World Health Organization

Malaria Policy Advisory Committee (MPAC) Meeting Agenda

Dates: 11-13 September 2012
Location: Salle C, 5th floor, WHO HQ, Geneva

Tuesday, 11 September 2012

Time	Session	Purpose of session, target outcomes and questions for MPAC	Type
	Session 1		open
09:00	Welcome from Chair, MPAC **(K Marsh)**		
09:15	Report from the Director, GMP **(R Newman)**	For information and discussion	
10:45	**Coffee/tea break**		
	Session 2		open
11:00	Drug Resistance and Containment/Presentation **(A Schapira)**	Report back from TEG (21-22 June meeting)	
12:30	**Lunch**		
	Session 3		open
13:45	Malaria Burden Estimation/Presentation **(P Smith)**	Report back from ERG (27-28 June meeting), discussion of future meetings	
14:45	**Coffee/tea break**		
	Session 4		open
15:00	RTS,S Vaccine/Presentation **(P Smith**)	Update from JTEG; policy process for SAGE & MPAC	
16:15	IPTp-SP /Presentation/Update **(B Greenwood/L Slutsker)**	Report back from ERG (9-11 July meeting); Policy Recommendation	
17:30	**End of day**		

Report from GMP Director: Departmental Activities and the Global Malaria Landscape

Malaria Policy Advisory Committee
Geneva, Switzerland
11 September 2012

Robert D. Newman, MD, MPH
Director, Global Malaria Programme

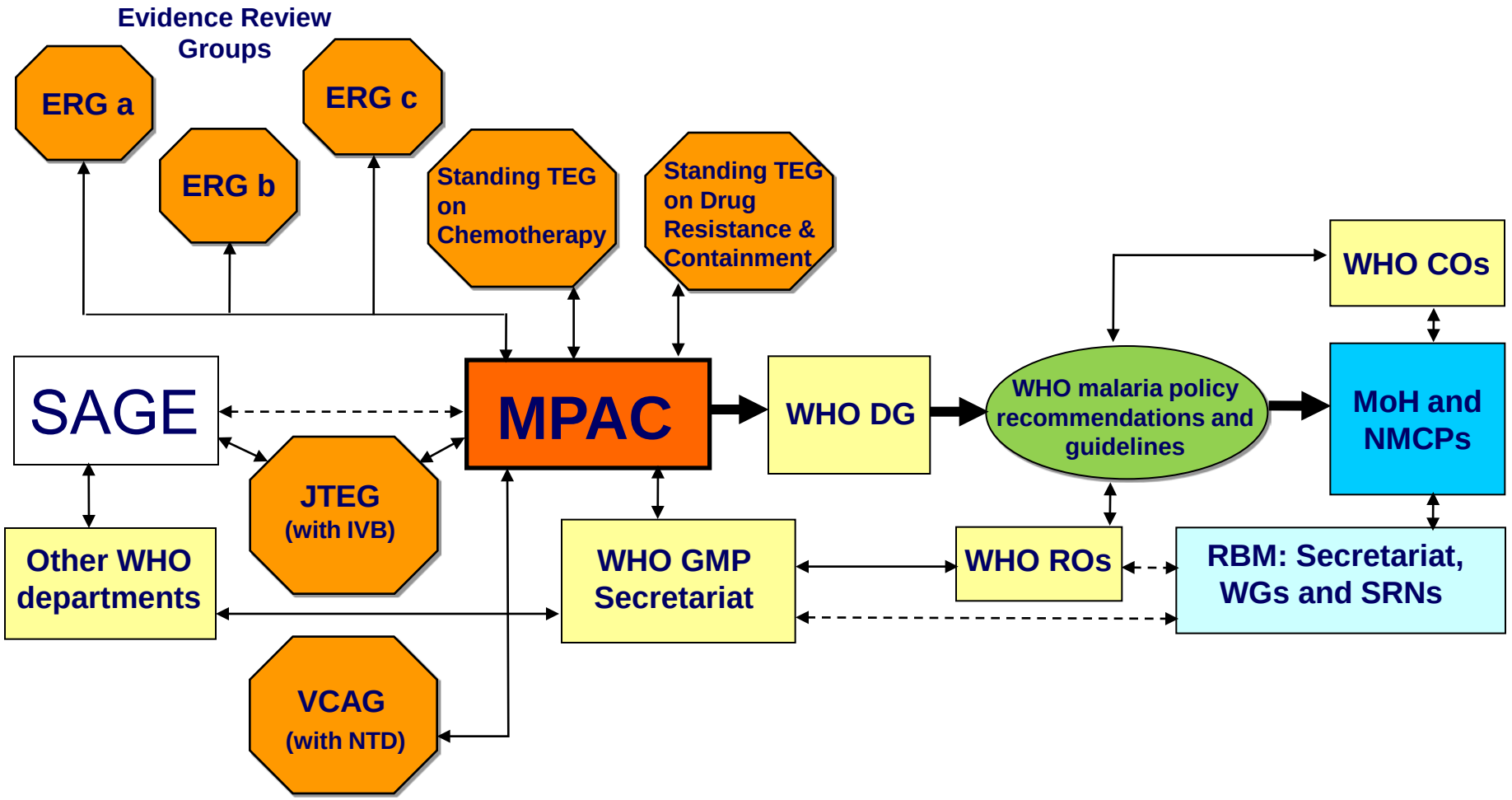
World Health Organization

GLOBAL MALARIA PROGRAMME

Outline

- **MPAC**
  - Updates on process and decisions since last meeting
- **Major GMP launches**
  - GPIRM
  - Surveillance manuals
  - T3
- **Other important departmental activities**
  - Capacity Building
  - Malaria Programme Reviews
  - Elimination Scenario Planning
  - Elimination Case Studies
  - Situation Room and ACT Supply Task force
  - Severe Malaria Handbook
  - Integrated Community Case Management (iCCM)
  - World Malaria Report 2012
- **The Global landscape**
  - Financial challenges
  - Australia and “Malaria 2012”
  - Global fund transformation
    - Malaria investment toolkit
  - WHO
    - World Health Assembly Resolution on malaria
    - Global Programme of Work 2014-2019

MPAC: organogram – September 2012



MPAC - Inaugural Meeting 2012

Overview - MPAC Inaugural meeting

- MPAC met 31 January to 2 February 2012 in Geneva
- Well attended open sessions, diverse voices, valuable inputs
  http://www.who.int/malaria/mpac/mpac_list_of_participants_meeting_jan2012.pdf
- Main recommendations (in order of immediate policy relevance):
  - Seasonal Malaria Chemoprevention: Policy Recommendation
  - Larviciding in sub-Saharan Africa: Interim position statement
  - RDT Procurement Criteria
  - Drug Resistance and Containment: Creation of a TEG
  - Malaria Burden Estimation: Convening of an ERG
- Detailed information http://www.who.int/malaria/mpac/feb2012/
- Meeting report http://www.malariajournal.com/content/11/1/137/abstract

Article has already achieved "highly accessed" status

World Health Organization

Global Malaria Programme

MPAC Feedback to and from RBM partners

- MPAC meets twice a year, every March and September
  - RBM ED (Dr. Fatoumata Nafo-Traore, newly appointed) is a standing observer at MPAC meetings
  - All meetings are conducted primarily in open session; other observers, including all RBM partners, welcome to attend
  - All pre-reads and presentations, including future meeting dates, available on http://www.who.int/malaria/mpac/mpacmeetings/
- Meeting Reports to be published approximately two months after meetings in the *Malaria Journal* and on MPAC website
- GMP (as RBM Board member) to provide feedback on MPAC conclusions and recommendations at Board meetings, every May and November, and gather suggestions for future meetings
  - MPAC session now a standing board agenda item
- Feedback also welcome at any time via mpacgmp@who.int

SMC: Process and Timelines

- TEG consultation (May 2011)
- MPAC endorsement – (February 2012)
- WHO Policy Publication – (March 2012)
- Field Implementation Guide manual
  - Development and drafting committee meeting (April 2012)
  - Finalization and editing of manual (September 2012)
  - Layout and printing (October 2012)
  - Launch (November 2012)

Larviciding – WHO Interim Position Statement

- In sub-Saharan Africa:
  - Larviciding measures should normally be used only as a supplement to core interventions (ITNs or IRS); larviciding should never be seen as substitute for ITNs or IRS in areas with significant malaria risk
  - Larviciding most likely to be cost-effective in urban areas, where breeding sites are more likely to be "few, fixed, and findable"
  - In rural settings, larviciding not recommended unless there are particular circumstances limiting the breeding sites, as well as evidence confirming that such measures can reduce the malaria incidence rate in the local setting
- WHO interim position statement now published and available: http://www.who.int/malaria/publications/atoz/larviciding_position_statement

Larviciding – a continuing challenge

- Strong special interest groups continue to push endemic countries in Africa regarding broader use of larviciding
- Recent ECOWAS statements are a vivid example
- Recent engagement with AFRO leadership on issue; agreement on a way forward

ECOWAS press release: 2 August 2012

"All hands should be on deck in support of the campaign by ECOWAS to eliminate malaria in the West African region by 2015, the President of the ECOWAS Commission, Ambassador Kadré Désiré Ouedraogo has affirmed….The President insisted that the goal of malaria elimination in the ECOWAS region is achievable, through the strengthening of the vector control component (biolarviciding) of an integrated strategy under a Tripartite Agreement between Cuba, Venezuela and the Commission. Implementation of the agreement emphasizes technology transfer, technical and financial support from Cuba and Venezuela to set up factories in West African countries (River States, Nigeria, Ghana and Cote d'Ivoire), for the production of biolarvicide by Cuba's Labiofam for large scale use for the region's malaria elimination campaign."

WHO Global Malaria Programme
Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs)
- 12 April 2012 -

Product	Catalogue number	Manufacturer	Re-tested product	RDT format	Performance criteria			
					A	B	C	D
Pan only								
Advantage Pan Malaria Card	IR013025	J. Mitra & Co. Pvt. Ltd.		Cassette				
CareStart™ Malaria pLDH (PAN)	G0111	Access Bio, Inc.		Cassette				
Clearview® Malaria pLDH	70884025	Orgenics Ltd. (Inverness Medical Innovations)	√	Cassette				
diagnosticks MALARIA (Pan) Cassette	MPNWBC1007.3	SSA Diagnostics & Biotech Systems		Cassette				
First Response® Malaria Ag pLDH	I12FRC30	Premier Medical Corporation Ltd.		Cassette				
FirstSign™ - PanCheck (Pan) Malaria Test	2104 CB-25	Unimed International Inc.		Cassette				
OnSight™ - PanScreen (Pan) Malaria Test	539-25-DB	Amgenix International, Inc.		Cassette				
Parabank™ Device - Rapid test for Malaria Pan	50301025	Zephyr Biomedical Systems	√	Cassette				
Pv only								
SD BIOLINE Malaria Ag Pv	05FK70	Standard Diagnostics, Inc.		Cassette	N/A			

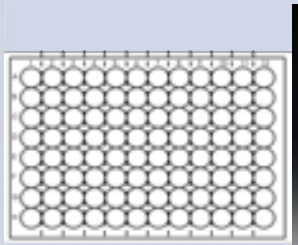
A: *P. falciparum* panel detection score ≥ 75% at 200 parasites/µl
B: *P. vivax* panel detection score ≥ 75% at 200 parasites/µl
C: False positive rate < 10%
D: Invalid rate < 5%

History & Future Product Testing and Lot Testing

	2003 -2011	2011-2014	2015-2016	2017
	Step 1: Start	Step 2: Develop	Step 3: Roll-out	Step 4: Implemented
	Establish patient-derived sample panels	Develop and evaluate recombinant antigen panels	Scale-up and launch recombinant antigen panels	Manufacture and distribute reference materials
	Establish lot testing process	Ongoing lot testing based on cultured parasites	Roll-out lot testing based on recombinant antigens	Local lot testing financed by purchaser
	Product testing round 1 to 3	Ongoing product testing round 4 & 5	Product testing based recombinant panel and partly financed by IVD suppliers	Product testing financed by IVD suppliers
Cost:	**$$$$**	**$$$$$**	**$$$**	**$**

FUNDED

Malaria recombinant antigens

Product	Product development	Demo & scale up	Stakeholder review	Roll out
Product testing panels	Evaluate recomb ag against parasites; assess feasibility, heat stability and determine ideal format  	Evaluate new combined panels (Ag, wildtype/culture samples + negatives); fee schedule		Centralized, continuous, IVD funded evaluation scheme
Lot testing panels		18 labs assessment; manufacturing and establish logistics		Manufacture, distribute & sell
Positive control wells		2 country demo projects		Manufacture, distribute & sell

RDT Product Testing: Rounds 1 - 4

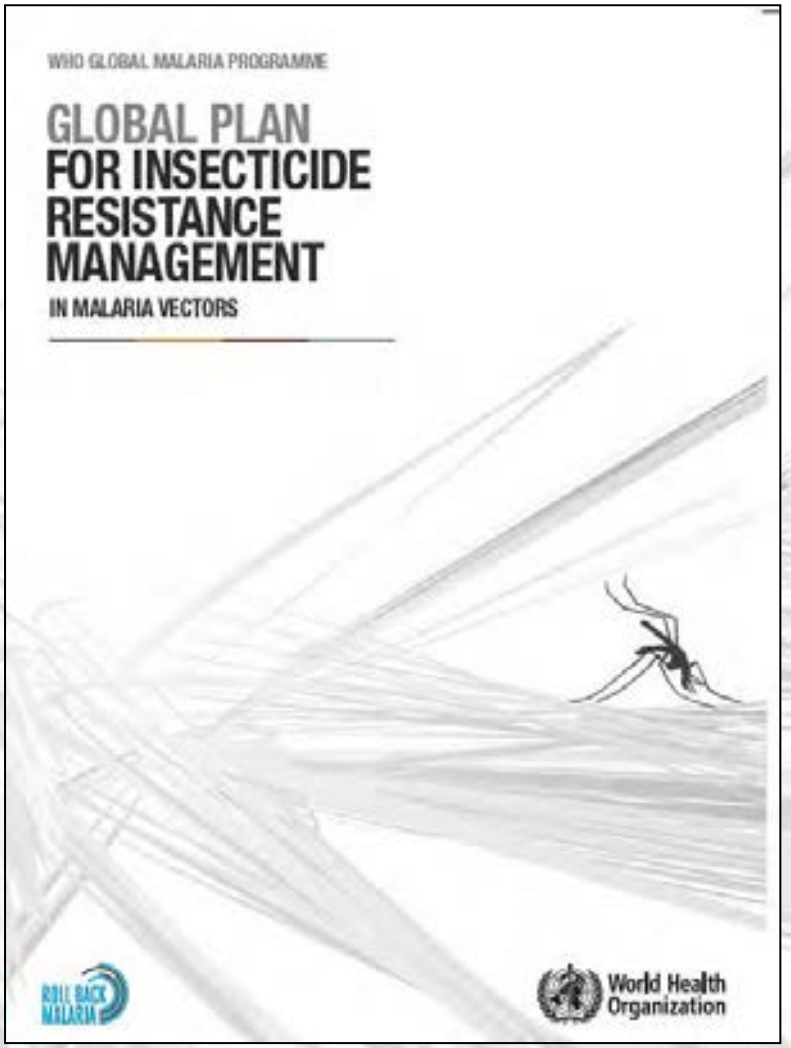
	Round 1	Round 2	Round 3	Round 4
No. products	41	29	50	48
No. manufacturers	21	13	23	27
Resubmissions	-	1	23	13
Median Pf PDS @ 200 p/ul (range)	70.2% (1.3-100%)	82% (22.0-98.0%)	83.84% (2.02 – 98%)	89.34% (32.7-100%)
Median Pv PDS @200p/ul (range)	30% (0-100%)	75% (0-95%)	51.43% (0 -97.1%)	51.30% (0-100%)
Median false positives against clean negatives (range)	1.8% (0-28.0%)	2.0% (0.0-37%)	1.0% (0.0-44%)	1.10% (0.0 – 99.1%)



RDTs meeting WHO procurement criteria (April 2012 following MPAC decision)

Test	Rounds 1-3	Round 4 (NEW!)	Total
Pf only	21	5	26
Pf + non-Pf species	12	15	27
Pv only	1	0	1
Pan	1	0	1

GPIRM – Official Launch 15 May 2012



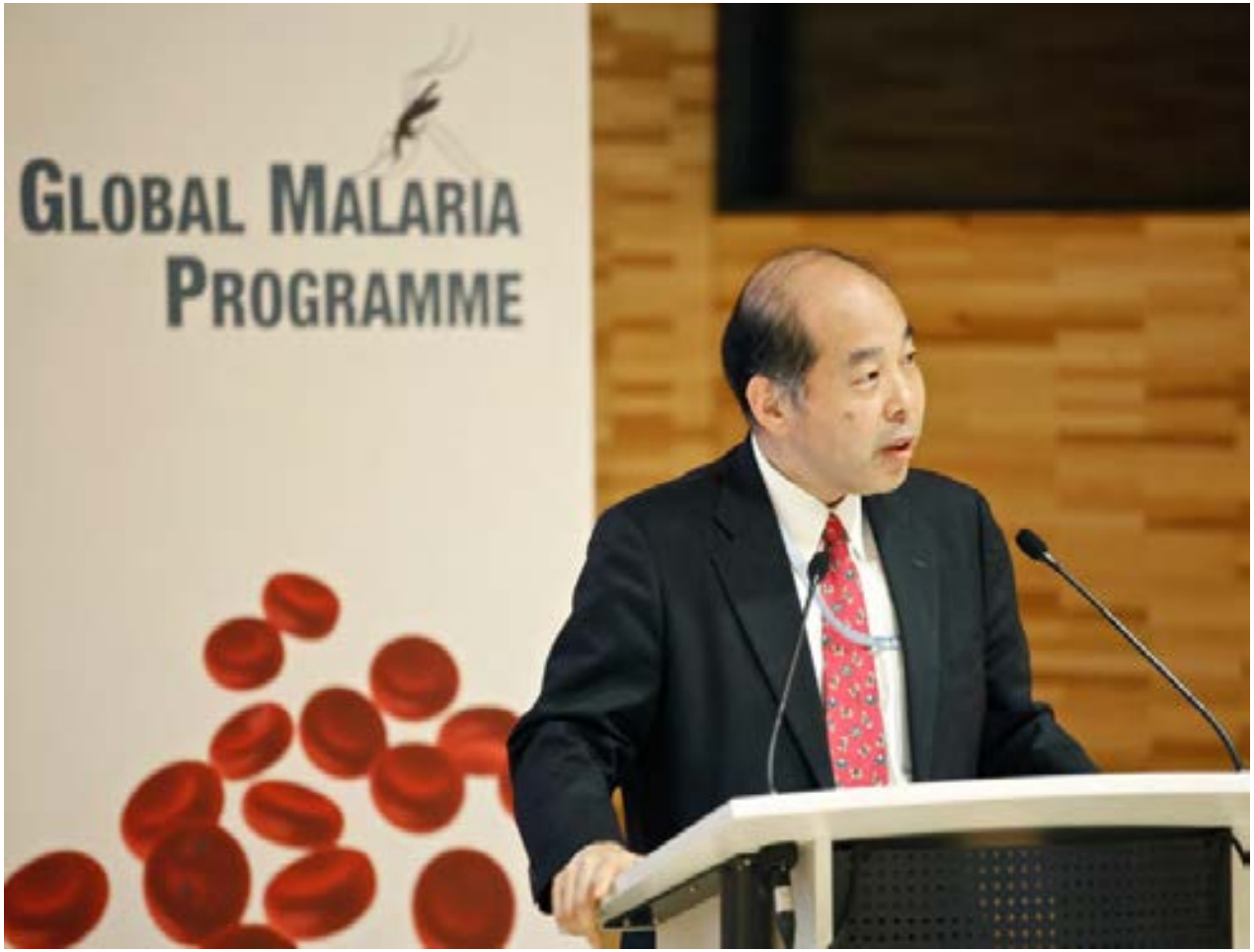
GPIRM goal:

maintain the effectiveness of malaria vector control

A call to action

If we take action now, we can stay ahead of the curve and maintain the fabulous gains that we have made.

Addressing the challenge



Insecticide resistance is a significant **challenge** that we need to address.

We must stand united and make sure that our existing vector control tools, including the current insecticides, remain effective until new active ingredients and compounds come to the market.

