

Nakazawa, S., Marchand, R. P., Quang, N. T., Culleton, R., Manh, N. D., & Maeno, Y. (2009). Anopheles dirus co-infection with human and monkey malaria parasites in Vietnam. *International Journal for Parasitology*, *39*(14), 1533–1537. http://doi.org/10.1016/j.ijpara.2009.08.005

Foster, D., Cox-Singh, J., Mohamad, D. S., Krishna, S., Chin, P. P., & Singh, B. (2014). Evaluation of three rapid diagnostic tests for the detection of human infections with Plasmodium knowlesi. *Malaria Journal*, *13*, 60–60. http://doi.org/10.1186/1475-2875-13-60

Divis PCS, Singh B, Anderios F, Hisam S, Matusop A, Kocken CH, et al. (2015) Admixture in Humans of Two Divergent *Plasmodium knowlesi* Populations Associated with Different Macaque Host Species. PLoS Pathog 11(5): e1004888. doi:10.1371/journal.ppat.1004888

Shearer FM, Huang Z, Weiss DJ, Wiebe A, Gibson HS, Battle KE, et al. (2016) Estimating Geographical Variation in the Risk of Zoonotic *Plasmodium knowlesi* Infection in Countries Eliminating Malaria. PLoS Negl Trop Dis 10(8): e0004915. doi:10.1371/journal.pntd.0004915

Singh, B., et al., *A large focus of naturally acquired Plasmodium knowlesi infections in human beings*. Lancet, 2004. **363**(9414): p. 1017-24

Zhu, H.M., J. Li, and H. Zheng, *[Human natural infection of Plasmodium knowlesi]*. Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi, 2006. **24**(1): p. 70-1.

References

Tan, C.H., et al., *Bionomics of Anopheles latens in Kapit, Sarawak, Malaysian Borneo in relation to the transmission of zoonotic simian malaria parasite Plasmodium knowlesi*. Malar J, 2008. **7**: p. 52.

Cox-Singh, J. and B. Singh, *Knowlesi malaria: newly emergent and of public health importance?* Trends in parasitology, 2008. **24**(9): p. 406-10.

Lee, K.S., et al., *Plasmodium knowlesi: reservoir hosts and tracking the emergence in humans and macaques.* PLoS Pathog, 2011. **7**(4): p. e1002015

Vythilingam, I., et al., *Natural transmission of Plasmodium knowlesi to humans by Anopheles latens in Sarawak, Malaysia*. Transactions of the Royal Society of Tropical Medicine and Hygiene, 2006. **100**(11): p. 1087-8.

Fong, Y.L., F.C. Cadigan, and G.R. Coatney, *A presumptive case of naturally occurring Plasmodium knowlesi malaria in man in Malaysia*. Trans R Soc Trop Med Hyg, 1971. **65**(6): p. 839-40.

Daneshvar, C., et al., *Clinical and laboratory features of human Plasmodium knowlesi infection.* Clin Infect Dis, 2009. **49**(6): p. 852-60.

Chin, W., et al., *A naturally acquired quotidian-type malaria in man transferable to monkeys*. Science, 1965. **149**: p. 865.

Barber, B.E., et al., *A prospective comparative study of knowlesi, falciparum, and vivax malaria in Sabah, Malaysia: high proportion with severe disease from Plasmodium knowlesi and Plasmodium vivax but no mortality with early referral and artesunate therapy*. Clin Infect Dis, 2013. **56**(3): p. 383-97.

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

EntoPest Unit of Sabah Health Department, Malaysia, 2016

References

Fatih, F.A., et al., *Susceptibility of human Plasmodium knowlesi infections to anti-malarials.* Malar J, 2013. **12**: p. 425

Grigg, M.J., et al., *Artesunate-mefloquine versus chloroquine for treatment of randomised controlled trial.* Lancet Infect Dis, 2015. 16(2): p. 180-8.