Hiroki Nakatani,
WHO Assistant Director-General
HIV/AIDS, TB, Malaria and Neglected Tropical Diseases

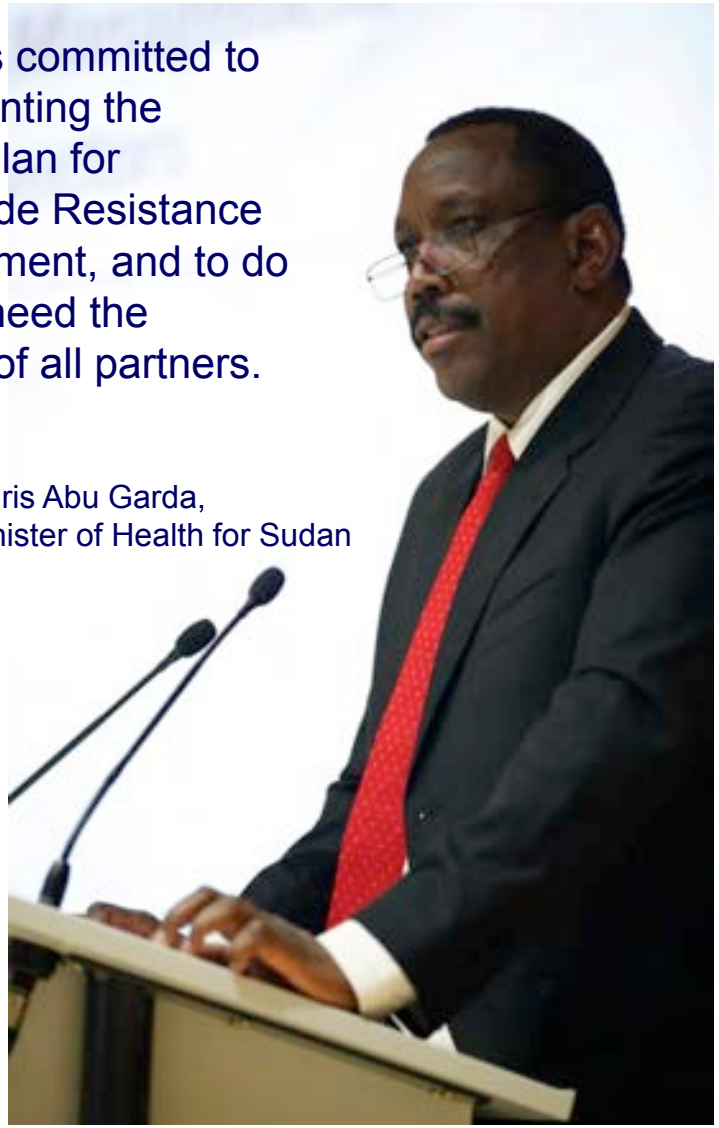
The view from endemic countries

This will require heavy investments, but there is no quick fix solution for our ambitious goal of eradicating malaria in the long run.

Dr Richard Kamwi,
Minister of Health and Social Services for Namibia

Sudan is committed to implementing the Global Plan for Insecticide Resistance Management, and to do this we need the support of all partners.

Dr Bahar Idris Abu Garda,
Federal Minister of Health for Sudan



Partner perspectives

Finding the resources

We will use the financial muscle of the Global Fund
to use the limited resources available
to build capacity for entomological monitoring
and to ensure that these strategies
to manage insecticide resistance are in place.

Scott Filler
The Global Fund to Fight AIDS, Tuberculosis and Malaria

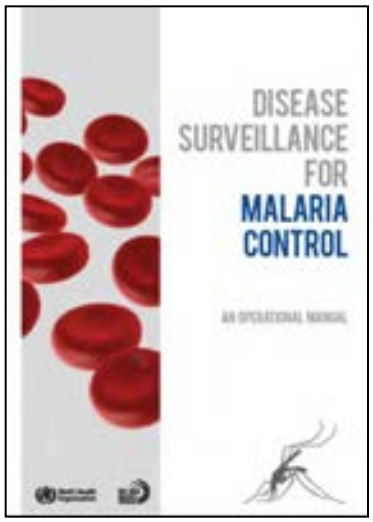
We need more tools.
We need to be committed
and we need to find the resources.

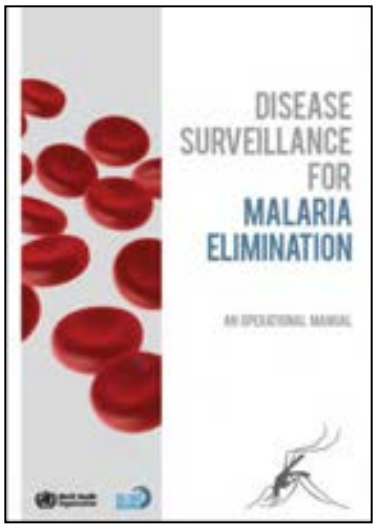
David Brandling-Bennett
Bill & Melinda Gates Foundation

Surveillance for malaria

Two new global manuals developed by GMP

- Providing guidance to endemic countries on the operation of malaria surveillance systems for control and elimination
- Focusing on program implementation and complementing other existing guidance on malaria indicators
- Updated surveillance guidance has not been issued by WHO since Global Malaria Eradication Programme era





Launched in Namibia by WHO Director- General

(24 April 2012)

Surveillance Manuals: Contents

Two volumes: (i) programs in control phase; (ii) programs in elimination phase

Contents

- Overview of Malaria Surveillance in Different Phases of Malaria Control
- Key Concepts in Malaria Surveillance
- Data Recording, Reporting, Analysis and Use
- Establishing Surveillance Systems

Annexes

- Diagnostic tests/ quality assurance
- Core surveillance indicators
- Registers, case investigation forms, report forms, sample analyses

“T3: Test. Treat. Track.” initiative

Coordinated international effort needed

- To support countries in scale-up of diagnostic testing, treatment and surveillance
- End goal is to ensure that
  - Every *suspected* malaria case is tested
  - Every *confirmed* case is treated with a quality-assured antimalarial medicine
  - The disease is tracked through timely and accurate surveillance systems

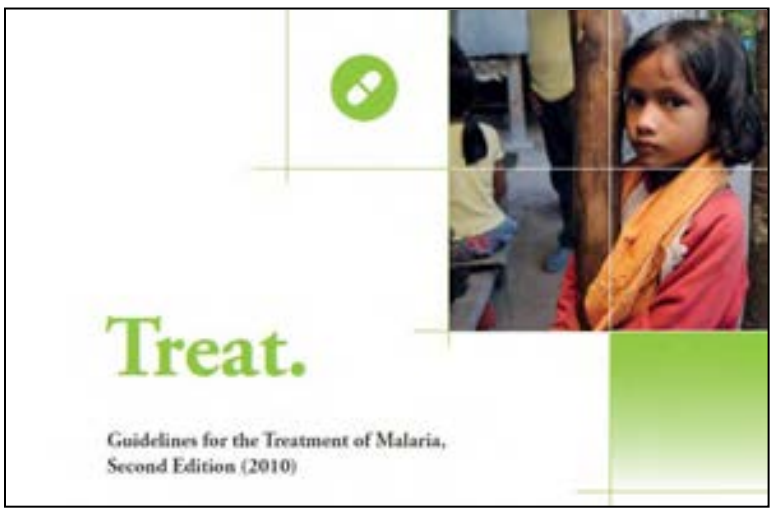
T3: Test. Treat. Track.
Worldwide Launch: Namibia, World Malaria Day 2012

Test.

Universal Access to Malaria Diagnostic Testing: an Operational Manual (2011)

KEY RECOMMENDATIONS

- Every suspected malaria case should be confirmed by microscopy or RDT prior to treatment
- All diagnostic tools must be quality-assured across all levels of the health system
- Scale-up of malaria diagnostic testing should be integrated with efforts to improve the management of other febrile illnesses

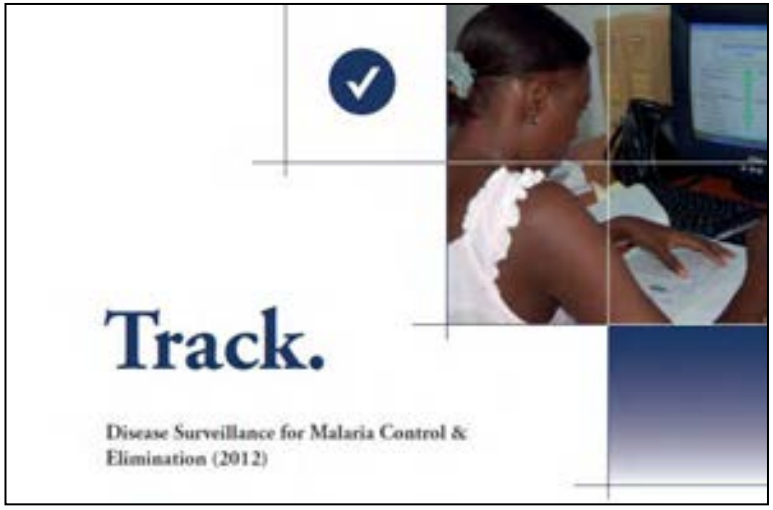


Treat.

Guidelines for the Treatment of Malaria, Second Edition (2010)

KEY RECOMMENDATIONS

- After diagnostic confirmation, every uncomplicated case of *P. falciparum* malaria should be treated with a quality-assured ACT
- Every severe case of *P. falciparum* malaria should be treated with intravenous or intramuscular artesunate, followed by a full course of an ACT
- Antimalarials should be routinely monitored for therapeutic efficacy



Track.

Disease Surveillance for Malaria Control & Elimination (2012)

KEY RECOMMENDATIONS

- Individual cases should be registered at health facility level. This allows for the recording of suspected cases, diagnostic test results, and treatments administered
- In the malaria control phase, countries should report suspected, presumed and confirmed cases separately, and summarize aggregate data on cases and deaths on a monthly basis
- Countries in elimination phase should undertake a full investigation of each malaria case

“T3: Test. Treat. Track.” initiative

Need to move from set of recommendations to <u>scale-up</u>

- Dedicate financial resources and intensify advocacy efforts
- Provide assistance to countries to develop scale-up strategies
- Develop case studies, share lessons learned, strengthen evidence base
- Promote South-South collaboration
- Reach out to wider audiences

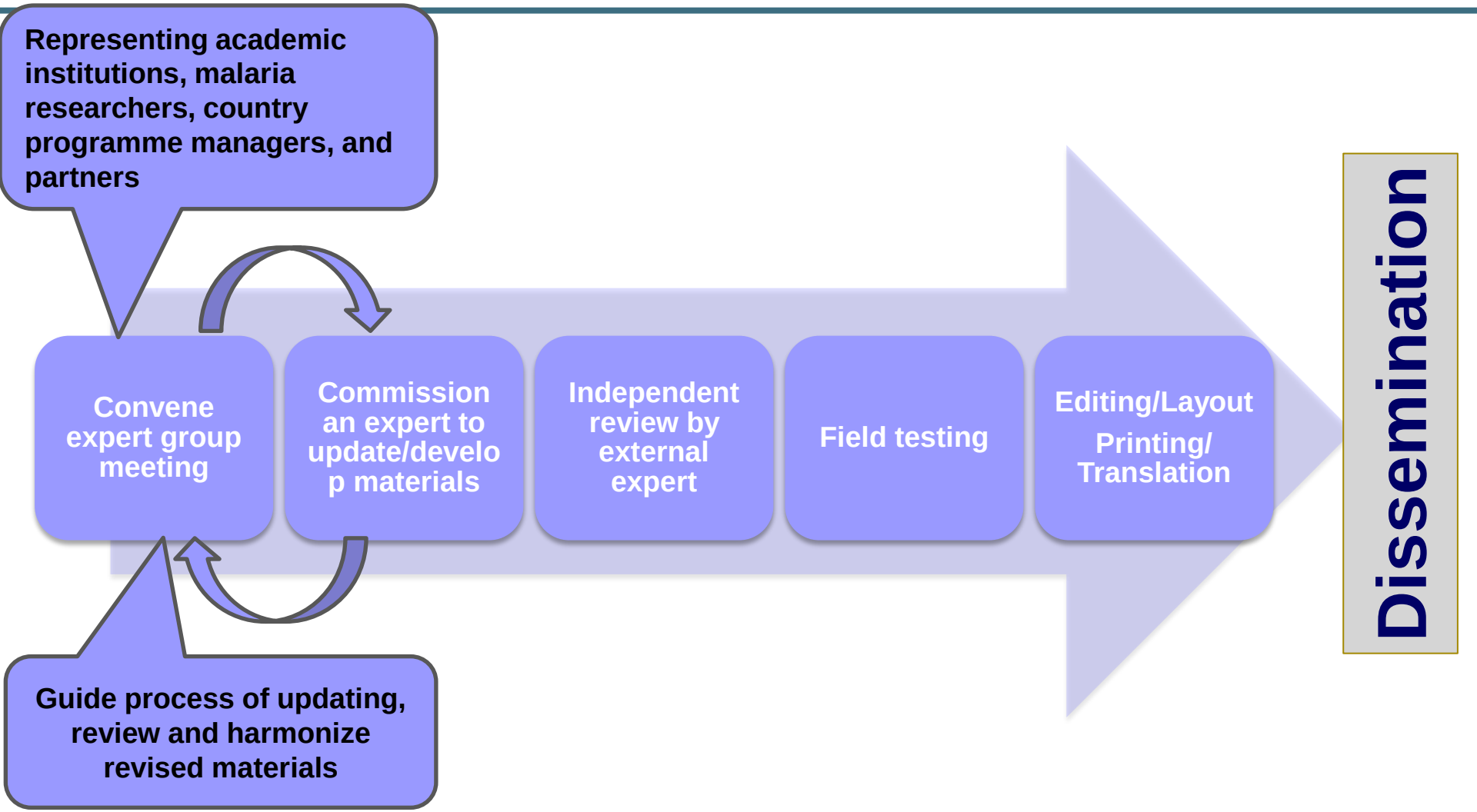
T3: Collaborating partners

WHO - Russian project to strengthen human resource capacity in malaria control and elimination

- Goal:
  - Strengthen human resource capacity for malaria control and elimination in malaria endemic countries targeting:
    - Malaria endemic countries in Africa
    - Commonwealth of Independent States (CIS): Armenia, Turkmenistan, Azerbaijan, Georgia, Kyrgyzstan, Tajikistan and Uzbekistan

- Activities:
  - Develop up-to-date training materials for national and district level health workers
  - Conduct international training courses for malaria control managers at national and subnational levels:
    - WHO regional malaria training courses (AFR & EMR)
    - Advanced training course on malaria surveillance, monitoring and evaluation for experts from malaria endemic countries in Africa and CIS
  - Strengthen the capacity of the malaria endemic countries in CIS in malaria elimination

Developing malaria training materials: Process



Developing training materials on malaria control and elimination

Materials finalized

Entomology and vector control
- Guide for participants
- Guide for tutors

Case management
- Guide for participants
- Guide for tutors

Epidemiological approach
- Guide for participants
- Guide for tutors

Planning and managing programme
- Guide for participants
- Guide for tutors

Materials under development

Field testing: Oct 2012

Malaria elimination
- Guide for participants
- Guide for tutors

E-learning training package: malaria case management *(to reach wider audience)*

District level capacity for malaria control

- Country level decentralization of health systems - focus on district level
- Limited technical competence and managerial skills at the district level
- Reducing transmission makes malaria more heterogeneous at local level

Need for capacity building of district managers

- Develop district manual for malaria control with up-to-date, practical and simplified guidance on malaria control at district level for planning, implementing and measuring malaria control locally (in process)
- Develop a generic WHO district malaria training package (learner's and tutor's guides) based on the district manual for malaria control (planned)

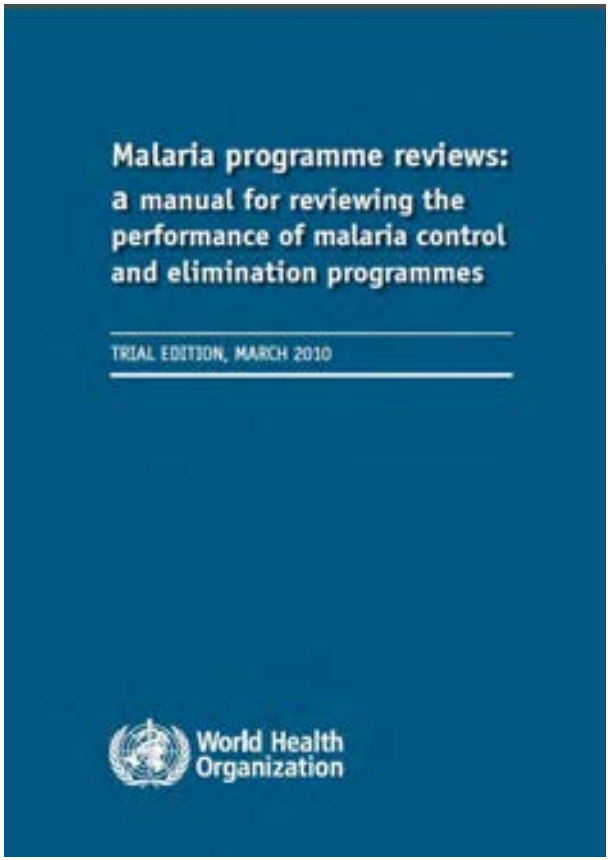
Support to training activities

Courses	2009	2010	2011	2012
International course on malaria control and its management for managers/health professional (AFR)				
• *Anglophone countries in Ethiopia,*	✓		✓	✓
• *Lusophone course in Mozambique*		✓		
• *Francophone countries in Benin*			✓	✓
International course on malaria control and its management for managers/ health professional (EMR)	✓		✓	✓
International course on malaria case management for clinicians (EMR)		✓		
Course malaria microscopy & quality assurance (EMR)	✓		✓	
1st international course on malaria elimination (EMR)				✓
International training course on malaria surveillance, monitoring and evaluation for African countries (AFR/EMR)	✓	✓	✓	✓
International malaria training course for facilitators/tutors (AFR/EMR)				✓
International training course on malaria surveillance, monitoring and evaluation for Commonwealth Independent States (EUR)				✓
Regional training course on medical entomology and vector control (EUR)				✓

Malaria Programme Review-Definition

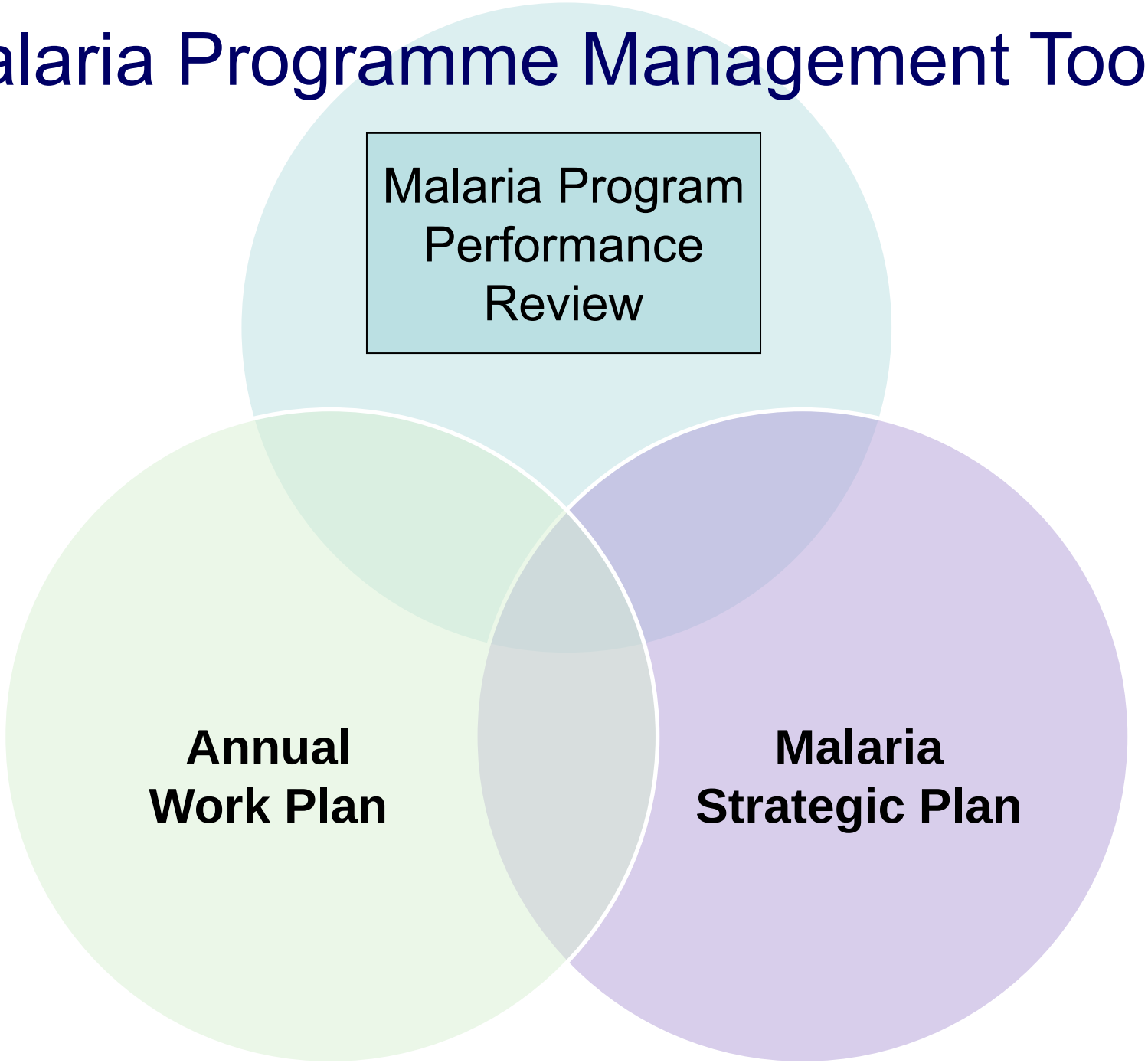
- Periodic, high-level joint programme management process:
  - To review and evaluate progress and performance of country programmes within the national health and development agenda
  - Aim of improving performance (related to program goals, objectives & targets) and/or redefining the strategic direction

Malaria Programme Reviews (MPR)



- Trial edition of guidance issued in 2010
- >20 countries have undertaken programme reviews using guidance
- Three steps
  - - desk review
  - - field investigation
  - - analysis and write up
- Undertaken every 3-5 years; duration 4-9 months
- Need to simply process

Malaria Programme Management Tools



Malaria Programme Reviews (MPR)

- Consultation held August 7-9, 2012 to review current guidance – programme managers, development partners
- Draft meeting report produced
- Timelines for revised MPR guidance
  - Updated by end 2012
  - Field tested Q1 quarter 2013
  - Finalized Q2 2013

MPR and MSP needs going forward

- Make MPR and MSP process and methods simpler and less time- and resource-intensive
- Improve quality of conducted MPR and MSP to meet minimum standards
  - Country leadership and ownership essential
- Set up systems to **follow up reviews**
  - Ensure relevant policy and operational project program changes are executed
- Review, revise, and formally publish manual for developing malaria strategic plans

Need for malaria elimination planning tool

- Substantial progress in fighting malaria worldwide
- Magnitude of progress in some countries raises question of malaria elimination
- Countries considering elimination would benefit from tool to provide rigor for program planning
  - Potential to provide realistic timelines
- WHO and partners (Clinton Health Access Initiative, Global Health Group, & Imperial College - London) developing **Elimination Scenario Planning (ESP)** tool

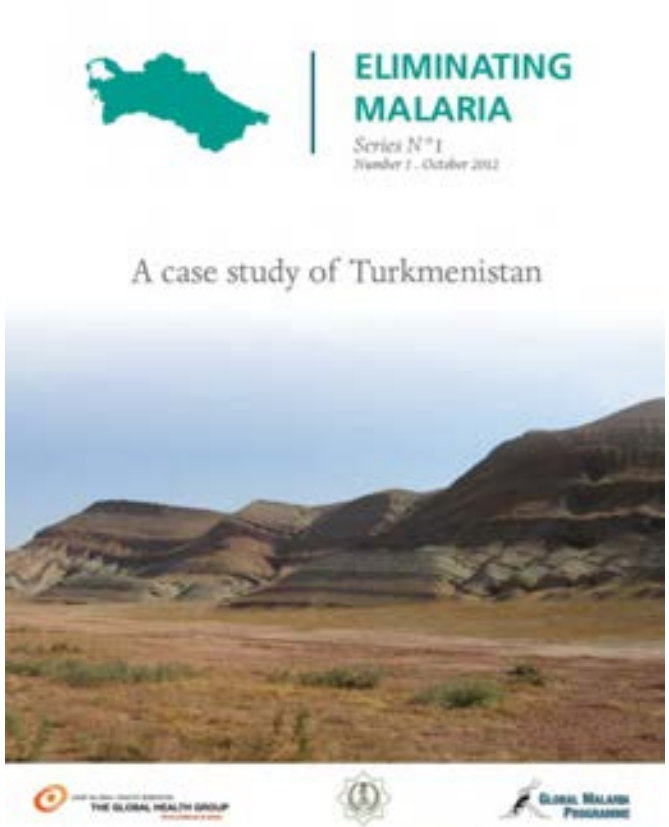
ESP tool components

- Manual
  - Reviews key concepts in elimination planning
  - Technical, Operational, Financial feasibility of elimination
- Malaria transmission model
  - Establish baseline transmission level
  - Explore effect of different combinations of interventions

ESP next steps

- Revise manual and software based on workshop feedback
- Share revised tool for limited peer review
- Release and dissemination
- In long-term, ESP tool could be adapted for settings with *P. vivax* as well as control scenarios (with cost effectiveness component) and tool for strategic program planning

Elimination case studies



- 10 case studies being produced jointly with Global Health Group
- Four to be launched in October at *Challenges in Malaria Research: Progress towards malaria elimination* - Cape Verde, Sri Lanka, Turkmenistan, Mauritius
- Detailed description of epidemiology, control strategies applied over time, successes and failures and lessons learnt.
- To help NMCPs and other partners contemplating elimination have a better understanding of process involved

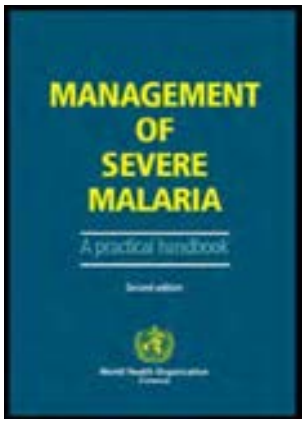
Monitoring results in countries with highest malaria burden

- WHO-GMP / RBM Malaria Situation Room to track progress (financing, commodities, intervention coverage and impact) in 10 countries in WHO African Region with highest burden
  - **Nigeria, DRC, Tanzania, Uganda, Mozambique, Ghana, Cote d'Ivoire, Burkina Faso, Niger and Cameroun**
  - Proactively identify bottlenecks requiring resolution: political, financial, procurement and supply chain
  - To be executed in collaboration with WHO-AFRO
    - Support data collection efforts of SHOC room
  - Proposal for funding submitted to major donor
    - Response pending

Inter-agency ACT Supply Taskforce

- **Established:** September 2011
- **Mandate:** Identify countries at risk of public sector ACT stock outs and promote mitigation actions
- **Members:** WHO/GMP, ALMA, CHAI, Global Fund (AMFm and VPP), USPMI, UNDP, and UNICEF
- **Methodology:** Quarterly monitoring of country ACT and (since Round 3) RDT stocks at central level, and triangulation of results with manufacturer and procurer data where appropriate, in order to predict supplies over subsequent 6-month periods. Mitigating action in case of confirmed supply risks
- **Impact:** Four rounds of data collection and analysis leading to prevention of stock outs in a number of countries through various mechanisms such as accelerated, split and/or new orders
- **Future:** The Taskforce is currently exploring options to improve its monitoring system and better meet country needs

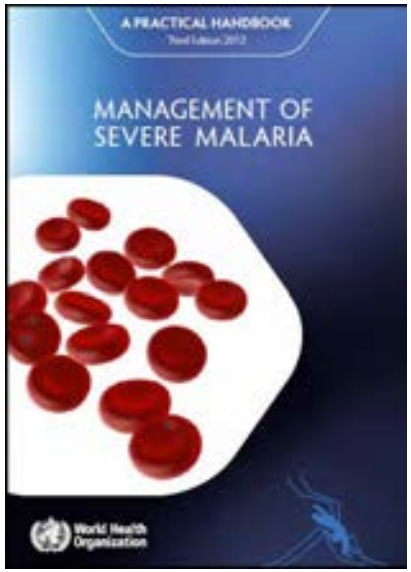
Management of Severe Malaria: A Practical Handbook - Background



- Last update in 2000 (2nd edition)
- Since then, updates in WHO recommendations for diagnosis and treatment of malaria, including severe disease
  - Guidelines for the Treatment of Malaria 2nd edition (2010)
  - Treatment of severe malaria (April 2011)
- Several recent data and publications on severe malaria (2000-2011)

Management of Severe Malaria: A Practical Handbook – Review Process

- **TEG on Malaria Chemotherapy meeting (September 2011) with following objectives:**
  - Review current evidence on epidemiology, pathology, pathophysiology and management of severe malaria
  - Update WHO practical handbook on the Management of severe malaria in line with current WHO Guidelines
- **Practical Handbook: Status**
  - Layout - August 2012
  - Printing and launch - October 2012
  - French translation - TBC

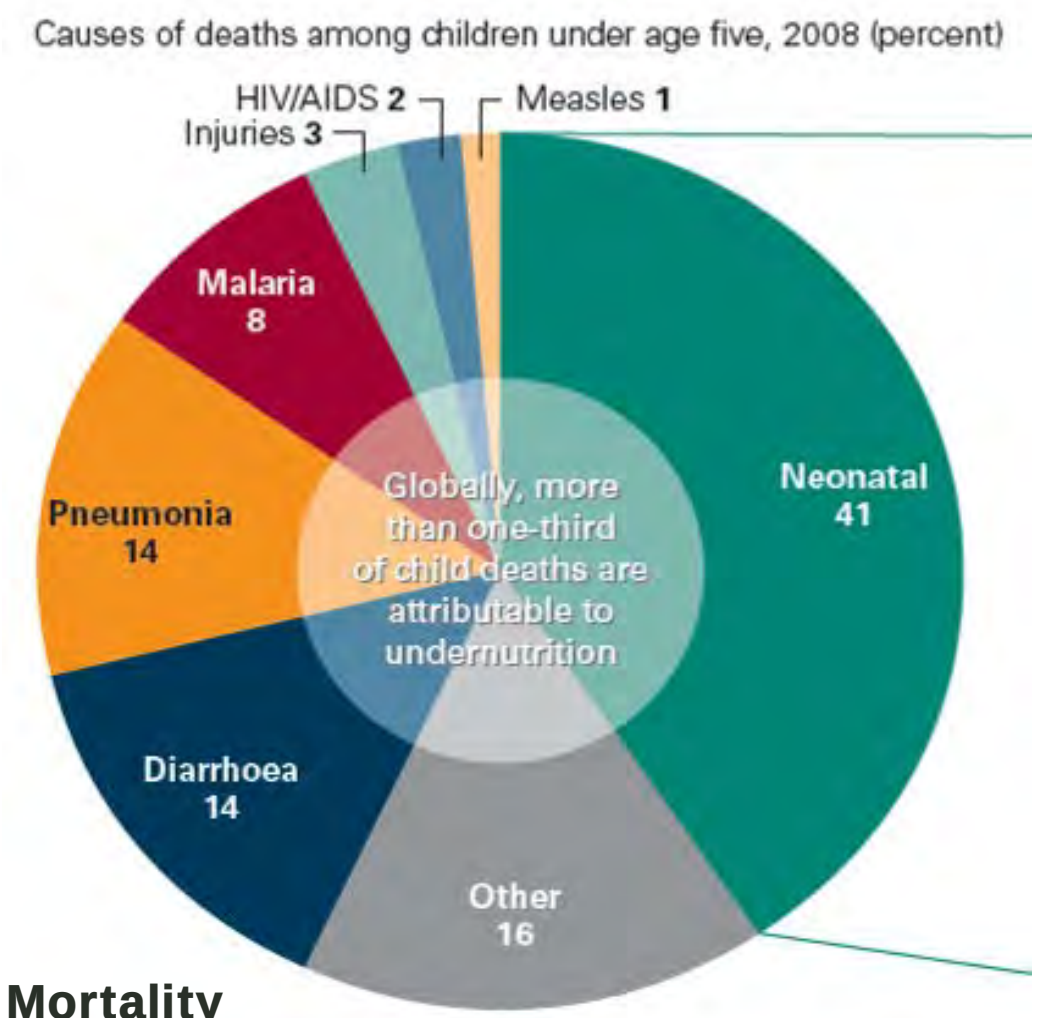


Why should interventions be delivered in community settings?

- Access and Equity
  - Health facility services less likely to be accessed by the poor
  - Not currently possible to achieve universal access without community based delivery mechanisms
- Impact
  - Cannot reach impact goals without universal coverage; therefore integrated Community Case Management (iCCM) critical for reaching health-related MDGs

HMM → CCMm → *i*CCM: an evolving concept

- Malaria, pneumonia and diarrhea are the 3 most important causes of post-neonatal death in U5s
- Large overlap in symptoms between malaria and pneumonia



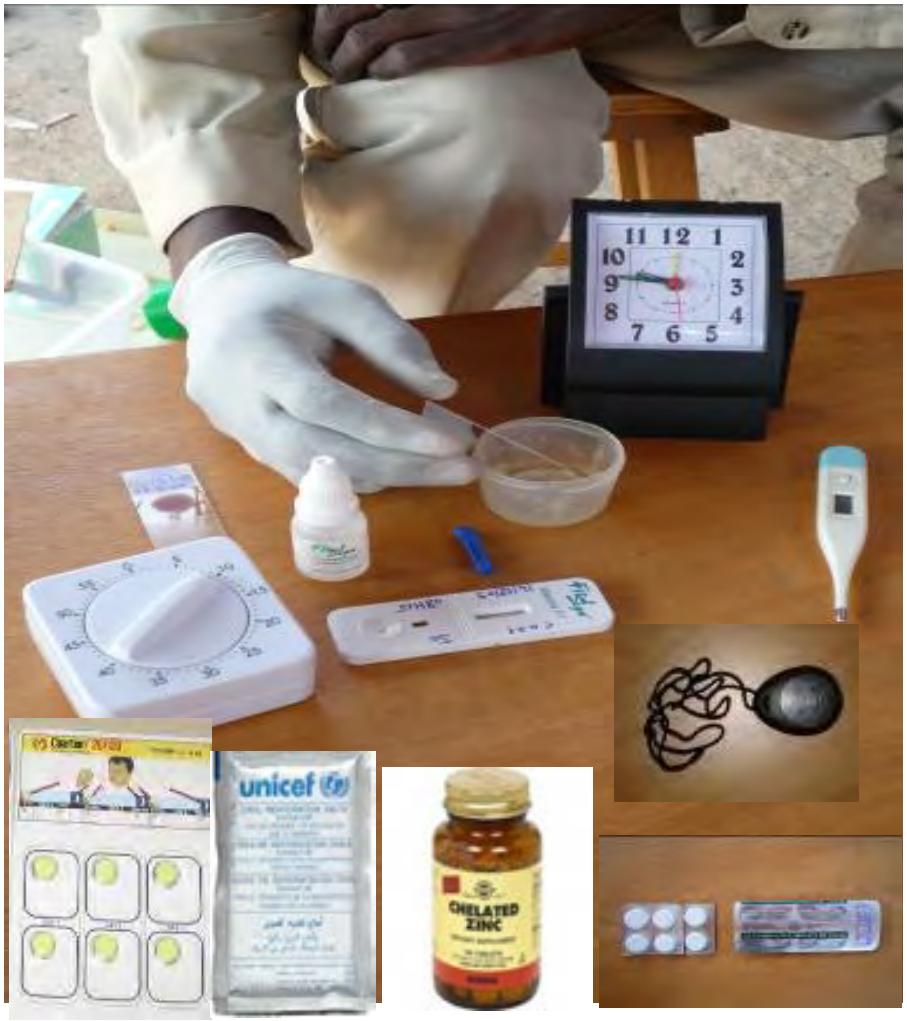
UN Child Mortality Report 2010

HMM → CCMm → *i*CCM: an evolving concept

- Need to introduce parasitological confirmation of malaria at all levels of the health care system
  - To improve patient care
    - Need to manage pts with negative RDTs

      → Provide Dx and Tx for other killer diseases (pneumonia, diarrhoea, neonatal sepsis)
  - To improve rationale use of antimalarials
  - For epidemiological monitoring in a context of declining malaria transmission (→ elimination)

Key elements of the iCCM package



- **Diseases**: malaria, pneumonia, diarrhea
  - Neonatal sepsis, severe malnutrition
- **Tools**: RDTs, RRtimers, ACTs, AB, Zinc, ORS
- **Workers**: different cadres in different countries
  ((j)HEWs, APE, HSA, RMM/C, ASC, etc)

The RAcE 2015 project (Rapid Access Expansion)

- **Five-year award from Canadian International Development Agency (CIDA) to WHO-GMP**
- **Main objective:** catalyze scale-up of iCCM as an integral part of government health services in sub-Saharan Africa
  - increase coverage of diagnostic, treatment, and referral services for major causes of childhood mortality
- **Secondary objective**: stimulate policy review and regulatory update in each country
  - generate evidence to inform WHO programmatic guidance on iCCM
- **DRC, Malawi, Mozambique, Niger, and Nigeria selected**

Operating Principles for WHO with regard to RAcE 2015

- Working across different layers of the WHO:
  - Vertically: HQ ←→ AFRO ←→ country offices
  - Horizontally: Malaria ←→ Child Health Departments
- Putting the MOH in a leadership position in each country
  - Malaria ←→ Child Health Departments
  - Letters of intent → Guidance workshops → Full grant applications → Grants

RAcE 2015: Next Steps

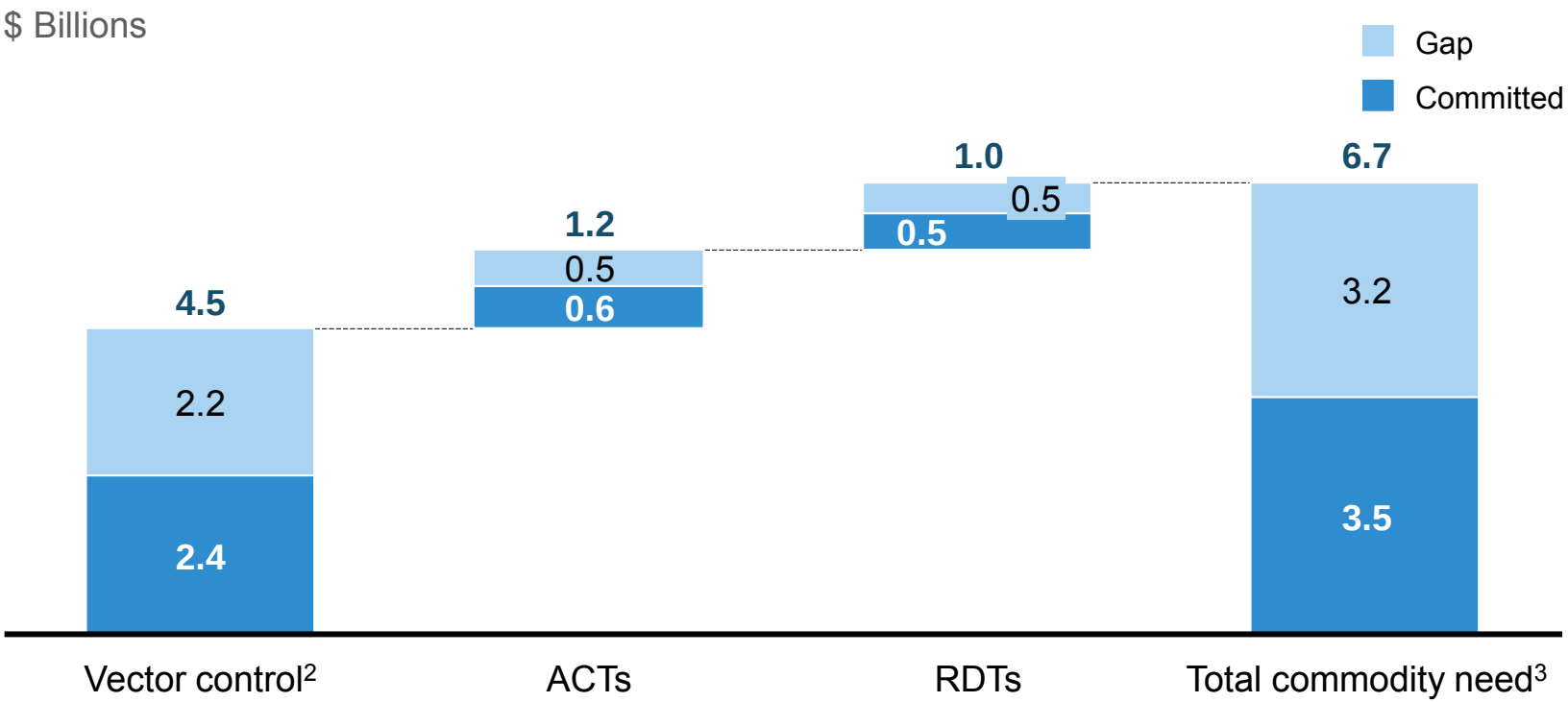
- Call for letters of interest: September-October 2012
- Guidance workshops in each country co-facilitated by WHO and MOH: October-November 2102
- Full proposals received and reviewed: January-February 2013
- Grants awarded April 2013