Anopheles (Cellia) balabacensis Baisas, 1936. (n.d.). Retrieved August 30, 2016, from http://www.map.ox.ac.uk/explore/mosquito-malaria-vectors/bionomics/anopheles-balabacensis/

Anopheles dirus. (2014). Retrieved August 30, 2016, from http://scientistsagainstmalaria.net/vector/anopheles-dirus

Forest Ecology. (2014, February 23). Retrieved August 30, 2016, from http://forestecology.ligercambodiablog.org/2014/02/23/tropical-forest-animals

Anopheles latens. (2014). Retrieved August 30, 2016, from http://scientistsagainstmalaria.net/vector/anopheles-latens

Warden, P. (2015). OpenHeatMap. Retrieved from http://www.openheatmap.com/

P. knowlesi. (n.d.). Retrieved September 06, 2016, from http://www.mcdinternational.org/trainings/malaria/english/DPDx5/HTML/ImageLibrary/M-R/Malaria/knowlesi/body_Malaria_knowlesi_il3.htm

Jungle Trekking. (n.d.). Retrieved September 06, 2016, from http://www.sabahtourism.com/activities/jungle-trekking

Anopheles dirus. (2014). Retrieved September 06, 2016, from http://scientistsagainstmalaria.net/vector/anopheles-dirus

Butler, R. (n.d.). Long-tailed Macaque on boardwalk at Rimba Lodge (Kalimantan, Borneo - Indonesian Borneo). Retrieved September 06, 2016, from http://travel.mongabay.com/indonesia/images/kali8960.html