World Malaria Report 2012

- Chapter on malaria surveillance systems: focusing on quality of data received
- Impact chapter to be shortened and more focused; much detailed information to be presented in new "regional profiles"
- Plan to present and analyze country-level burden estimates (2010 estimates)
- Maps in country profiles being produced in conjunction with Malaria Atlas Project
- To be launched December 11

Delivered commodity needs to meet 2015 targets in Sub-Saharan Africa total $6.7B, with $3.5B committed to date

Sub-Saharan Africa funding needs, commitments, and gap by commodity, 2012-2015[1]

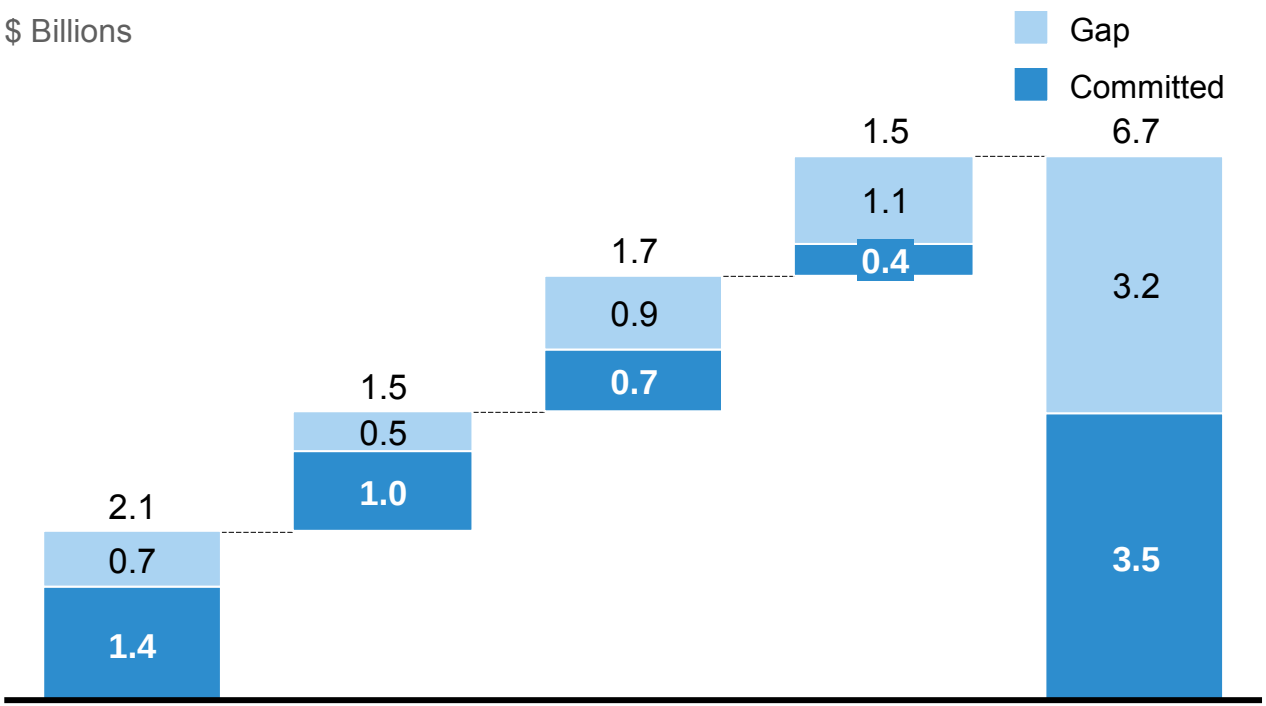


Additional investments are required to support strengthening health systems (e.g., CHWs, M&E)

1 Malaria Commodities Gap Analysis, ALMA, April 18, 2012
2 LLINs and IRS; costs will vary depending on IRS use
3 Includes procurement and distribution costs

The yearly projected commodity gap is increasing between 2012-2015

SSA funding commitment and gap by year, 2012-2015[1]

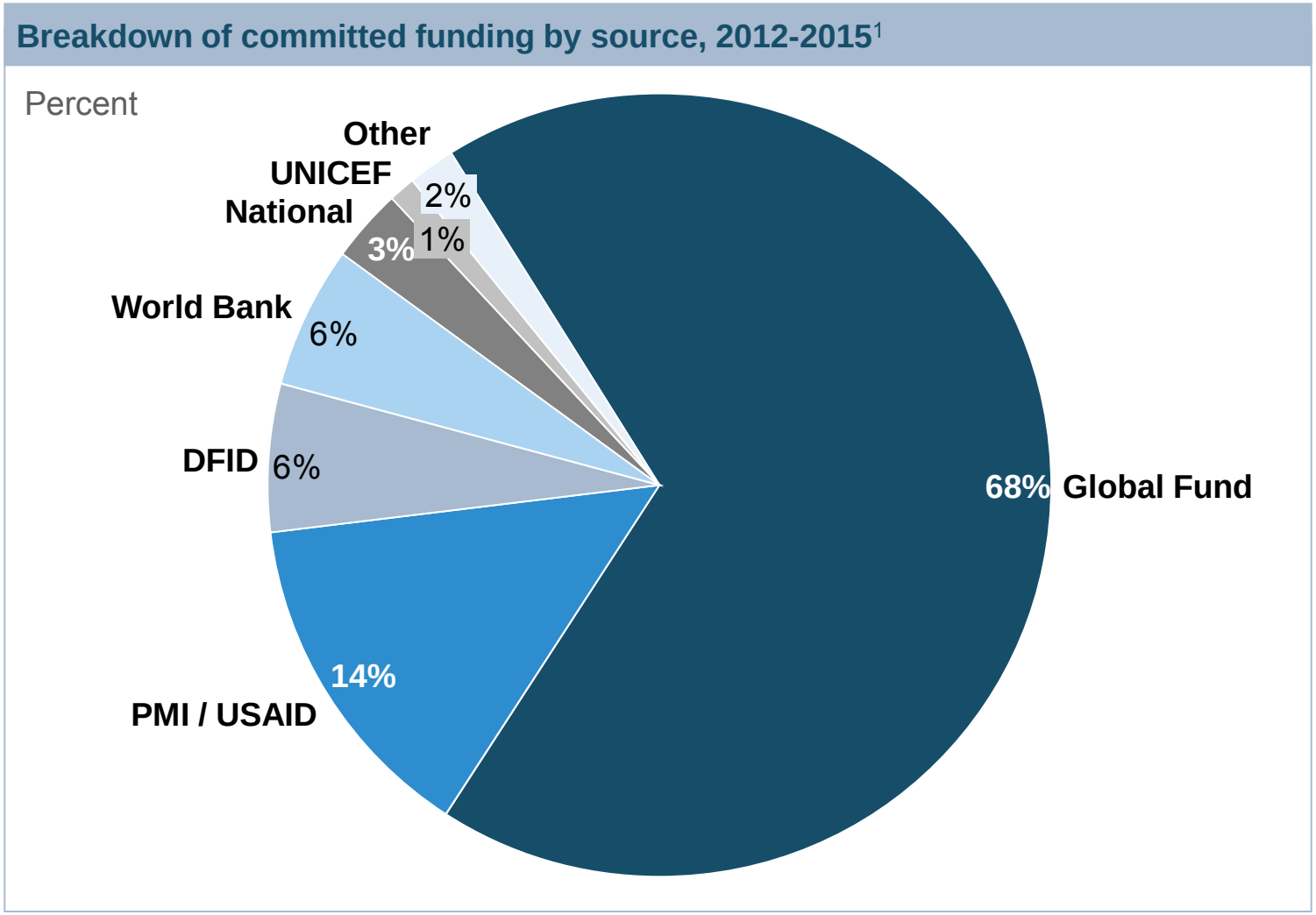


- The Global Fund aspires to cover 2/3 of the $3.2B gap, focused on addressing the 2014-15 need
- Need to focus near-term efforts on addressing ~$1.1B gap in 2012-13 through other means

1 Malaria Commodities Gap Analysis, ALMA, April 18, 2012

The Global Fund accounts for the majority of funding already committed between 2012 and 2015

Breakdown of committed funding by source, 2012-2015[1]



1 RBM Secretariat financing survey of 47 African countries

Australia – increasing engagement in malaria

- "Saving Lives from Malaria in the Asia-Pacific Region"
  - Oct 31- Nov 2 2012 in Sydney: 2-day policy discussion followed by ministerial and senior agency representatives meeting
- Focus is on areas for action, covering:
  1) Regional political commitment and role of regional institutions
  2) Sustainable financing
  3) Access to quality medicines and commodities
  4) Priority countries / programming
  5) Research and development
  6) Role of private and non-state sector
- Goal: Accelerate progress towards achieving global target of 75% reduction in malaria cases & deaths in the Asia Pacific region by 2015
  - invigorating and sustaining regional and international action to control and eliminate malaria in the Asia Pacific region, and
  - protecting the gains to date in malaria control and elimination in the Asia Pacific region and beyond by addressing malaria drug resistance by 2015

Request from Global Fund for Malaria Investment Framework

- UNAIDS published an investment framework last year
  - High level global document
  - Well received by Global Fund
- Request to have similar document for TB and malaria
  - Driven by evidence of mismatch in some cases between public health needs and investment for HIV and TB
- Push-back from malaria community
  - Already have a functioning system to guide investments through a country driven process
  - Eventual agreement to produce a meta-document that groups components of malaria investment tool kit in one place

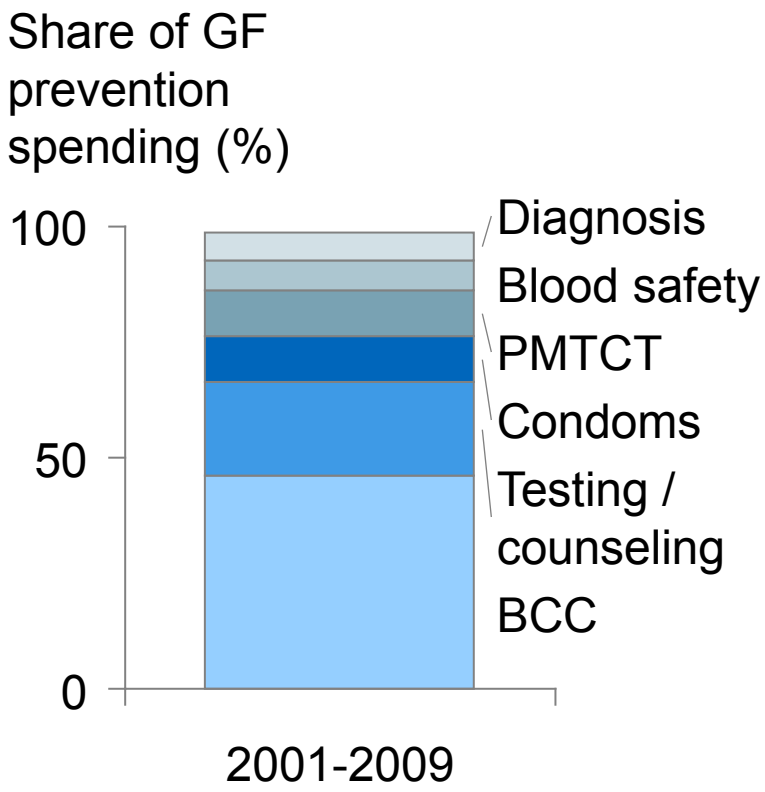
Four tools support strategic investment

Demand forecasts	**Provide quality estimates of demand, programmatic and financial gaps**
Investment framework	**Inform the development of requests through common guidance**
Unit cost benchmarks	**Provide costing guidance** **Built into framework when ready**
Portfolio analysis	**Allow monitoring and optimization of investments (presented at July SIIC)**

Focus of this session

Why apply an investment framework?

HIV and AIDS: high investment in BCC with low evidence of impact



High MDR-TB country: limited funds to share between DOTS / MDR-TB

Phase 1: DOTS strategy only

Phase 2: Reprogramming to MDR-TB, covering only 300 cases[1]

Challenge under limited funding: share of funding between DOTS and MDR-TB

Caveats: other donor spending not accounted for and differing costs by interventions. Definitional / data challenges.
1. Less than 15% of total MDR-TB cases in the country
Source: UNAIDS, Global Fund

Potential uses in the Global Fund process

	Process stage	Potential use
1	Concept note	Influence funding requests Inform dialogue[1]
2	Independent technical review	Potential cross-check for strategic investment
3	Grant-making	
4	Renewals and Reprogramming	Guide Secretariat and potentially TRP recommendations

Note: Exact use of framework will be depend on its final content
1. As part of the guidance package including indicative funding levels, Secretariat information / analysis, minimum standards, investment framework

Malaria Investment Tool Kit

RBM
Global Malaria Action Plan

RBM harmonization working group implementation guidance

Malaria programme performance review & Malaria strategic planning in each country

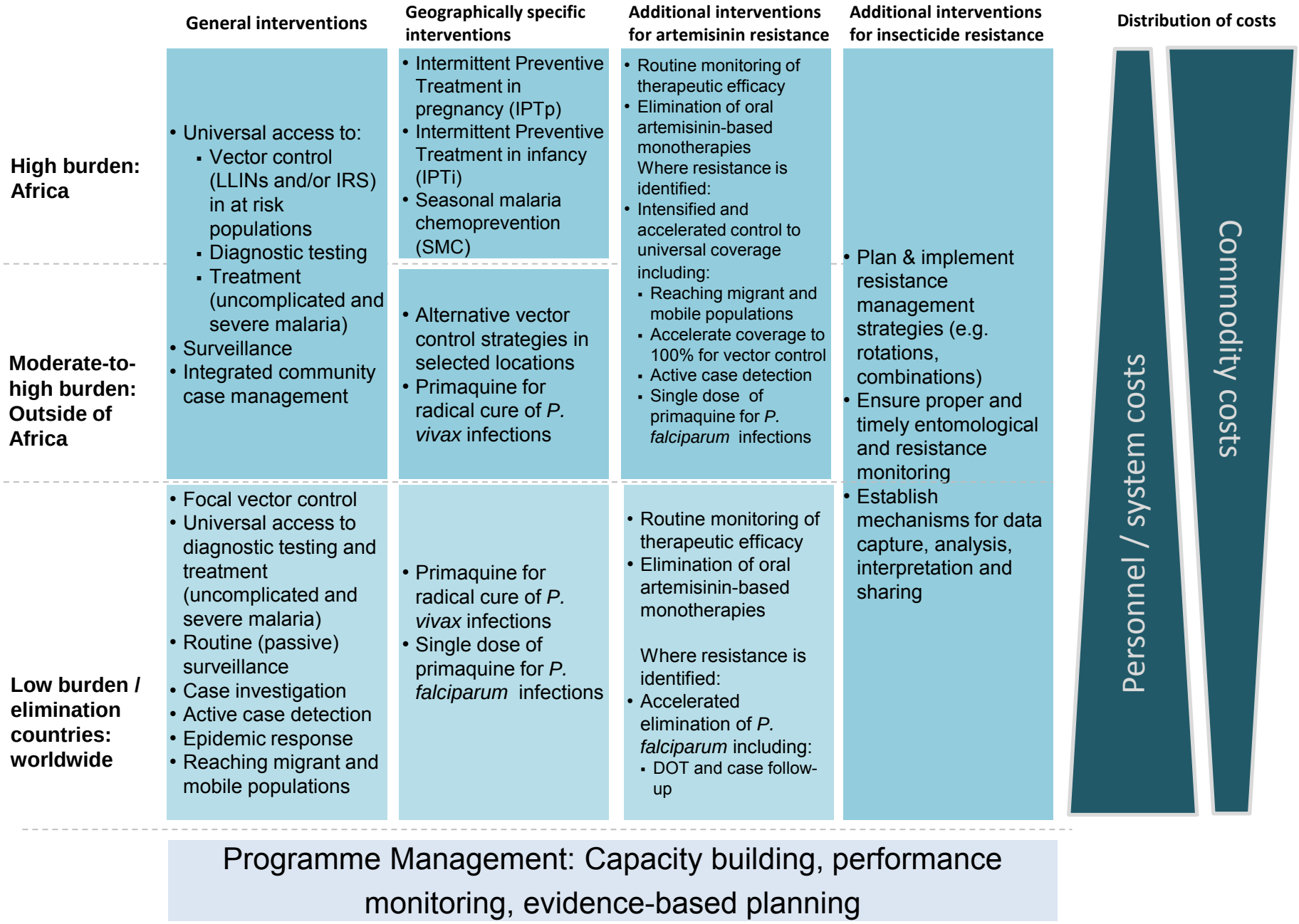
Monitoring progress – annual World Malaria Report

Programmatic and financial gap analysis and costing tool

Quality-assured and value-for-money commodities:
WHO Rapid Diagnostic Test Performance;
WHOPES (LLINs);
WHO prequalification (antimalarials)

WHO technical recommendations &
WHO *Global Fund proposal development: Policy brief on malaria*

Strategic interventions for malaria control and elimination



Malaria investment tool kit

1. **Costed National Malaria Strategic Planning based on rigorous Malaria Programme Performance Review is at heart of tool kit**
2. **Track record: tool kit already in widespread use with strong results; no evidence of mis-spend in malaria portfolio**
3. **Core malaria response options generally very similar across countries**
4. **Underlines risk of resurgence resulting from failure to maintain vector control and treatment – need for Continuity of Services**
5. **Strong emphasis on role of malaria in strengthening MCH service delivery at facility and community level**
6. **Emphasizes return on investment and value-for-money perspectives**
7. **Provides added clarity on roles of key malaria partners**

Malaria Resurgences

- Recent review found vast majority (>90%) of malaria resurgences over past 80 years due, at least in part, to weakening of malaria control programmes; resource constraints most commonly identified factor
- Failure to replace a single LLIN before it is worn out places individual lives at risk, especially as continuous protection against malaria diminishes acquisition of partial immunity
- Failure to replace a cohort of LLINs in a timely manner places entire populations at risk of dramatic resurgences in malaria transmission

Continuity of Services for Malaria

- To ensure malaria does not resurge, need similar CoS approach as for TB and HIV/AIDS
- Preliminary analysis accounting for when grants end, and what has previously been funded by GF, estimates maximum need should CoS policy be applied to malaria control in Africa, as outlined in table below
- Given next funding modality being launched soon, unlikely that many of projected costs for 2014 will be required, further reducing potential costs
- Currently under discussion by the GF SIIC

	LLINs gap	ACTs gap	RDT gap	total
2012	$13,625,468	$553,927	$1,344,927	$15,524,321
2013	$55,360,985	$9,580,244	$14,490,731	$79,431,960
2014	$102,737,602	$11,303,186	$13,807,142	$127,847,931
Total	$171,724,055	$21,437,357	$29,642,800	$222,804,212

WHA Resolution 64.17 on malaria

- Passed by 64th World Health Assembly in May 2011, urging Member States to intensify efforts in fight against malaria, and calling on WHO to:
  - Continue to update evidence-based norms, standards, policies and guidelines
  - Monitor global progress and provide support to countries in validating and analysing data from surveillance systems
  - Help countries to strengthen their human resource capacities
  - Support countries with GPARC implementation, and develop the GPIRM;
  - Promote transfer of technology to ACT manufacturers, strengthen country capacities to meet WHO prequalification standards
  - Support countries in monitoring ACT accessibility and affordability;
  - **Report to WHA in 2013 and 2015 on implementation of resolution, through Executive Board**

World Health Organization

TWELFTH GENERAL PROGRAMME OF WORK 2014–2019 - DRAFT STRATEGIC OVERVIEW

MISSION

To act as the directing and coordinating authority on international health work, towards the objective of the attainment by all peoples of the highest possible level of health as a fundamental right.

Principles, values and fundamental approaches

- Equity and social justice
- Global solidarity
- Gender equality
- Emphasis on countries and populations in greatest need
- Multilateralism
- Due consideration to the economic, social, and environmental determinants of health
- Science and evidence-based
- Public health approach

WHO's core functions

- Providing leadership
- Shaping the research agenda
- Setting norms and standards
- Articulating policy options
- Providing technical support and building capacity
- Monitoring and health trends

Criteria for priority-setting

- Current health situation
- Existence of evidence-based, cost-effective interventions
- Needs of countries for WHO support
- Internationally agreed instruments
- WHO's comparative advantage

IMPACT

OUTCOMES

CATEGORIES & PRIORITIES

Communicable diseases	Noncommunicable diseases	Promoting health through the life course	Health systems	Preparedness, surveillance and response
• HIV/AIDS; tuberculosis; malaria • Neglected tropical diseases (including vector-borne diseases) • Vaccine-preventable diseases	• Heart disease, cancers, chronic lung diseases, diabetes (and their major risk factors tobacco use, unhealthy diet, physical inactivity, harmful use of alcohol) • Mental health • Violence and injuries • Disabilities (including blindness and deafness), and rehabilitation • Nutrition	• Maternal and newborn health • Adolescent sexual and reproductive health • Child health • Women's health • Healthy ageing and health of the elderly • Gender and human rights mainstreaming • Health and the environment • Social determinants of health	• National health policies, strategies, and plans • Integrated people-centred services • Regulation and access to medical products	• Alert and response capacities • Emergency risk and crisis management • Epidemic- and pandemic-prone diseases • Food safety • Polio eradication

CORPORATE SERVICES

- Leadership in health
- Country presence
- Management and administration
- Governance and convening
- Strategic policy, planning, management and resource coordination
- Strategic communications
- Knowledge management
- Accountability and risk management

Next 10 years: need to fight false dichotomies

Tools for malaria control vs. Tools for malaria elimination	We need both
New tools vs. Existing tools	We need both
Facility interventions vs. Community-based interventions	We need both
Donor funding vs. Domestic funding	We need both
Research vs. Programme	We need both

Minutes of the Drug Resistance and Containment Technical Expert Group

21–22 June 2012

Crowne Plaza Hotel, Geneva, Switzerland

World Health Organization

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Acknowledgments

This meeting was funded by the Department for International Development (DFID).

The Global Malaria Programme would like to acknowledge with gratitude the contribution made by all the TEG members. The minutes were drafted by Amy Barrette, Lise Riopel and Charlotte Rasmussen and finalized by Lise Riopel.

Abbreviations

ACD	Active case detection
ACT	Artemisinin-based combination therapy
ARCE	Artemisinin resistance containment
AusAID	Australian Government Overseas Aid Program
BMGF	Bill & Melinda Gates Foundation
DFID	Department for International Development
DRC	Drug resistance and containment
ERG	Evidence review group
FSAT	Focused screening and treatment
GMS	Greater Mekong subregion
GPARC	Global plan for artemisinin resistance containment
IHR	International Health Regulations
LLIN	long lasting insecticide treated net
MDA	Mass drug administration
MFLT	Multiple first-line treatments
MPAC	Malaria policy advisory committee
MSAT	Mass screening and treatment
NMCP	National malaria control programme
PCR	Polymerase chain reaction
Pfmdr1	Gene coding for *P. falciparum multidrug resistance 1*
PHEIC	Public Health Emergency of International Concern
TEG	Technical expert group
TES	Therapeutic efficacy studies
USAID	United States Agency for International Development
WHA	World Health Assembly
WHO	World Health Organization

Summary and recommendations

Messaging and political commitment

The technical expert group (TEG) agreed on designating resistance to artemisinin[1] and partner drugs a growing regional emergency that represents a major threat to global malaria control and elimination efforts if not contained and eventually eliminated. The TEG supports the prompt implementation of a strengthened regional emergency plan with an appropriate structure for monitoring its effectiveness, and rapidly responding to changes in the distribution of antimalarial drug resistance, and emphasizes that fighting antimalarial drug resistance must be a global effort starting with the implementation of the Global plan on artemisinin resistance containment (GPARC) recommendations in all endemic countries. The TEG considers strengthening and sustaining political commitment and awareness of artemisinin resistance in the Greater Mekong subregion (GMS) to be a high priority. The TEG determined it premature and currently inappropriate to call artemisinin resistance a "Public Health Emergency of International Concern" (PHEIC), following presentations by the Department of International Health Regulations (IHR) and the Global Polio Eradication Initiative. This view could change with time should circumstances change.

Global messaging will be developed using an evidence-based approach, with input from other partners across the Roll Back Malaria (RBM) partnership. Messaging should avoid both overstating as well as understating the problem of artemisinin resistance, and recognize that emerging resistance to certain partner drugs directly jeopardizes artemisinin-based combination therapy (ACT) efficacy in the region, and that no novel alternative antimalarial drugs are currently available and are unlikely to be available in the near future.

Definitions of artemisinin resistance

The flow chart in the meeting minutes (Annex 1) outlines the recommended steps required for the decision making process for the interpretation and response relative to therapeutic efficacy

[1] Unless otherwise indicated, the word "artemisinin" is used in this document to refer to artemisinin and its derivatives, artesunate, artemether and dihydroartemisinin.

studies (TES) findings. To summarize, the proportion of patients positive on day 3 is a valuable, albeit imperfect, indicator for the presence of artemisinin resistance in a given population. If the proportion of patients positive on day 3 is > 10%, further investigation to confirm artemisinin resistance is warranted, including assessment of parasite clearance rate with a 7-day course of artesunate, or a 3-day course of artesunate followed by an ACT. The 10% threshold for the proportion of patients positive on day 3 will be re-assessed following modeling based on available datasets, and will consider the effect of the initial parasite density and the sample size of the study. In addition to baseline parasitaemia, it is also recommended that the interpretation of "day 3 positivity" rates considers trends over time and any changes in transmission intensity (which may affect study population immunity, which also influences parasite clearance rates). The proportion of treatment failure of an ACT is strongly associated with the efficacy of the partner drug. If TES of an ACT have failure rates of > 10%, studies on the efficacy of alternative ACTs to inform policy will be urgently needed and a new policy should be implemented as soon as possible.

Tier classification (as outlined in GPARC) should be made by national health authorities in collaboration with WHO, in consultation with the TEG. Tier I areas should be defined wherever resistance is confirmed or strongly suspected. The TEG recommends more vigilance regarding monitoring of artemisinin resistance and strict implementation of the GPARC recommendations in all areas, and recommends a wider area designated as tier II than currently applied, in order to widen the net to prevent spread of resistance.

Artemisinin resistance outside the GMS

There is no evidence currently available that indicates that artemisinin resistance exists outside the GMS. However, continued vigilance is mandatory.

Improve existing containment tools

Based on the experience of containment efforts to date, the elimination of certain foci of resistance can be envisaged in Cambodia, Thailand and Viet Nam. However, this will require the vigorous and simultaneous implementation of the most effective malaria control tools as outlined in the GPARC. While the ultimate goal of containment efforts remains the elimination

of resistant parasites, the epidemiological realities in Myanmar are such that interim objectives shall be containment of artemisinin resistant falciparum malaria, which is understood as maximum reduction of the parasite load in the population and maximum effort to prevent or delay the spread of resistant parasites. This will require:

- mitigation of the health effects in the affected populations;
- reduction of the parasite reservoir to the lowest possible levels;
- protection of mobile and migrant populations from infection;
- reduction of the receptivity and the vulnerability of threatened areas (i.e. tier II).

A regional emergency response plan is currently being prepared by the WHO Drug Resistance and Containment (DRC) Unit. The TEG expresses a keen interest to be involved in the preparation of the plan. The TEG recommended that the following components be particularly emphasized in the plan:

- community-based early diagnosis and treatment with follow-up wherever possible;
- mobile, migrant and marginalized populations;
- vector control (long lasting insecticide treated nets [LLNIs], long lasting insecticide treated hammock nets and personal protection).

Further recommendations will be made once the TEG reviews a draft of the plan.

Potential novel containment tools

The TEG identified the following potential novel containment tools:

- multiple first-line treatments (MFLT);
- extension of current ACT regimens to five days.

These two tools are promising and need urgent further evaluation.

Gaps in research

The TEG identified the following research priorities:

High priority:

- MFLT including statistical modeling; observational studies in areas with and without MFLT with molecular markers as indicators for drug resistance; operational aspects and feasibility;
- extension of current ACT regimens from three to five days;
- observational studies of artesunate efficacy in severe malaria, in areas affected by artemisinin resistance;
- primaquine use as a gametocytocidal drug (this will be discussed in a separate evidence review group [ERG] in August 2012);

Also considered important were:

- modeling of population movement to estimate the speed and magnitude of the spread of resistance in varying epidemiological settings using different interventions;
- further modeling of specific containment strategies which will be formulated in the emergency response plan;
- epidemiological and economic modeling of the regional consequences of resistance to artemisinin and partners medicines;
- evaluation of novel vector control methods, including the use of protective clothing for forest workers;
- entomological studies on transmissibility of artemisinin resistant *P. falciparum*; the mapping of *Anopheles* vectors and their resistance to insecticide; operational research on implementation of protective measures;
- use of molecular diagnostics as an epidemiological tool.

In addition the following ongoing research topics were considered of high importance:

- molecular markers for artemisinin resistance;
- new antimalarial drug development;
- behavioral research on mobile and migrant populations.

1. Meeting Background

1.1 Background

The TEG on drug resistance and containment is a standing committee established following the recommendations elaborated at the inaugural meeting of the Malaria Policy Advisory Committee (MPAC) to the WHO in January 2012. The TEG is tasked to advise MPAC on policy and recommendations regarding antimalarial drug resistance and containment. The specific roles and responsibilities of the TEG are described in the term of references attached in Annex 2. In brief, these include: evaluating the data being generated on drug resistance; providing evidence-based advice on standards for monitoring antimalarial drug resistance; providing recommendations on the strategies to detect drug resistance and to prevent its spread; and identifying research priorities on drug resistance and containment. MPAC will review the TEG recommendations, which are ultimately approved by the WHO Director General. The TEG is constituted of up to 15 members (currently 14), including a chair who is nominated for three years. The TEG will meet at least once a year, and whenever possible, will meet jointly with the standing TEG on chemotherapy.

1.2 Agenda and list of participants

The agenda and the list of participants are provided in Annex 3 and 4, respectively. All members attended except C. Karema, due to a conflicting meeting. The Australian Agency for International Development (AusAID), The Bill & Melinda Gates Foundation (BMGF), Medicines for Malaria Venture (MMV), UNITAID, and the World-Wide Antimalarial Resistance Network (WWARN) were invited as observers. Representatives of the Department for International Development (DFID) and United States Agency for International Development (USAID)/President Malaria Initiative (PMI) were also invited as observers but were not able to attend.

1.3 Modus operandi

There were two components to the TEG meeting: the first half day was devoted to presentations on Drug Resistance and Containment (DRC) Unit activities. The next one and a half day was devoted to interactive sessions. Presenters for each sessions are indicated in the

agenda. Recommendations were formulated by the TEG members during a close session at the end of the meeting.

2. Activities of the Drug Resistance and Containment Unit

2.1 Description of the unit

The DRC Unit was formed in October 2010, and currently comprises six collaborators: one coordinator, one team assistant, one medical officer and three technical officers. The DRC Unit is expected to: monitor drug resistance; communicate data to external partners with the goal of updating country drug policy; define product profile and research and development priorities; stimulate the innovation of tools and strategies for monitoring and containing drug resistance; and advocate and provide global coordination for the drug resistance containment plan. The DRC unit is working in close collaboration with the Regional Malaria Advisors of the six WHO Regional Offices as well as with international and national programme officers based in WHO Country Offices. Monitoring of drug efficacy is further strengthened by the contribution of regional networks in various part of the world. However, some of the regional networks are currently not active because of shortage of funding.

2.2 Monitoring the efficacy of antimalarial drugs

TES remain the most reliable tool to monitor antimalarial drug efficacy. Data from these studies are key drivers to policy change. The WHO protocol for surveillance of antimalarial drug efficacy has been subject to several revisions since its first implementation in 1964, which was then focused on detecting chloroquine resistance. In its latest and current version[2], the protocol provides the same definition of treatment outcomes at all levels of transmission, allows for 28 or 42 days follow-up depending on which medicine is being tested and mandates the systematic use of polymerase chain reaction (PCR) to distinguish between recrudescence and re-infection. It is important to note that the assessment schedule provides information on

[2] WHO (2009). *Methods for surveillance of antimalarial drug efficacy.* Geneva, World Health Organization.

the proportion of subjects who remain parasitaemic at day 3 i.e. 72 hours following the initiation of treatment (known as "day 3 positivity" – see below).

A template protocol of TES is available in English and French languages[3]. The template offers several advantages: it meets ethical requirements of the Council for International Organizations of Medical Sciences (CIOMS) guidelines and is cleared by the WHO Ethics Review Committee. It provides standardized methods for the conduct, analysis and reporting of the study data with provisions for quality control and quality assurance. The protocol template also includes a data management system using MS Excel. It is programmed to perform real-time "per-protocol" and Kaplan-Meir analyses after double data entry is completed. The system is easy to use in settings with limited information technology (IT) infrastructure, allows export and import of data in and from different softwares, and facilitates feedback to WHO.

The WHO antimalarial drug efficacy database was built over the past 12 years and now includes approximately 4000 studies in 268,000 patients. The data come from the TES and other sources such as: published scientific literature and unpublished reports comprising information from Ministries of Health, national malaria control programmes (NMCPs), non-governmental organizations, research institutions and drug development partners. The recent WHO report on monitoring antimalarial drug efficacy accounts for 1120 studies in 81,848 patients and highlights the value of enhanced monitoring of antimalarial drug efficacy in updating drug policy and the early detection of artemisinin resistance[4]. WHO plans to make these data available online using a mapping system for which a website is currently under construction.

2.3 Building capacity for effective monitoring of antimalarial drug efficacy

In order to ensure that efficacy testing is implemented on a routine basis in all malaria endemic countries it is imperative to strengthen the capacities of the national teams involved in malaria control. In collaboration with WHO regional and country offices, DRC is providing support to

[3] WHO (2009). *Methods for surveillance of antimalarial drug efficacy.* Geneva, World Health Organization.
[4] WHO (2010). *Global report on antimalarial drug efficacy and drug resistance: 2000–2010*. Geneva, World Health Organization.

NMCPs or partners in the implementation or monitoring of TES. Capacity building efforts aim at the proper implementation of TES, including accuracy and reliability of the generated data. Fourteen subregional network workshops on antimalarial drug-efficacy testing were organized between 2009 and 2011, covering more than 80% of all falciparum-endemic countries. WHO conducted training courses focusing on TES in seven countries. In addition, groups of clinicians and microscopists were trained as consultants in order to create a pool of regional experts who will provide technical support to countries conducting TES with the aim of ensuring high quality data. During the same period, WHO supported over 40 malaria endemic countries on issues regarding antimalarial drug efficacy, including technical advice on protocol development, data analysis, and the supply of quality-assured antimalarial drugs and/or PCR services.

2.4 Current global status of antimalarial drug resistance in P. falciparum

This section uses data published in the recent WHO report on antimalarial drug resistance, with updates where applicable[5].

Resistance of *P. falciparum* to chloroquine is present in most malaria endemic areas. In Central America, presence of molecular markers of chloroquine resistance have been detected in Haiti, Honduras and Nicaragua. However, in Honduras and in Nicaragua, chloroquine remains fully effective clinically. Studies from China, Kenya, Malawi and Viet Nam suggest partial reversal of chloroquine resistance based on in vitro sensitivity testing and molecular markers of chloroquine resistance; however treatment failure rates with chloroquine remain high in China and Viet Nam.

The combination of artesunate with sulfadoxine–pyrimethamine is failing in many settings in Africa but is still highly effective in Afghanistan, India, the Islamic Republic of Iran, Pakistan, Sudan and Somalia. With the exception of West African countries, the combination of artesunate and amodiaquine is also failing in many areas. Comparison of treatment failure rates between patients treated with artesunate + sulfadoxine–pyrimethamine versus sulfadoxine–

[5] WHO (2010). *Global report on antimalarial drug efficacy and drug resistance: 2000–2010*. Geneva, World Health Organization.

pyrimethamine alone, and between artesunate + amodiaquine versus amodiaquine alone indicate that significant reduced efficacy of the partner drug (sulfadoxine–pyrimethamine or amodiaquine) results in reduced efficacy of the corresponding artemisinin combination therapy.

Although treatment failure rates reaching 10% have been observed with artemether–lumefantrine in Ghana and Burkina Faso, this combination generally remains highly effective in most of Africa. Likewise, artemether–lumefantrine is still effective in the GMS except in western Cambodia where treatment failure rates exceed 20%.

Mefloquine resistance is high in Cambodia and Thailand. In Myanmar and Viet Nam, treatment failure rates with mefloquine monotherapy in a dose of 15 mg/kg were high in early 2000; there are few recent data available from these two countries on the efficacy of artesunate–mefloquine combination or on *P. falciparum multidrug resistance 1* (*Pfmdr1*) gene multiple copy number, a good marker of mefloquine resistance. However, high failure rates of artesunate–mefloquine are currently reported from the Thailand and Cambodia (both countries with presence of artemisinin resistance) suggesting that this combination may no longer be efficacious in these countries. Thailand is currently considering new treatment options, and Cambodia has changed its first-line treatment for uncomplicated falciparum malaria to dihydroartemisinin–piperaquine, except in Pailin, western Cambodia, where atovaquone–proguanil (see below).

Resistance to piperaquine was first reported in 1985 in the Southern provinces of China, where it had been deployed massively as a prophylactic and treatment intervention from 1974 to 1992. As much as 214 metric tons (equivalent to 140 million adult doses) were used during this period. An increase of the total adult dose to 1.5 g had little impact on treatment failures rates. Although the combination of dihydroartemisinin–piperaquine has only been introduced recently, there is a suggestion that this combination has reduced efficacy in some parts of western Cambodia (although the absolute numbers of patients studied remain small). Failure rates in Cambodia are currently not supported by in vitro sensitivity data for piperaquine, so more definite conclusions regarding the current situation of piperaquine resistance are pending. However, findings from studies in Pailin suggest that treatment failure with dihydroartemisinin–

piperaquine is associated with presence of a single copy of *Pfmdr1*, the major determinant of mefloquine sensitivity. Whether this implies exclusion of mutual resistance to mefloquine and piperaquine simultaneously is an important question for further study. Increased efficacy of artesunate–mefloquine observed in 2010–2011 in an area where treatment failure with dihydroartemisinin–piperaquine is high, supports this hypothesis. Dihydroartemisinin–piperaquine treatment failure rates ≥ 10% have also been reported in Rwanda and Papua New Guinea.

Pyronaridine was developed in China in the 1970's, and used to treat acute uncomplicated and severe falciparum malaria starting in the 1980's. Reports as early as 1982–1983 on cross-resistance between pyronaridine and chloroquine, piperaquine and quinine prompted the Chinese authorities to investigate and use pyronaridine in combination with several other drugs, including artemisinin derivatives. Artesunate–pyronaridine is a new fixed combination recently approved by the European Medicines Agency under article 58 for single course of treatment in areas with known resistance to other ACTs, and will be registered shortly in several malaria endemic countries where these conditions apply. In clinical trials, artesunate–pyronaridine showed therapeutic efficacy of 98%, except in Pailin, where treatment failures reached 10% after 42-days of follow-up.

The efficacy of atovaquone–proguanil can be easily compromised by resistance to atovaquone, which is associated with a single mutation in the gene coding for cytochrome *b*. Failures in prophylactic or curative use of this drug, as well as presence of mutations related to atovaquone resistance, have been reported from French Guyana, India, and in several countries in Africa. However, mutations related to atovaquone resistance have not been reported in South-East Asia. Atovaquone–proguanil is currently temporarily used as first line treatment on both sides of the border between Cambodia and Thailand in a limited area and under closely supervised conditions. This was decided because of high failure rates against the available ACTs in that region.

Artemisinin resistance is suspected or confirmed in four countries in the GMS: Cambodia, Myanmar, Thailand and Viet Nam. The proportion of "day 3 positivity", a marker for suspected

artemisinin resistance, differs between individual sites. This partly depends on the ACT, since the partner drug contributes to some degree to the initial parasite clearance rate and thus the proportion of "day 3 positivity" could be affected if the partner drug is failing. Also, the dose of artemisinin derivatives used in the different studies varies between 2 and 4 mg/kg body weight per day, which has some impact on the initial parasite clearance in areas with emerging artemisinin resistance. Studies from the border regions between Cambodia and Thailand, and Myanmar and Thailand show reproducible results of increased proportions (> 10%) of "day 3 positivity". Data reported from the border region between Myanmar and China need further confirmation. Proportion of "day 3 positivity" has reached a plateau in Pailin province over the past several years (around 50% of patients are still parasite positive at day 3).

2.5 Update on artemisinin resistance containment activities

The GPARC[6] was launched in January 2011 with the overarching goal of protecting ACTs as an effective treatment for *P. falciparum* malaria. GPARC defines priorities to contain or eliminate artemisinin resistance where it already exists, or to prevent it where it has not yet appeared. These priorities are: stop the spread of resistant parasites; increase surveillance to evaluate the presence and spread of artemisinin resistance; improve access to diagnostics and rational treatment with ACTs and invest in artemisinin resistance-related research. Success of the implementation of these recommendations depends on the ability to motivate and coordinate action and mobilize resources.