Update on development of the *Global vector control response*

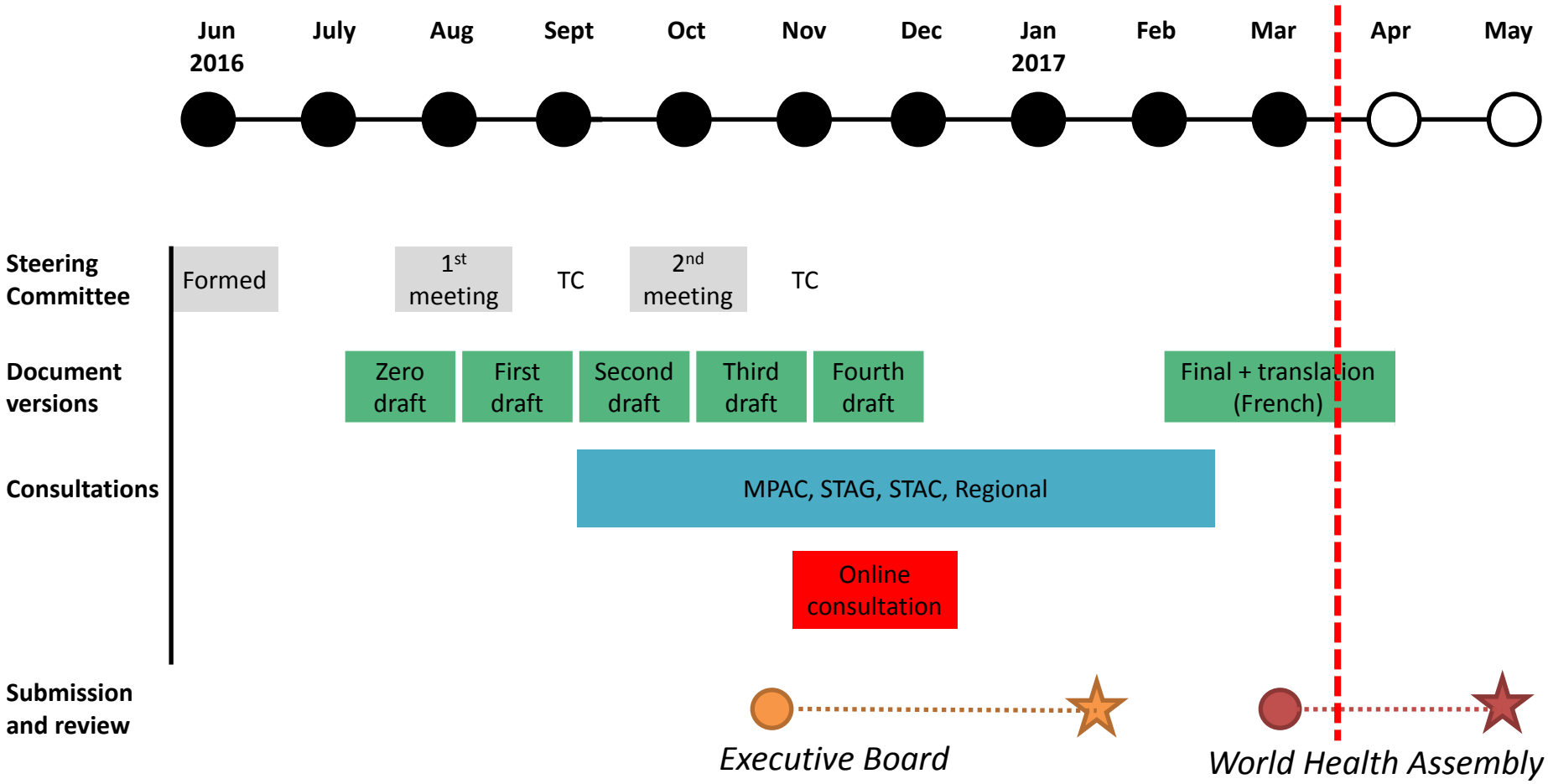
GMP/NTD/TDR

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

World Health Organization

Development timeline

Status: Fifth draft (v5.1) produced based on feedback from online consultation and Executive Board 140th session (held 28 January 2017)



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**.

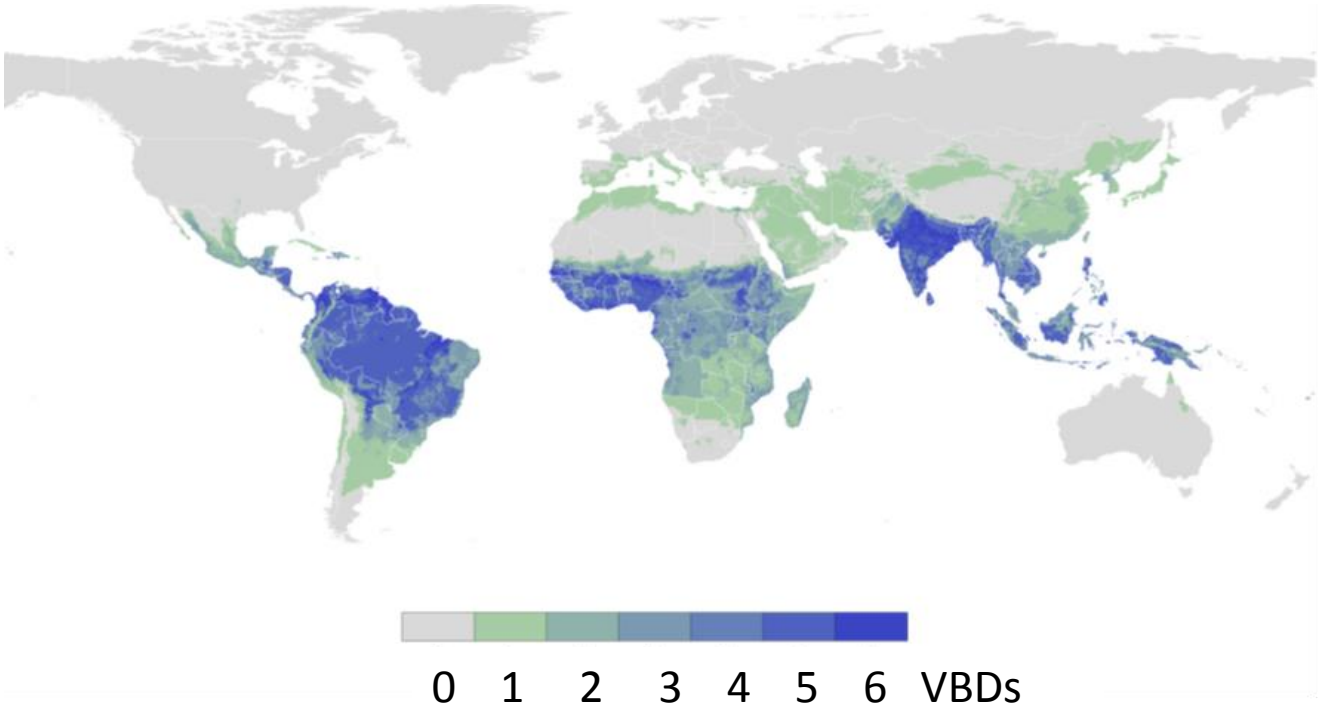
Margaret Chan

Director-General World Health Organization

Opening Address at World Health Assembly 69th session

May 2016

Global distribution of major vector-borne diseases



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

Rationale for a global vector control response (1)