The GPARC defines tiers based on the evidence of artemisinin resistance. Tier I areas are those for which there is credible evidence of artemisinin resistance. Tier II areas are those with significant inflows of people from tier I areas, including those immediately bordering tier I. Tier III areas are those with no evidence of artemisinin resistance and limited contact with tier I areas. Each country is expected to evaluate its level of risk and implement containment or control activities accordingly alongside appropriate monitoring and evaluation.

[6] WHO (2011). *Global plan for artemisinin resistance containment.* Geneva, World Health Organization.

The TEG called attention to the fact that the distinction in containment activities defined in GPARC between tier I and tier II is subtle. There is a need to increase the perimeter for containment around the areas where resistance is found, thus an increase of the tier I zones, since spread of resistance will first affect these adjacent areas. The TEG recommended that tier classification should be determined by the national health authorities in collaboration with WHO, in consultation with the TEG.

In tier I areas, an immediate and multifaceted response should be launched with the goal to contain and, if feasible, eliminate resistant parasites. This includes accelerated control to reach universal coverage, elimination of oral artemisinin-based monotherapies, focus on mobile and migrant populations, considering the use active case detection (ACD), mass screening and treatment (MSAT), focused screening and treatment (FSAT) and mass drug administration (MDA).

In tier II areas, the goal should be to intensify and accelerate malaria control activities, to implement specific tactics to manage the potential spread of resistant parasites from tier I with a focus on mobile and migrant populations, to actively eliminate the use of artemsinin-based monotherapies and intensify monitoring of therapeutic efficacy.

In tier III areas, the main goal is to prevent the emergence of artemisinin resistance through effective control measures with prompt parasitological diagnosis for all suspected malaria patients and effective ACT treatment for all confirmed cases, scaling up vector control, increasing routine monitoring of therapeutic efficacy and eliminating oral artemisinin-based monotherapies and poor quality drugs.

The GPARC was developed when the artemisinin resistance containment (ARCE) project was ongoing on the Cambodia-Thailand border. The ARCE project ran from 2008–2011[7]. A number of key lessons were learned from the project. The project managed to rapidly increase access to prompt diagnosis and effective treatment – partly through an extensive network of village malaria workers in Cambodia. Banning oral artemisinin-based monotherapies as well as

[7] http://www.who.int/malaria/diagnosis_treatment/resistance/en/index.html

enforcing the ban were successful in drastically reducing the number of offending drug sellers. Overall, the containment project proved very effective in lowering the burden of falciparum malaria in Pailin province. However, because of continued artemisinin drug pressure and by definition higher efficacy of ACTs against sensitive parasites, the proportion of artemisinin resistant infections among the remaining parasite population has increased in Pailin. This implies that ultimately containment can only be achieved through elimination of *P. falciparum* in areas of artemisinin resistance. A further key challenge for the project was to sustain initial progress. Very high coverage rates with LLINs were achieved, but maintaining the coverage was difficult, in part due to high population mobility.

At present, containment activities are ongoing in four tier I countries. In Cambodia, current containment activities are funded under the Global Fund round 9 programme. Activities in Thailand are ongoing in 22 provinces covering eastern and western Thailand and funded under the Global Fund round 10 programme. In Myanmar, the Ministry of Health and involved partners agreed on the Myanmar artemisinin resistance containment (MARC) framework in 2011 and activities started in mid-2011. In Vietnam, containment activities have only recently started.

A joint assessment of the response to artemisinin resistance in the GMS was conducted from November 2011 till February 2012, and was funded by AusAID and the BMGF. This assessment concluded that the general approach, as outlined in GPARC and several associated national level strategies and plans, is appropriate, but that the containment plans and strategies are not implemented with sufficient intensity, coverage and quality. The report from the joint assessment proposes ten fields of priority actions:

- intensify current field operations and manage them for results;
- strengthen leadership as well as coordination and oversight mechanisms;
- secure adequate financial resources;
- build political support;
- clarify and implement policy decisions on diagnosis and treatment;
- maintain, expand and improve drug efficacy surveillance networks;

- accelerate priority research;
- target migrant and mobile populations and engage with relevant employment sectors;
- prioritize Myanmar (while maintaining a strong response to artemisinin resistance in all GMS countries);
- engage with the pharmaceutical sector.

3. Artemisinin resistance: messaging and political commitment

3.1 The International Health Regulations

The IHR are a legally-binding global agreement about procedures to protect public health by preventing the international spread of disease[8]. The IHR result from direct instructions from Member States to the WHO secretariat (not the other way around). The Secretariat facilitates and advocates the implementation of the regulations by all parties, but has no power to enforce compliance or sanction non-compliance.

The IHR do not establish mechanisms for surveillance of drug resistance, nor are they intended to provide a framework for longer-term programmatic responses to specific diseases. However, drug resistance is a feature that may be considered in the assessment of events by Member States when deciding to notify WHO. IHR, through the obligations of States Parties, can contribute to the development of national capacities necessary for the identification and response to acute public health events.

IHR has several provisions for routine generic measures related to transportation, human travel, conveyances and points of entry. An example of measures related to travel is the obligation of yellow fever vaccination in travelers to and from yellow fever endemic areas.

IHR can include the following provisions:

- temporary recommendations lasting from 12 to 23 months maximum which are issued through a declaration of PHEIC and require advice from an IHR Emergency Committee;

[8] WHO (2005). *International Health Regulations*. Geneva, World Health Organization.

- standing recommendations of indefinite duration, following advice from an IHR review committee.

In the context of artemisinin resistance, only standing recommendations would be relevant here, as this problem will remain beyond the time limit of 23 months.

A more flexible method of providing recommendations to governments, travelers and specialists in travel medicine is through the WHO publication International Travel Health (ITH). Some recommendations related to artemisinin resistance already exist in this document, which is updated annually[9].

When considering measures related to travel, it is important to not only regard the scientific evidence base, but also consider the socio-political acceptability of measures, which are often viewed as punitive by the affected countries and populations. Efforts must also be made to minimize stigmatization in order to maintain the trust and cooperation of the affected countries.

In the context of artemisinin resistance it is not evident that declaration of a PHEIC mechanism or standing recommendation under IHR has added value in addition to clear and comprehensive WHO programmatic priorities offering evidence-based technical guidance for countries. For comparison, IHR are currently not used for addressing the problem of multidrug resistant tuberculosis.

3.2 The example of polio

The experience of the Global Polio Eradication Initiative was shared with the TEG. Obtaining an agreement on the declaration of polio as a "programmatic global health emergency" (which is not the same as a PHEIC) took several years of negotiation with partners and many consultations within the Executive Board, the World Health Assembly (WHA) and ad hoc bodies. Declaring a health threat as a global emergency raises high expectations regarding the full containment of the emergency; if this is not achieved the global community will consider this as

[9] WHO (2012). *International travel and health*. Geneva, World Health Organization.

a failure. Emergency status also does not equate with financial support: for instance, the polio eradication programme has needed to scale back activities in 2012 due to funding gaps.

Durable political commitment is ultimately more important than using global emergency classification mechanisms. The declaration of a global health emergency is a slow process and cannot be imposed from outside the country by WHO or others; the countries themselves need to understand the nature and the magnitude of the health problem nationally and regionally. Polio was declared an emergency at a national level in several countries, before the WHA declared polio as a programmatic global health emergency.

3.3 Messaging and political commitment

While it may not be a PHEIC or standing recommendation under IHR, or a "programmatic global health emergency" (like the polio programme), artemisinin resistance is clearly a growing regional emergency with potential devastating global consequences if not contained and eventually eliminated. Artemisinin resistance in *P. falciparum* is currently suspected or confirmed in four countries (Cambodia, Myanmar, Thailand and Viet Nam). It is not known yet if the foci detected along the Myanmar-Thailand border represent spread or de novo emergence of resistance. Resistance to partner drugs (including amodiaquine, lumefantrine, mefloquine, piperaquine and sulfadoxine–pyrimethamine) has also been identified in several regions in South-East Asia, and development of resistance to the partner drug is facilitated by the presence of artemisinin resistance. Importantly, the combination of resistance to both components of ACT results in decreased efficacy of ACTs in parts of these countries, with no or very few alternative treatment options currently available for the treatment of *P. falciparum* malaria. It is thus important to note that artemisinin resistance is not just a problem of slower parasite clearance in the patient with malaria. This situation represents a major threat to global malaria control and elimination efforts. Myanmar has the highest malaria burden in the region, and – based on historical data on the spread of chloroquine and sulfadoxine–pyrimethamine resistance – is a potential gateway for the spread of artemisinin resistant parasites to Bangladesh and/or India and subsequently to Africa. Containment activities are ongoing in all four countries of the GMS but funding gaps and other constraints preclude full implementation,

especially in Myanmar and Viet Nam. Other constraints in some regions include extensive cross-border movement of mobile workers who have poor access to health services, widespread availability of oral artemisinin-based monotherapies and/or poor quality medicines, poor health infrastructures, and sub-optimal regional collaboration on both pharmaceutical regulation and malaria control activities.

Fighting antimalarial drug resistance must be a global effort starting with the implementation of the GPARC recommendations in all endemic countries. It is essential to increase implementation of prompt diagnostic testing, effective treatment and enhanced surveillance of malaria as well as strengthen routine monitoring for drug therapeutic efficacy in all malaria endemic countries.

With the commitment of partners, including AusAID, BMGF, DFID and USAID, an emergency response plan for the GMS is currently in development with a provision to include country-specific roadmaps. The coordination of the plan, for which WHO is responsible, will rest on five main pillars:

- strengthening leadership;
- improving drug efficacy surveillance networks and accelerating priority research;
- ensuring access to quality care for, particularly for migrants and mobile populations;
- facilitating implementation of containment activities in Myanmar and Viet Nam; and
- engaging the pharmaceutical sector.

Getting the messaging right is critical to galvanize the political commitment in affected countries, engage all key stakeholders, and mobilize resources. Good communication can rally support, build political commitment and secure the financial resources. Poor or uncoordinated communication can disrupt ongoing efforts, confuse partners and lead to adverse consequences. There will be a need to design a tailor-made set of messages in order to reach out to a broad group of stakeholders including governments of affected countries, donors and funders, inter-governmental platforms, industry partners, NGOs and the media.

Regarding messaging around artemisinin resistance, it is WHO's aim to emphasize the urgency of the problem, which represents a major threat to global malaria control and elimination efforts. However, the message should not suggest that artemisinin resistance is unraveling the progress made towards global malaria control and elimination.

Points for consideration around messaging discussed by the TEG can be summarized as follows:

- ACTs are currently failing in a geographically limited region, where resistance to both the artemisinin and ACT partner drugs is present, causing severe and worrying limitations to the available treatment options for falciparum malaria in these regions. This message should be balanced against the fact that over 200 million people are successfully treated globally with ACTs each year, and that access to ACT treatment has contributed importantly to the current reduction in malaria morbidity and mortality. A general statement that ACTs are failing could endanger production and supply of ACT and reduce confidence in its use, jeopardizing the success achieved to date;
- Although the general content of messages around artemisinin resistance obviously needs to be consistent, messages need to be individually crafted towards funders, individual countries, NGOs, and other constituencies;
- Messaging should be encouraged, but stigmatization (for instance of migrant and mobile populations, or of Ministries of Health in countries with confirmed artemisinin resistance) should be avoided;
- Messaging would be stronger if the problem of artemisinin resistance was built on the foundation of mathematical modeling although calibration will be very challenging. In order to provide numerical data on this, modeling efforts will be conducted in several areas:
    - to make the investment case (deaths and/or DALYs averted in GSM, economic impact);
    - to clarify possible impact of spread or emergence in Africa;
    - to show how different interventions impact on malaria disease and economic burden.
- Messaging has to make use of clear statements, without oversimplifying the problem;

- The TEG discussed whether messaging should convey that containment of artemisinin resistance is still feasible or that it is inevitable that artemisinin drug resistance will eventually emerge elsewhere, and that the current efforts are only buying time for the development of alternative antimalarial therapies. There are no current data to strongly support either view and the containment plans (GPARC) cover both scenarios. In both scenarios, containment efforts are essential since no novel alternatives medicines to ACT will be available for at least the next few (> 5) years;
- The TEG also discussed whether the activities in tier I should be described as elimination or containment efforts. While elimination should be the end objective, it is clear that in certain settings such as Myanmar, elimination efforts will need to be preceded by a more realistic shorter term goal of malaria control aimed at preventing or delaying the spread of artemisinin resistance as well as reducing the parasite reservoir and decreasing the burden of disease;
- It was noted that currently there is inadequate awareness about the magnitude, urgency and seriousness of the problem of artemisinin resistance in governments of some affected countries, even among senior Ministry of Health officials. Additionally, Ministries who have had negative experiences (e.g. with MDA) are likely to be less receptive to requests involving raising the alert level. The question of how to raise the level of awareness and obtain political commitment will need to be addressed at subsequent meetings.

Based on the above considerations, and following the presentations by the Department of International Health Regulations and the Global Polio Eradication Initiative, the TEG determined it is premature and currently inappropriate to call artemisinin resistance a PHEIC. The TEG agreed on designating resistance to artemisinin and partner drugs a growing regional emergency that represents a major threat to global malaria control and elimination efforts if not contained and eventually eliminated. The TEG supports the prompt implementation of a strengthened regional emergency plan with an appropriate structure for monitoring its effectiveness, and rapidly responding to changes in the distribution of ACT resistance.

4. Review of current artemisinin resistance definition

WHO recommends that each country should monitor the therapeutic efficacy of first- and second-line drugs every 2 years. This routine monitoring allows for:

- Assessment of treatment failures: treatment policy has to change when the treatment failure rate exceeds 10% by the end of follow-up (28 or 42 days, depending on the half-life of the drugs being monitored);
- Assessment of the proportion of patients still parasitaemic at day 3 (i.e. 72 hours after start of antimalarial treatment with ACT): studies conducted in GMS suggest that increasing prevalence of "day 3 positivity" is a useful indicator to detect emerging artemisinin resistance.

There is currently no consensus on the definition of artemisinin resistance. WHO is using the following working definition, which was used in the GPARC:

- an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
- a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence of parasites after day 7 within 28 or 42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance).

The proportion of patients who are parasitaemic after 3 days of treatment has been found to be a suitable though imperfect tool for screening for artemisinin resistance. It is highly dependent on several variables including the initial parasitaemia, acquired immunity against *P. falciparum* and skills of the microscopists; the efficacy of the partner drug influences also this measure. In studies with more frequent parasite counts, the parasite clearance half-life can be calculated accurately using the parasite clearance estimator recently developed[10]. This half-life, based on the slope of the log-linear parasite clearance curve, is unaffected by the initial

[10] Flegg JA *et al.* Standardizing the measurement of parasite clearance in falciparum malaria: the parasite clearance estimator. *Malar J*, 2011; 10:339.

parasitaemia. A drawback is that frequent (e.g. 6-hourly) sampling for assessment of parasite density is required, which will not be feasible in many settings. Measuring parasitaemia every 12 hours allows calculation of the parasite clearance rates but systematically overestimates the slope half-life compared to measurement made every 6 hours. High correlation between "day 3 positivity" rate and slope half-life was detected (r = 0.88) based on data collected during ARCE and coordinated by WHO. However, "day 3 positivity" is not predictive of treatment outcome when the partner drug used in the ACT is still effective. Despite high "day 3 positivity" rate, the number of patients failing after a treatment with ACT remains extremely low (2.5%) in areas of artemisinin resistance but with retained sensitivity to the partner drug.

In the current absence of a molecular marker for artemisinin resistance, artemisinin resistance is mainly defined by delayed parasite clearance. The current recommendation state that if > 10% of patients are still parasitaemic at day 3, more detailed studies to confirm the presence of artemisinin resistance in the area are needed. However, this confirmation should not delay containment activities. Based on initial modeling exercises, the TEG discussed whether the 10% threshold was too insensitive. However, data are still insufficient to recommend a new threshold, so the TEG recommends that NMCPs also considers an increasing prevalence of "day 3 positivity" a possible marker of artemisinin resistance, provided that study populations are similar, at least in terms of initial parasitaemia and level of acquired immunity.

WHO currently advocates confirmatory studies using a 7-day supervised course of artesunate monotherapy (4 mg/kg/day over 7 days) including:

- frequent blood sampling for parasitaemia (6- or 8-hourly) to calculate parasite clearance time, slope half-life and parasite reduction rate;
- plasma blood sampling (multiple) for artesunate and DHA concentration[11];
- whole blood sampling and depletion of white blood cells for genome sequencing; and

[11] WHO (2011).*Methods and techniques for assessing exposure to antimalarial drugs in clinical field studies*. Geneva, World Health Organization.

- in vitro testing.

An alternative option is the 3-day course of artesunate monotherapy followed by a full (3-day) ACT course as currently used in the Tracking Resistance to Artemisinin Collaboration (TRAC) project. In contrast to the 7-day artesunate study, this approach does not provide information on treatment failure rates of artesunate monotherapy, but it can be disputed whether this information is essential for defining the presence of artemisinin resistance (as recrudescence with 7 day artesunate treatment were reported prior to the emergence of artemisinin resistance). While these approaches are generally considered acceptable and recommended, they are not always feasible due to ethical considerations or lack of research capacity – and they do not provide information on the efficacy of the treatment policies in use. As an alternative the TEG suggests that accurate assessment of the parasite clearance rate (at least 8 hourly) with 28 or 42-day efficacy with the ACT used or under consideration be monitored. It should be noted that the partner drug will have some impact on the initial parasite clearance rate.

The TEG emphasized that caution is required about the extrapolation of a definition of artemisinin resistance based on clearance data from South-East Asia to Africa. A threshold of 10% may not be suitable for Africa due to host immunity, even among young children. The TEG recommended that in addition to baseline parasitaemia, the interpretation of "day 3 positivity" rates should take into consideration the trends over time, and changes in transmission intensity over time (which may affect population immunity). The 10% threshold for "day 3 positivity" rate will be re-assessed following modeling and new evidence.

5. Artemisinin resistance outside Greater Mekong subregion

Published in vitro studies using artemisinin or artemether, and studies on SERCA type *PfATPase6* polymorphism, reported to be linked to artemisinin resistance. These reports and other published clinical studies were presented to the TEG for review. This review of the literature detected only one clinical study reporting a parasite positivity rate at day 3 over 10%

in Indonesia[12]. For most of the reports reviewed the TEG felt that methodology was flawed, data were too incomplete for assessment or that the evidence was at least inconclusive. Based on reviewed data, the TEG concluded that there is currently no evidence of artemisinin resistance in *P. falciparum* outside the GMS. However, the TEG recommends continued and intensified surveillance on ACT efficacy outside GMS and encourages consultation with the TEG whenever new data raise concerns.

6. Improve the use of existing containment tools

In areas with artemisinin resistance an immediate and multifaceted response is required. The recommended response is summarized in the GPARC document and reviewed in the "joint assessment report" mentioned above. A regional emergency response plan is currently being prepared by WHO, and the TEG should be closely involved in the reviewing and updating of this plan. Although it was not the aim of the current TEG meeting to review containment plans, several aspects of the response plan were briefly discussed by the TEG.

It was recognized that plans designed for regions with limited health infrastructure should focus on scaling up basic malaria control interventions such as early diagnosis and effective treatment, including rapid expansion of community-based approaches. Particular emphasis should be focused on vulnerable and mobile populations. The plan should also aim for universal coverage of vector control.

ACD, MSAT, FSAT and (focused) MDA are additional strategies mentioned in the GPARC for consideration. In September 2010, a consensus meeting on MDA was held[13]. During MDA, every individual in a defined population or geographic area is required to take an antimalarial on a given day or over a given period of days. Although modeling suggests that repeated rounds of MDA could lead to elimination of the artemisinin-resistant strain, the meeting concluded

[12] Asih PB *et al*. Efficacy of artemisinin-based combination therapy for treatment of persons with uncomplicated *Plasmodium falciparum* malaria in West Sumba District, East Nusa Tenggara Province, Indonesia, and genotypic profiles of the parasite. *Am J Trop Med Hyg*, 2009; 80(6):914-8.

[13] WHO (2010) *Consideration of mass drug administration for the containment of artemisinin-resistant malaria in the Greater Mekong subregion*. Geneva, World Health Organization

that the repeated implementation, and achieving the high coverage required for elimination, would be difficult to achieve in most areas.

Improving access for migrant and mobile populations is a key pillar in the ongoing containment efforts. Current activities include distribution of hammock nets in Cambodia, distribution of nets through worksites, net loan schemes, training malaria volunteers among the migrant workers, piloting setting up screening points offering testing and treatment for malaria in areas such as bus terminals, and targeting migrants with behavior change communication. In addition, surveys and migrant mapping have been ongoing to collect information on migrants. The wide range of measures required to contain artemisinin resistance are known; however, resources being limited, the priority is now to identify interventions that need modification.