- Major vector-borne diseases of humans include malaria, dengue, lymphatic filariasis, Chagas disease, onchocerciasis, leishmaniasis, chikungunya, Zika virus disease, yellow fever, Japanese encephalitis and schistosomiasis. Other vector-borne diseases are of local importance in specific areas or populations.
- These diseases account for around 17% of the estimated global burden of communicable diseases and disproportionately affect poorer populations. They impede economic development through direct medical costs and indirect costs such as loss of productivity and tourism.
- Social, demographic and environmental factors strongly influence transmission of vector-borne pathogens, with major outbreaks of dengue, malaria, chikungunya, yellow fever and Zika virus disease since 2014.

Rationale for a global vector control response (2)

- Most vector-borne diseases can be prevented by vector control, if it is implemented well. Major reductions in the incidence of malaria, onchocerciasis and Chagas disease have been largely due to strong political and financial commitment.
- For other vector-borne diseases, vector control has not been used to its full potential or had maximal impact. This situation can be reversed by realigning programmes to optimize the delivery of interventions that are tailored to the local context.
- This response calls for improved public health entomology capacity, a well-defined national research agenda, better coordination within and between sectors, strengthened monitoring systems, availability and use of novel interventions with proven public health value, and community involvement in vector control.

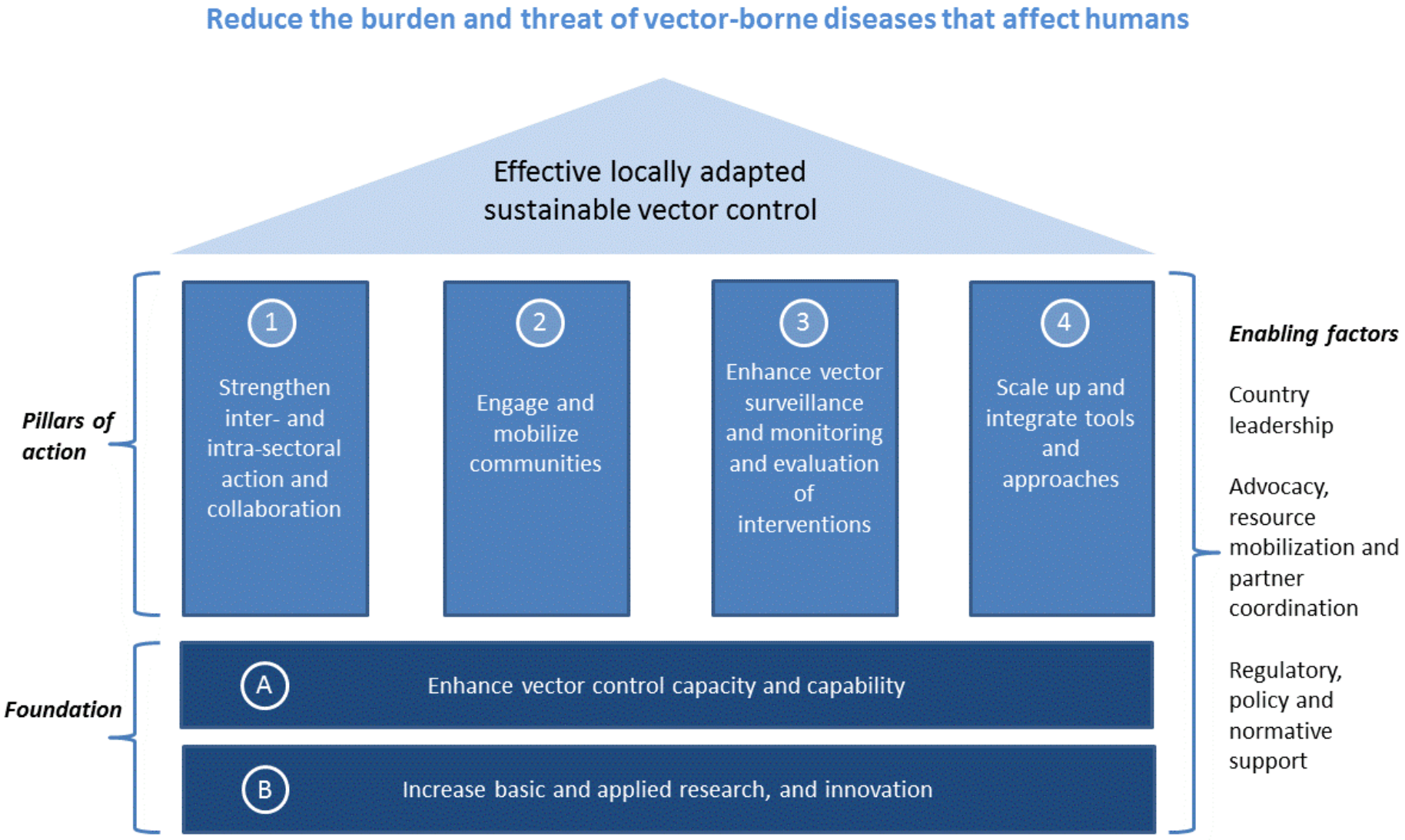
Vision, aim and goals

- **Vision**: A world free of human suffering from vector-borne diseases.
- **Aim:** Reduce the burden and threat of vector-borne diseases through effective locally adapted and sustainable vector control.

Goals	Milestones		Targets
	2020	2025	2030
Reduce mortality due to vector-borne diseases globally relative to 2016	At least 30%	At least 50%	At least 75%
Reduce case incidence due to vector-borne diseases globally relative to 2016	At least 25%	At least 40%	At least 60%
Prevent epidemics of vector-borne diseases*		In all countries without transmission in 2016	In all countries

** Rapid detection of outbreaks and curtailment before spread beyond country.*

Overview


Reduce the burden and threat of vector-borne diseases that affect humans
Effective locally adapted sustainable vector control
Pillars of action
1
Strengthen inter- and intra-sectoral action and collaboration
2
Engage and mobilize communities
3
Enhance vector surveillance and monitoring and evaluation of interventions
4
Scale up and integrate tools and approaches
Foundation
A
Enhance vector control capacity and capability
B