The TEG made the following general observations; additional recommendations will follow when the draft response plan is being discussed:

- Although elimination of artemisinin resistant parasites should remain the end goal for containment of artemisinin resistance, this should be preceded by realistic shorter term goals in settings where artemisinin resistance has emerged in a context of limited health infrastructure and malaria control measures. These more limited objectives should include prevention of and delaying spread of artemisinin resistance;
- An important component for formulating a response plan is addressing population migration. Implementation of basic control measures particularly in marginalized and migrant populations, is essential for prevention of spread of artemisinin resistant *P. falciparum*. Modeling using available data on population migration can be helpful to address this important factor. Getting technical support from geographers would be useful, as collecting reliable information on population movements is a challenge;
- Ownership of and responsibility for a malaria control programme by local, district, provincial and national health services is critically important;
- Providing access to prompt diagnosis and effective treatment, including the use of a community-based approach, is pivotal in any containment plan. Good coordination of village malaria workers and the use of mobile malaria workers is essential;

- It is important for the implementation of the GPARC to also focus on Africa. ACTs are being deployed on a large scale in Africa and there is a chance that resistance to artemisinin and/or partner drugs could also emerge there. Preventing spread from any foci where artemisinin resistant parasites emerge will be key to containment;
- In the absence of new drugs, strategies to halt the loss of ACT efficacy could include using multiple first-line antimalarial drugs, or prolonging the course of ACT treatment to 5 days. It has been shown that splitting the 6-dose regimen of artemether-lumefantrine over 5 days without increasing the total dose, improves drug exposure of lumefantrine and efficacy of artemether-lumefantrine. For other ACTs, if the total dose is meant to be increased, it is critical to conduct well-designed studies to assess the safety and the efficacy of prolonged ACT treatment, in particular, that of partner drugs.

7. Gaps in research for antimalarial drug resistance monitoring and containment activities

Strategies requiring further modeling exercises

Evaluation of multiple first-line treatments (MFLT) strategy with regards to:

- the effect of MFLT deployment on the risk of drug resistance (while this is expected to decrease resistance, some argue that it could in fact increase resistance);
- whether the risk of resistance is reduced most by using different ACTs sequentially or at the same time, same or different ACT in the private and public sectors or a different ACT in adults and children.

The preliminary modeling results shall be presented at the next TEG meeting and the recommendations discussed with the TEG on chemotherapy. It was noted that operational research on feasibility and implementation of MFLT is also essential.

Modeling migration

The effect on the spread of antimalarial resistance of both population migration and the effectiveness of various interventions targeted at migrant populations need to be included in ongoing modeling of containment strategies. There is a need to better understand migration of people across continents and migration of parasites (see above).

Economics

The economic impact of losing ACTs to resistance is thought to be huge, but it will be important to quantify this impact, even when confidence intervals are large. Modeling should include national, and if possible regional, health and economic impacts on individuals and health systems, comparing implementation of a regional emergency plan with current control measures. The analysis would draw on both epidemiological and cost data. The potential macro-economic losses of delaying containment are difficult to evaluate and could be explored as a separate analysis. The feasibility of calculating the costs of the spread of resistance to sub-Saharan Africa based on historical data for chloroquine and sulfadoxine–pyrimethamine resistance will be explored. Research groups best placed to conduct the necessary modeling of health and economic consequences of resistance both in Asia and Africa will be identified and the findings will be presented at a next TEG meeting.

Approaches to testing new drugs, regimens or combinations

Since reduced sensitivity to artemisinin may compromise the use of artesunate for the treatment of severe falciparum malaria, the TEG recommends establishing a registry system to monitor treatment outcome measures in patients treated with intravenous artesunate for severe malaria in tier I and II areas.

As noted above, a 5-day course of ACT could be evaluated in tier I areas, preferably in western Cambodia. Safety and tolerability as well as efficacy of a prolonged treatment course with an increase in total dose, in particular of dihydroartemisinin–piperaquine, need to be established in clinical trials. In areas such as western Cambodia, where patient numbers are small with almost no treatment alternatives, implementation and research can take place simultaneously.

Vector and entomology

Vector control is important and the only way to reduce the parasite biomass without increasing the antimalarial drug pressure. The TEG recommended entomology research projects addressing the following topics:

- mapping of *Anopheles* vectors and their capacity to transmit artemisinin resistant parasites; and in particular, whether the artemisinin resistant parasites are capable of infecting other main vectors such as *A. gambiae* and *A. arabiensis*;
- operational research on implementation of personal protective measures, especially in settings with outdoor biting vectors.

Molecular markers

There is currently a large research effort to identify a molecular marker for artemisinin resistance, and a validated marker could be available within the next 6 to 12 months. Once a marker becomes available additional research can be directed at developing easy to use methods, including from filter paper blood. As soon as a molecular marker for artemisinin resistance becomes available, the TEG will draft recommendations on sampling and monitoring strategies.

Strategies for translating results of operational research into programme implementation for monitoring and containing resistance

The TEG recognizes the importance of operational research for informing strategies to monitor for and contain antimalarial resistance. However, this should not delay implementation of containment measures, but rather be an intrinsic part of the implementation of the new interventions.

Use of the gametocytocidal effects of primaquine as a containment tool

An ERG on primaquine will take place in Bangkok in August 2012. The TEG recognizes the importance of this subject and would appreciate being informed on the outcomes of this meeting. The TEG called attention to the importance of using optimal study design to address the unanswered questions on the pharmacokinetics of primaquine.

Monitoring effectiveness during chemoprevention interventions

There are important study design questions to address for informing studies monitoring chemoprevention interventions (intermittent preventive treatment or seasonal malaria chemoprevention), including the definition of efficacy endpoints and impact (effectiveness). An

in depth discussion of this topic was beyond the scope of the current meeting and the TEG agreed that a dedicated group such as an ERG should address this topic.

8. Formulation of TEG recommendations and next steps

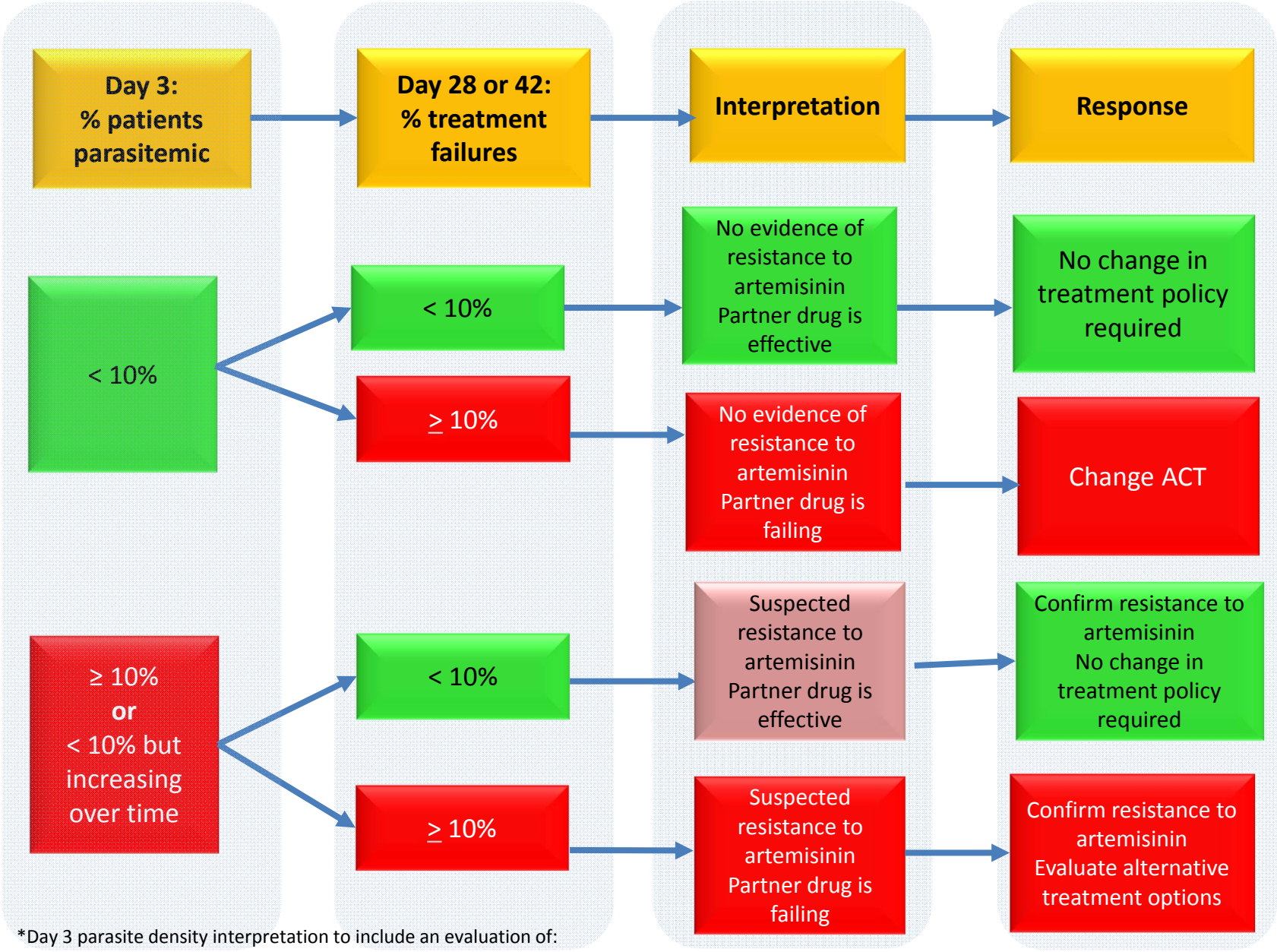
The TEG members formulated recommendations that are listed in the Summary and recommendations section of this report. The TEG also made the following suggestions for the next meeting:

- Representatives from NMCPs and research institutions from endemic countries in South-East Asia, and preferably those with experience in containment of antimalarial drug resistance, should be added to the TEG;
- The agenda of the current meeting was very full and the next meeting should provide more time for discussion;
- In situations where the WHO requires feedback on issues regarding antimalarial drug resistance or containment in between meetings, TEG members will be available to provide this.

9. List of annexes

Annex 1: Decision making for TES studies
Annex 2: Terms of reference of the TEG
Annex 3: Agenda
Annex 4: List of participants

Annex 1: Decision making for TES studies



*Day 3 parasite density interpretation to include an evaluation of: baseline parasitemia, host immunity, trends over time

Malaria Policy Advisory Committee

Technical Expert Group on Antimalarial Drug Resistance and Containment

Terms of Reference

I. Background and rationale

The Malaria Policy Advisory Committee (MPAC) has been constituted to provide independent advice to the World Health Organization (WHO) for the development of policy recommendations for the control and elimination of malaria. The mandate of MPAC is to provide strategic advice and technical input, and extends to all aspects of malaria control and elimination. MPAC can recommend that specific technical issues are analyzed through a time-limited Evidence Review Group (ERG) or a standing Technical Expert Group (TEG).

The MPAC recommends a standing TEG on antimalarial drug resistance and containment as there is now - and will be in the future - a continual need to review new evidence on drug resistance, make recommendations on necessary actions, and set research priorities.

II. Role and functions of the Technical Expert Group on antimalarial drug resistance and containment

The TEG on drug resistance and containment is tasked with reviewing evidence, providing guidance and making draft recommendations on issues of drug resistance and containment. The TEG is constituted by and reports to the MPAC. While the issue of resistance to artemisinins is of urgent concern, resistance to other antimalarials is also of prime importance.

As the issue of drug resistance and containment is evolving quickly, the TEG may provide advice directly to GMP when necessary.

The responsibilities of the TEG on antimalarial drug resistance and containment will be to:

- Evaluate the accuracy and integrity of data on antimalarial drug resistance, in particular data suggesting new foci of artemisinin resistance;
- Provide evidence-based advice on norms, standards and technical guidelines on monitoring of antimalarial drug resistance;
- Provide evidence-based advice on policies, strategies and approaches for drug resistance prevention and containment in general, as well as in specific situation. This includes:
    - Determining the triggers for emergency response related to the detection of artemisinin resistance or resistance to an ACT partner drug;
    - Provide recommendations, based on ongoing evaluation and evidence, on the effectiveness and impact of the implementation of strategies to detect, prevent and contain antimalarial drug resistance;
- Identify priority research areas in the field of drug resistance or containment.

III. Membership and structure of the TEG

The TEG will have up to 15 members. TEG members will serve in an independent, personal and individual capacity.

The TEG composition should strive for appropriate geographical representation and gender balance, and should comprise individuals representing different areas of expertise and experience within antimalarial drug resistance and containment.

Members of the TEG must have excellent technical knowledge, scientific publications in peer-reviewed journals and more than 10 years experience in at least one of the areas listed below.

The following areas of expertise should be represented in the TEG:

- Molecular markers of antimalarial drug resistance
- In vitro assays of antimalarial drugs
- *Plasmodium vivax* drug resistance
- Clinical trials of antimalarial drugs
- Pharmacokinetics of antimalarial drugs
- Modelling on malaria control and elimination
- Cultural geography or political science with a focus on population movement
- Entomology / vector control
- Public health economics

In addition, the TEG should include members who have worked or are currently working as national malaria control programme managers with experience in conducting routine monitoring of antimalarial drug efficacy, as well as general malaria control.

The TEG members will be selected by a nomination panel appointed by MPAC and GMP. Members of the TEG shall be appointed to serve for an initial term of up to three years, renewable once, for a period of up to an additional three years.

Membership in the TEG may be terminated by WHO, including for any of the following reasons:

- failure to attend two consecutive TEG meetings;
- change in affiliation resulting in a conflict of interest;
- a lack of professionalism involving, for example, a breach of confidentiality.

Prior to being appointed as a TEG member and prior to renewal of term, nominees shall be subject to a conflict of interest assessment by WHO, based on information that they disclose on the WHO Declaration of Interest (DOI) form (Annex 1). In addition, TEG members have an ongoing obligation throughout their tenure to inform WHO of any changes to the information that they have disclosed on the DOI form. Summaries of relevant disclosed interests that may be perceived to give rise to real or apparent conflicts of interest will be noted in TEG reports.

In addition, prior to confirmation by WHO of their appointment as TEG members, TEG nominees shall be required to sign a WHO confidentiality agreement (See Annex 2). Although all papers presented at the TEG may be made publicly available on the GMP website, pre-publication manuscripts or confidential documents will be clearly labeled as such and will only be provided to TEG members for discussion.

IV. Responsibilities of TEG members

Members of TEG have a responsibility to provide MPAC with high quality, well considered, evidence-informed advice and recommendations on matters described in these ToR. The TEG has no executive or regulatory function. Its role is to work with the GMP secretariat to provide draft recommendations to MPAC.

TEG members may be approached by non-WHO sources for their views, comments and statements on particular matters within antimalarial drug resistance and containment, and asked to state the views of TEG or details related to TEG discussions. TEG members should refer all such enquiries to WHO/GMP.

V. Structure

GMP will submit a nomination for the first chairperson of the TEG to MPAC for endorsement. The chairperson will serve for 3 years, renewable once. Future chairpersons will be selected from among the appointed TEG members. A rapporteur will be elected at each meeting. Drug Resistance and Containment unit, GMP will serve as secretariat for the TEG.

VI. Working Procedures

With the coordinator of the Drug Resistance and Containment unit, the chairperson of the TEG will develop a plan for routine operations of the TEG. The TEG will meet at least once per year and have additional meetings and/or teleconferences as needed. When practicable, the TEG meetings will be scheduled in association with meetings of the TEG on chemotherapy and will share a session with the TEG on chemotherapy. TEG meetings should be anticipated at least three months in advance of the meeting. WHO will provide support for travel and accommodation for the purpose of TEG meetings.

Decisions on TEG recommendations will, as a rule, be taken by consensus. In the exceptional situation that consensus cannot be reached the chairperson shall report the majority and minority views. It is also the chairperson's responsibility to ensure there is clarity for TEG members on what exactly is being decided.

A representative from the Medicines for Malaria Venture (MMV) and a representative from the WorldWide Antimalarial Network (WWARN) will be invited to participate as standing observers in the TEG meetings. WHO/GMP may also invite other observers to the TEG meetings, including representatives from non-governmental organization, international professional organizations, technical agencies, and donor organizations. Additional experts, and Technical Resource persons, may also be invited to meetings by the secretariat with approval of the chairperson, as appropriate, to further contribute to specific agenda items. However, only TEG members can participate in voting or decision by consensus. Observers shall not take the floor unless requested to do so by the chairperson and shall under no circumstances participate in the formulation of TEG recommendations.

Relevant staff from WHO Headquarters and Regional Offices will attend as members of the Secretariat.

VII. Dissolution of TEG

The relevance of the TEG will be assessed annually by the MPAC. The terms of reference will also be reviewed once a year by the TEG. Any proposed changes in the ToR must be submitted to and approved by the MPAC.

World Health Organization

DRUG RESISTANCE AND CONTAINMENT: TECHNICAL EXPERT GROUP

21-22 June 2012 – Crowne Plaza Hotel, Geneva, Switzerland

PROGRAMME		
Thursday, 21 June 2012 – Salle Copenhague		
09.00 - 09.30	Welcome – Introduction **A. Dondorp - Chair TEG DRC**	
09.30 – 09.45	TEG DRC Terms of reference, declarations of interest, expected outcomes and modus operandi **P. Ringwald**	
09.45 -10.00	Presentation of the Drug Resistance and Containment (DRC) Unit **P. Ringwald**	
10.00 – 10.15	**Coffee break**	
10.15 - 11.00	Monitoring antimalarial drug efficacy **A. Barrette** Capacity strengthening **M. Warsame** Discussion	
11.00 – 11.45	Situation on artemisinin and other major antimalarial drugs resistance **P. Ringwald** Discussion	
11.45 – 12.30	Update on containment activities **C. Rasmussen** Discussion	

12.30 - 14.00	**Lunch**	**Salle Meyrin**
14.00 – 16.00	**Session 1** – Artemisinin resistance: messaging and political commitment **M. Hardiman, International Health Regulation** **B. Aylward, ADG Polio, Emergencies and Country Collaboration** **R. Newman, Global Malaria Programme** Discussion	Expected outcome: Advise on what should be the message of WHO around artemisinin resistance and the development of an emergency plan.
16.00 – 16.15	**Coffee/tea break**	
16.15 – 17.30	**Session 2** – Review of current working definition of artemisinin drug resistance **P. Ringwald** **A. Dondorp** Discussion	Expected outcome: Discussion on whether the definition should be changed and if so, on which basis. What are the current protocols used for screening and confirmation of artemisinin resistance and should these be harmonized including for Africa? By whom should the decision around Tier I, II, III mapping be made?
17.30 – 18.30	**Session 3** – Artemisinin resistance outside Greater Mekong Sub-region **P. Ringwald** Discussion	Expected outcome: Discussion on artemisinin resistance outside South-East Asia. What is the evidence?
18.30	**Reception**	**Foyer**
Friday, 22 June 2012 – Salle Copenhague		
08.30 – 9.45	**Session 4** – Improve the use of the existing containment tools **C. Rasmussen** Discussion	Expected outcome: Advise on future and ongoing containment activities with focus on: whether it is possible to improve the use of the available tools (case tracking, MSAT, FSAT), how better to target migrant and mobile populations, and how to improve the use of vector control in containment efforts.
09.45 - 10.00	**Coffee/tea break**	

10.00 - 12.30	**Session 5** – Gaps in research for antimalarial drug resistance monitoring and containment activities **A. Dondorp**	Expected outcome: Recommendation on which topics should be further investigated and presented at the next TEG.