Increase basic and applied research, and innovation
Enabling factors
Country leadership
Advocacy, resource mobilization and partner coordination
Regulatory, policy and normative support

Feedback from WHO Executive Board

Discussed as agenda item 9.2 at the EB 140th session on 28 January 2017:

- Interventions made by 22 countries (16 EB members, 6 non-EB members) and 1 IGO
- Support was overwhelmingly positive with constructive suggestions for further strengthening of the GVCR prior to finalisation
- Development of a resolution for consideration at WHA70 was proposed by Fiji and supported by five other EB members (Canada, China, Colombia, New Zealand, USA) and four EB non-members (Australia, Brazil, Panama, Switzerland)
- Five countries offered to work on the resolution (Fiji, Australia, China, Colombia, New Zealand)

➢ The Executive Board noted the Report by Secretariat and decided that the Secretariat would work in conjunction with interested Member States to develop a draft resolution for consideration at WHA70 in May 2017

Updates following the WHO Executive Board session

The fifth draft of the Global vector control response was modified to adequately address:

- Schistosomiasis
- Ethical considerations around vector control
- Reference to a change in the evaluation pathway of vector control tools has been included
- Approaches for vector-borne disease control beyond vector control
- Coordination with other WHO initiatives, including Health Emergencies Programme, International Health Regulations, and R&S D blueprint for action to prevent epidemics.
- Pillars were re-ordered for logical progression.
- Costing for implementation

Costing approach

- Estimated cost for full implementation of the priority activities defined for the interim period of 2017-2022
- Included costs for **staffing, surveillance and coordination**
- Excluded the cost of vector control commodities and their deployment, as well as research and innovation implementation costs.
- Three-step approach:
  1. Country categorisation by a) historic risk (2000 – 2015), b) current burden (2016) and c) number of major VBDs. Adjusted based on knowledge of other VBDs (eg. of local significance)
  2. Estimate of population as risk from at least one of the major VBDs (estimates generated by Oxford University)
  3. Estimate of resources required based on a) burden level, and/or b) per capita (eg. # subnational meetings or sentinel sites per 500,000 pop basis)
  4. Country-specific cost estimates for defined resources generated using WHO-CHOICE method

Costing outcome (preliminary)

- Preliminary estimates* of total cost for implementation:

  Full implementation = US$460 million annually

  = US$0.06 per person per year

  Varies by country mainly due to population size and income level, but also due to vector-borne disease burden.

- Average per capita represents a **relatively modest investment in relation to implementation of core interventions** eg. for malaria, insecticide-treated nets (US$ 1.27 per person protected per year), indoor residual sprays (US$ 4.24 per person protected per year); for *Aedes*-borne diseases, community-based activities for dengue prevention (<US$1.00 per person protected per year).
- Anticipate that accurate estimates of national resource requirements and costs will be developed through comprehensive national vector control needs assessments at country and subnational levels.

** Note that estimates were subsequently revised based on refined estimates of populations at risk and classifications of burden/risk. The total revised global cost for annual implementation is US$ 330 million or US$ 0.05 per capita at risk of at least one vector-borne disease.*

World Health Organization

Costing outcome (preliminary)

Table 1. Annual estimated average cost per capita per country in US$ for full implementation of priority activities defined for 2017-2022, by vector-borne disease risk category and income level. Excludes small nations, defined at having population at risk of <100,000.

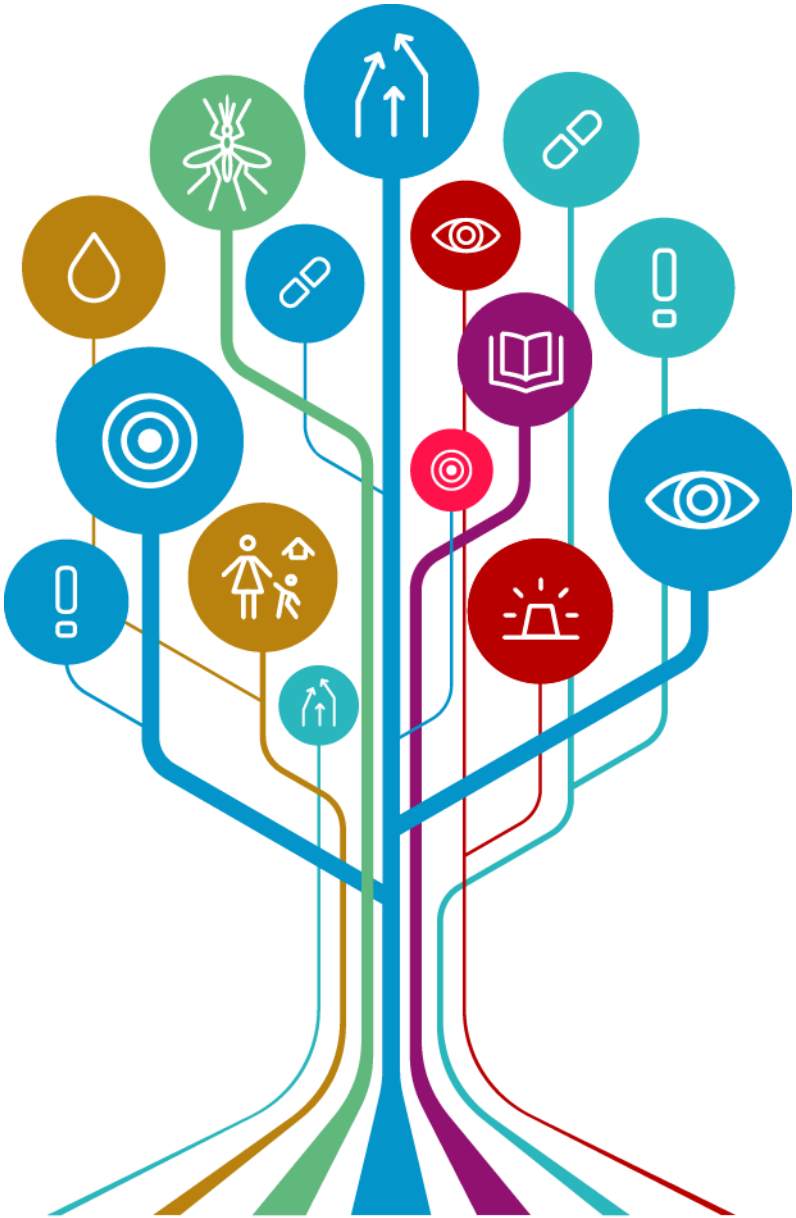
Country risk category	Country income level		
	Low	Medium	High
Low	0.02	0.04	0.16
Medium	0.02	0.04	0.17
High	0.05	0.05	0.89

GVCR current status

- Sixth draft currently being formulated for completion by 28 March
  - will be translated to French and provided online
- Costing under completion – for 31 March
- Resolution under development – for 31 March.
- GVCR slated as agenda item 14.2 for discussion at the World Health Assembly - 22 – 31 May 2017
- Work on comprehensive national vector control needs assessments template is ongoing

Contributed to development

Lead	GMP, NTD, TDR
Steering Committee	Co-Chairs: Prof. Thomas Scott, Dr Ana Carolina Santelli Other leading experts
WHO regional focal points	AFRO, EMRO, EURO, PAHO, SEARO, WPRO
Presented for discussion at:	• Initial consultation on response, Johannesburg • Asia-Pacific Malaria Elimination Network meeting, Bangkok • African Network for Vector Resistance meeting, Brazzaville • DDT expert group meeting, Geneva • Global Collaboration for Development of Public Health Pesticides meeting, Geneva • Pan-African Mosquito Control Association 3rd meeting, Lagos • International Congress of Entomology, Florida • WHO Vector Control Advisory Group meeting, Geneva • PAHO Vector Control Strategic Advisory Group, Washington • Information session for Member State missions, Geneva • European Mosquito Control Association meeting, Bečići • Roll Back Malaria Vector Control Working Group, Geneva • WHO Executive Board 140th session, Geneva • TDR Scientific and Technical Advisory Committee meeting, Geneva • Malaria elimination meeting, Geneva • Vector Control Technical Expert Group meeting, Geneva
Online consultation	Responses from Member States, research/academia, private sector, donor agencies, other UN agencies, NGOs (n = 80)



Global **Malaria** Programme

Online mapping tool for malaria vectors and parasites

(Under development)

Malaria Policy Advisory Committee Meeting

Geneva, Switzerland

22 – 24 March 2017

Global **Malaria** Programme

World Health Organization

Rationale (1)

- The Global Technical Strategy for malaria recognises key biological challenges to malaria control and elimination
  - GMP is responsible for tracking the status of these to guide the formulation of global policy and guidance
- Databases exist for malaria vector insecticide resistance and antimalarial drug efficacy and drug resistance data
  - GMP databases contain data as reported by Member States, including data not (yet) released in scientific publications
- For hrp2/3 gene deletion data there has been no established public database to date
  - GMP was in a good position to liaise with Member States and leverage collaborations with scientists to compile and report data

Rationale (2)

- Geographical mapping technologies can be leveraged for rapid visualisation and interpretation of complex data sets, such as temporal or spatial data series.
  - GMP has an established interactive mapping platform for antimalarial drug efficacy data.
  - A prototype malaria vector insecticide resistance interactive map was developed that leveraged the mapping platform used in the Ebola response.
- The need was identified for a harmonised mapping tool that consolidates multiple data sets under the umbrella of “biological threats” to malaria control and elimination
- Collection, analysis, publication and dissemination of data is a core part of WHO’s mandate

Scope: key biological challenges

Vector insecticide resistance (bioassays, mechanisms)

hrp2/3 gene deletions (single and double)

Antimalarial drug efficacy and drug resistance (TES results, molecular markers)

Development process

- Application specifications were developed on the basis of a prototype malaria vector insecticide resistance mapping tool completed in July 2016.
- Technical specifications were developed by the respective GMP units (EVC, PDT, DER).
- Coordination of Phase I development was undertaken by EVC with support provided by PDT and DER.
- Significant work was required to harmonize the three databases (and establish the hrp2/3 database).
- Significant work was required to ensure the application would function within the established WHO IT infrastructure.

Status

	Vector resistance	hrp2/3 gene deletions	Antimalarial drug efficacy and drug resistance
Database status	95% up-to-date	100% up-to-date	100% up-to-date
Number of records	1 493 sites 20 029 bioassays 4 612 mechanisms	101 sites 120 population-level	673 sites 1 338 TES studies 551 K13 studies
Mapping application	80% complete	60% completed	50% completed

- Originally planned for completion by Q1 2017
- Significant delays mean that Phase I (beta version) is projected for release in late Q2 2017
- Consultations will follow
- Phase II version will be developed accordingly