	• Which strategies need further modelling:
	  o Multi-drug first line;
	  o Effect of population movement for spread of resistance (in various epidemiological/intervention scenarios);
	  o Consequences over coming 20 years of failure of containment beyond Greater Mekong Sub-region with focus on India and Africa;
	  o Country and region specific elimination/containment strategies.
	• Approaches for testing new drugs in areas with artemisinin resistance
	• Entomology studies (transmissibility of resistant parasites to Indian/African vectors)	

12.30 - 14.00	**Lunch**	**Salle Lisbonne**
14.00 - 15.30	• Strategies for translating results of operational research and monitoring of resistance into programme implementation • Discussion on additional urgent research questions and funding strategies • Use of primaquine for gametocytocidal effect • Monitoring drug effectiveness during chemoprevention interventions (IPTi, IPTp, SMC)	
15.30 - 16.00	**Coffee break**	
16.00 - 17.30	Formulation of TEG recommendations and next steps Dates and agenda of the next meetings	
17.30	Close of the meeting	

TECHNICAL EXPERT GROUP ON DRUG RESISTANCE AND CONTAINMENT

21-22 JUNE 2012, CROWNE PLAZA HOTEL, Geneva, Switzerland

List of Participants

TECHNICAL EXPERTS

Professor Arjen DONDORP, Chair
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Bangkok, THAILAND

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Eijkman Oxford Clinical Research Unit
Jakarta, INDONESIA

Professor Karen BARNES
University of Cape Town
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WHO SECRETARIAT

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Drug Resistance and Containment Unit

Ms Zsofia SZILAGYI
Communication Officer/advocacy
Director Office

Report from Drug Resistance and Containment Technical Expert Group (DRC TEG) Meeting 21–22 June 2012

Meeting of the Malaria Policy Advisory Committee
Geneva, 11-13 September, 2012

Dr Allan Schapira
Member of MPAC and DRC TEG

World Health Organization

GLOBAL MALARIA PROGRAMME

PARTICIPANTS

- Dr Arjen DONDORP, Mahidol-Oxford Research Unit, THAILAND (Chair)
- Dr Kevin BAIRD, Eijkman Oxford Clinical Research Unit, INDONESIA
- Prof. Karen BARNES, University of Cape Town, SOUTH AFRICA
- Dr Lesong CONTEH, Institute of Global Health Innovation, Imperial College, UK
- Prof. James ELIADES, Mailman School of Public Health, Colombia U., USA
- Dr Ian HASTINGS, Liverpool School of Tropical Medicine, UK
- Dr Sylvia MEEK, Malaria Consortium, UK
- Dr Harald NOEDL, Medical University of Vienna, AUSTRIA
- Prof. Chris PLOWE, University of Maryland, USA
- Prof. Christophe ROGIER, Institut Pasteur, MADAGASCAR
- Dr Allan SCHAPIRA, PHILIPPINES
- Dr Frank SMITHUIS, MYANMAR
- Dr Julie THWING, CDC, USA

Building capacity for effective monitoring of antimalarial drug efficacy

- 14 subregional network workshops on antimalarial drug-efficacy testing were organized between 2009 and 2011, covering more than 80% of all falciparum-endemic countries.
- 7 countries: WHO training courses on TES
- Groups of clinicians and microscopists were trained as consultants to create a pool of regional experts who will provide technical support
- WHO supported over 40 malaria endemic countries on issues regarding antimalarial drug efficacy, including technical advice on protocol, data analysis, quality-assured antimalarials, PCR services.

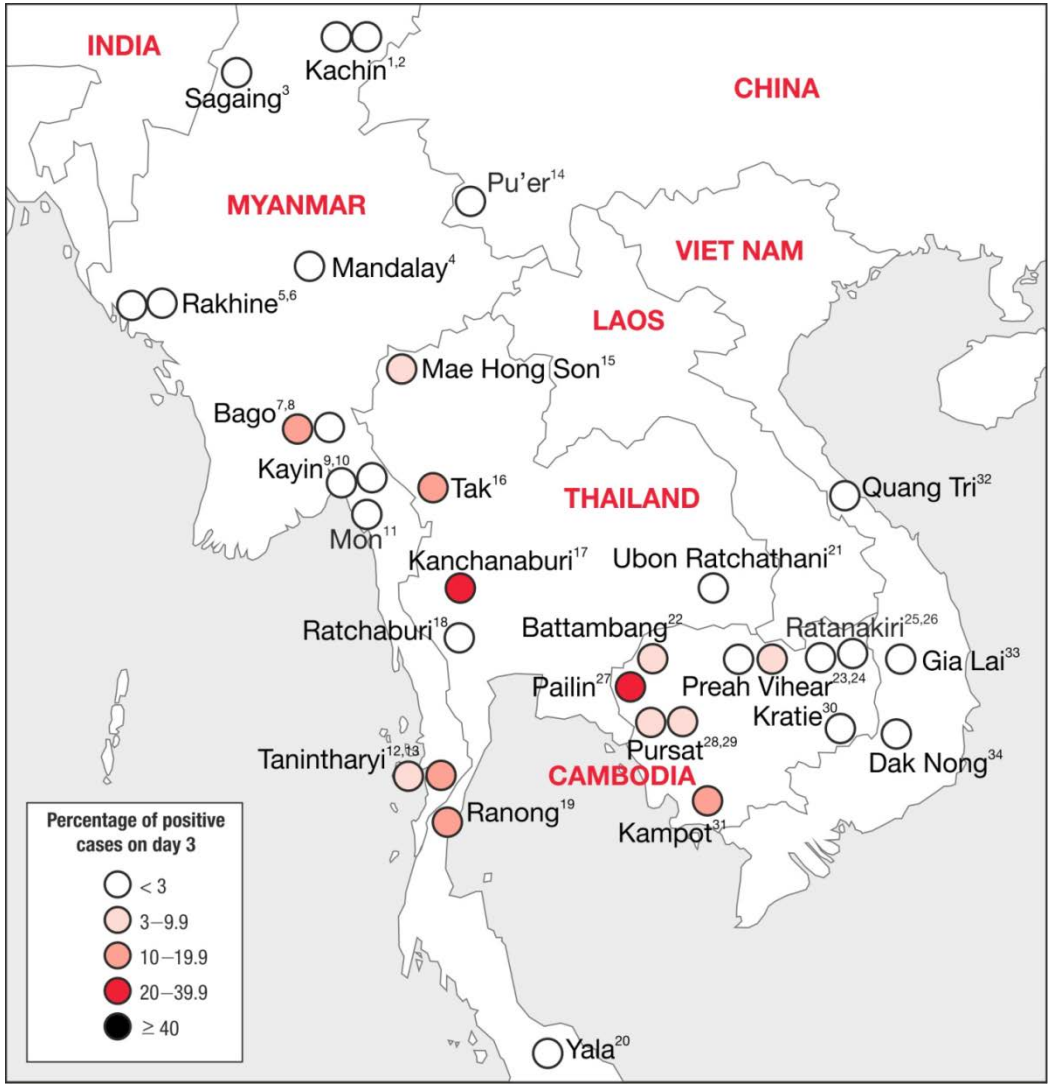
Current status of *P. falciparum* resistance

- Artesunate + SP: Failing in many settings in Africa but still highly effective in S and W Asia, Sudan and Somalia.
- Artesunate + amodiaquine: Failing in many areas, but not in West Africa
- Artemether + lumefantrine: Still effective everywhere, except western Cambodia
- Artesunate + mefloquine: High failure rates in W. Cambodia, parts of Thailand
- Dihydroartemisinin-piperaquine: High failure rates in W. Cambodia. Also, it seems, in some areas of Papua New Guinea and Rwanda
- Artesunate–pyronaridine : Efficacy of 98%, except in Pailin (W. Cambodia), where treatment failures reached 10%

Atovaquone-proguanil

- A-P is now used as first-line treatment under strict control in certain areas of Cambodia and Thailand
- Mutations related to atovaquone resistance, have been reported from French Guyana, India, and in several countries in Africa. Not in South-East Asia.
- Some discussion and uncertainty about the risk of spread in case of emergence of such mutations in South-east Asia.

‘The region, where malaria parasite very clever than man’



April 2012 WHO update

%age positive Day 3 , on ACT treatment

Circles: Before Nov 2010
Triangles: After =“=

World Health Organization

Global Malaria Programme

Global plan for artemisinin resistance containment (GPARC) launched January 2011

To contain or eliminate artemisinin resistance where it already exists, or to prevent it where it has not yet appeared.

- stop the spread of resistant parasites;
- increase surveillance to evaluate the presence and spread of resistance;
- improve access to diagnostics and rational treatment with ACTs
- invest in artemisinin resistance-related research.

Tier I: areas for which there is credible evidence of artemisinin resistance.

Tier II: areas are those with significant inflows of people from tier I areas, including those immediately bordering tier I.

TEG comment: the distinction in containment activities between tier I and tier II is subtle. There is a need to increase the perimeter for containment

Lessons from containment in Cambodia, Thailand since 2008

- The project managed to rapidly increase access to prompt diagnosis and effective treatment –village malaria workers/volunteers in Cambodia.
- Banning oral artemisinin-based monotherapies as well as enforcing the ban were successful in drastically reducing the number of offending drug sellers.
- Very high coverage rates with LLINs were achieved, but maintaining the coverage was difficult, in part due to high population mobility.
- The lowering of the burden of falciparum malaria in Pailin province (W. Cambodia) associated with increased proportion of artemisinin resistant infections.

Joint assessment of the response to artemisinin resistance in the GMS November 2011 -February 2012, funded by AusAID and BMGF

Plans and strategies are not implemented with sufficient intensity, coverage and quality. Therefore (among others):

- strengthen leadership, coordination and oversight;
- secure adequate financial resources;
- build political support;
- clarify and implement policy decisions on diagnosis and treatment;
- prioritize Myanmar while maintaining a strong response in all GMS countries

Messaging and political commitment

- There is inadequate awareness about the magnitude, urgency and seriousness of the problem of artemisinin resistance even in governments of some affected countries.
- Under *International Health Regulations*, declaring a health threat as a global *Public Health Emergency of International Concern (PHEIC)* raises high expectations regarding full containment of the emergency; if not achieved, it will be considered failure. It took years to achieve consensus that polio re-emergence is a *programmatic global health emergency*, and then the polio eradication programme has still had to scale back activities in 2012 due to funding gaps.
- The TEG found it is currently inappropriate to call artemisinin resistance a PHEIC. The TEG agreed on designating resistance to artemisinin and partner drugs a growing regional emergency that represents a major threat to global malaria control and elimination efforts if not contained and eventually eliminated.

Messaging suggested by DRC TEG

- ACTs are currently failing in a geographically limited region, where resistance to both the artemisinin and ACT partner drugs is present, causing severe and worrying limitations to the available treatment options for falciparum malaria in these regions.
- This message should be balanced against the fact that over 200 million people are successfully treated globally with ACTs each year, and that access to ACT treatment has contributed importantly to the current reduction in malaria morbidity and mortality.
- Fighting antimalarial drug resistance must be a global effort starting with the implementation of the Global plan on artemisinin resistance containment (GPARC) recommendations in all endemic countries.

Precisely which objectives are attainable

- The TEG discussed whether messaging should convey that containment of artemisinin resistance is still feasible or that it is inevitable that artemisinin drug resistance will eventually emerge elsewhere, and that the current efforts are only buying time. There are no current data to strongly support either view. In both scenarios, containment efforts are essential, since no novel alternatives medicines to ACT will be available for at least the next few (> 5) years;
- While elimination should be the end objective, it is clear that in certain settings such as Myanmar, elimination efforts will need to be preceded by a more realistic shorter term goal of malaria control aimed at preventing or delaying the spread of artemisinin resistance as well as reducing the parasite reservoir and decreasing the burden of disease;

Strengthening the messaging

- Messaging would be stronger if built on mathematical modeling. Efforts will be conducted in several areas:
  - to make the investment case;
  - to clarify possible impact of spread or emergence in Africa;
  - to show how different interventions impact on malaria disease and economic burden.

Artemisinin resistance definition

There is currently no consensus on the definition of artemisinin resistance.

WHO Working definitions:

- an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
- a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence of parasites after day 7 within 28 or 42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance).
- Identification of molecular markers are a top research priority.

Operational definitions/triggers

- If > 10% of patients are still parasitaemic at day 3, more detailed studies to confirm the presence of artemisinin resistance in the area are needed.
- However, this confirmation should not delay containment activities.
- TEG recommends that NMCPs also considers an increasing prevalence of “day 3 positivity” a possible marker of artemisinin resistance, provided that study populations are similar.
- The TEG emphasized: Threshold of 10% may not be suitable for Africa due to host immunity, even among young children. Interpretation should take into consideration trends over time, and changes in transmission intensity. The 10% threshold for “day 3 positivity” rate will be re-assessed following modeling and new evidence.

Outside Greater Mekong subregion

Based on reviewed data, the TEG concluded that there is currently no evidence of artemisinin resistance in *P. falciparum* outside the GMS.

Containment interventions

- For areas with limited health infrastructure : focus on scaling up basic malaria control interventions, including rapid expansion of community-based approaches. Universal coverage of vector control.
- village malaria workers and mobile malaria workers
- Active case detection, mass or focused screening and treatment and (focused) mass drug administration are additional strategies mentioned in the GPARC for consideration. Although modeling suggests that repeated rounds of MDA could lead to elimination of the artemisinin-resistant strain, the meeting concluded that the repeated implementation, and achieving the high coverage required would be difficult to achieve in most areas.

Priorities for modeling

1. Multiple first-line treatments (MFLT)

- The effect of MFLT on the risk of drug resistance: while expected to decrease resistance, some argue that it could increase it, depending on genetics;
- whether the risk of resistance is reduced most (if at all) by different ACTs sequentially or at same time, same or different ACT in private and public sectors or different ACT in adults and children.
- The preliminary modeling results shall be presented at next TEG meeting and the recommendations discussed with the TEG on chemotherapy

2. Migration

3. Burden including economic losses

Testing new drugs, regimens or combinations

- TEG recommends a registry system to monitor treatment outcomes in patients treated with intravenous artesunate for severe malaria in tier I and II areas.
- A 5-day course of ACT could be evaluated in tier I areas, preferably in western Cambodia. Safety and tolerability as well as efficacy of a prolonged treatment course with an increase in total dose, to be established in clinical trials.

Entomology-related research priorities

- mapping of *Anopheles* vectors and their capacity to transmit artemisinin resistant parasites; and in particular, whether the artemisinin resistant parasites are capable of infecting other main vectors such as *A. gambiae* and *A. arabiensis*;
- operational research on implementation of personal protective measures, including protective clothing, especially in settings with outdoor biting vectors.

WHO Evidence Review Group:
Malaria Burden Estimation

WHO Headquarters, Geneva, 27-28 June 2012

Meeting Report

Opening remarks

Dr. Robert Newman, director of the WHO Global Malaria Program (GMP), welcomed the members of the Malaria Burden Estimates Evidence Review Group (MBE-ERG) and outlined some of the issues relevant to its work. He noted that the scale-up of malaria control interventions has focused attention on measuring progress in reducing the global malaria burden, including WHO's malaria burden estimates reported in the World Malaria Report (WMR), as well as those reported by other groups. The specific tasks for the MBE-ERG, outlined in its Terms of Reference (see attached), include mapping a way forward in producing malaria burden estimates, with a focus on use of the estimates by WHO headquarters and member states, as well as describing how to obtain better data for input into those estimates.

Dr. Peter Smith, the MBE-ERG chair, described the group's general timeline. Currently, three meetings are scheduled over approximately 18 months, with supportive work by group members in between. The first meeting is designed to outline relevant issues, the second to elicit further expert opinion, especially from groups directly involved in malaria burden estimation, and the third to develop recommendations to Malaria Policy Advisory Committee (MPAC) on the way forward, which will be included in the final meeting report.

Overview of malaria burden estimation, use of burden estimates and scope of the MBE-ERG

Brief overview of malaria burden estimate methods

The group was provided with a brief overview of the different malaria burden estimates currently employed related to numbers of clinical cases and numbers of deaths.

For estimating the number of malaria cases, approaches can be grouped into two broad categories. One approach is case report based, in which reported cases are adjusted for health facility attendance, level of diagnostic effort, and underreporting in the health sector. The second can be described as risk based, in which geographical areas are categorized by level of malaria risk; risk is converted to malaria incidence based on relationships derived from longitudinal studies and adjusted for the estimated deployment of preventive measures (e.g.

bed-nets); the malaria incidence is multiplied by the relevant population to obtain the number of malaria cases.

Approaches to estimates of malaria deaths fall into three categories, two of which are similar to those for case estimates. There is a risk-based approach, in which the level of malaria risk is linked to malaria mortality rates and population through mapping. Another can be described as case report based, in which adjusted case counts are multiplied by a fixed case fatality rate (CFR) to derive number of malaria deaths. Lastly, a vital registration (VR) based approach has also been used, which may provide direct estimates from recorded deaths.

Group discussion noted: that uncertainty varies in these approaches; ultimately we need better reporting; implementation of diagnostics can be transformative in understanding malaria burden in a given area; it can be useful to understand motivations for reporting as these may drive changes in reported numbers.

Uses of estimates at international level

Uses of malaria case and death estimates at the international level were reviewed. These include: 1) Global advocacy for malaria control; 2) Global reporting to targets, such as for Millennium Development goals (MDG); 3) Global burden of disease analysis and the prioritization of malaria in relation to other conditions; 4) Prioritization of countries for resource allocation (e.g. Global Fund) – it was noted to be problematic for prioritization when different burden estimates were derived for a country with different methods. Discussion noted that, for these uses, estimates for malaria cases and deaths need to include the ability to measure change over time.

Uses of estimates at national level

Discussion on use of malaria burden estimates for Brazil, India, Tanzania, and Ghana highlighted how their use differs by country. For example, some countries made little use of the WHO estimates and used their own data, whereas others used WHO data for Global Fund applications. It was noted that WHO is required to follow a country consultative process for clearing estimates by country. Because this process currently takes several months, by the time country level estimates for one year are cleared, new global and regional estimates for the next year are ready for the WMR. Consequently, country level estimates for the previous year are out of date and global and country level estimates have not been released together.

The scope and purpose of burden estimation: what does ERG want to achieve?

The discussion on the scope and purpose of burden estimation noted that some of the first malaria mortality burden estimates proved useful for advocacy, even though the methods were crude. Methods for burden estimates need to further improve to meet needs of tracking progress in control. ERG should also consider how to improve the data inputs as well as the estimation methods, and that scale up of malaria diagnostic testing will be a key component of improved burden estimation. The group may also consider how plasmodium infection surveillance, in sentinel populations and in the community, could feed into malaria burden

estimates, as well as the role of tracking asymptomatic infections and measuring level of infection in individual patients.

Review of malaria burden estimates

The group was provided with supportive documents describing recently completed malaria burden estimates for cases and deaths (see page 8 for references). The different methods were summarized and discussed.

Methods for malaria morbidity estimation: the Malaria Atlas Project (MAP) approach

In brief, the MAP group uses a risk-based approach for all countries with stable malaria risk, a fixed incidence (1 case/10,000) for unstable areas, and accepts national reported case counts for seven countries considered to have complete and reliable national reporting. For countries with stable risk, MAP has constructed a map of *P. falciparum* parasite prevalence (PfP) based on community surveys conducted over 1985-2008. Parasite prevalence is converted to malaria incidence using a modeled relationship derived from malaria incidence survey data. Malaria incidence rates are then applied to a map of human population density in malaria endemic areas to derive malaria case counts. This results, for 2010, in an estimated 451 (349-553) million malaria cases globally, 271 (24-301) million in Africa, 177 (89-271) million in Asia, and 3 (1.2-6.8) million in the Americas. India accounts for most of the uncertainty in the global estimate due to the relative dearth of parasite prevalence data available.

Discussion of the MAP approach focused on how PfP surveys used may be biased in time and place and on the validity of the modeled prevalence-incidence relationship. The most recent PfP surveys available for certain countries may have been conducted many years ago and may not reflect the current malaria situation, or the surveys were conducted in areas not representative of the country as a whole. All-age clinical incidence is modeled from malaria incidence surveys matched by time and place to age-standardized PfP surveys and results in a large uncertainty range in the prevalence to incidence conversion. Availability of more recent nationally representative surveys may address these issues.

Methods for malaria morbidity estimation: the WHO approach

WHO employs a case based approach (Method 1) for countries considered to have reliable case reporting systems, and a risk based approach (Method 2) for high transmission countries considered to have less reliable case reporting systems. In Method 1, case reports are adjusted for facility attendance for fever from DHS surveys, the proportion of suspect malaria cases tested (derived from country reported slide positivity rate), and completeness of reporting (from country reports to WHO). WHO Method 2 starts with the MARA map, a risk map based on climactic suitability for malaria transmission. (WHO did not previously have access to the MAP PfP based map, though an agreement has now been reached for WHO to access the MAP data.) Transmission levels in MARA map (high and low) are converted to incidence using a modeled relationship derived from malaria incidence studies, stratified by three age groups (<5, 5-14, and 14+ years) . Incidence for each risk-age category is multiplied by population to

calculate the number of cases. Incidence is reduced by 0.5% for each 1% increase in percentage of households owning an ITN.

WHO estimated 216 (149-274) million cases in 2010, 176 (113-293) million in Africa, 28 (23-35) million in Southeast Asia, all less than MAP. For Africa, the largest difference is for Nigeria; in Asia, India accounts for the largest difference. WHO questions MAP estimates for India, as they imply higher malaria incidence than anywhere in Africa, and would require a much higher SPR than reported or higher fever incidence than seems reasonable.

Discussion on Method 1 focused on how treatment-seeking and health facility reporting rates could be overestimated; for Method 2, use of the MARA map, validity of the transmission to incidence relationship and the effect of ITN coverage in the model were questioned.

Methods for malaria mortality estimation: the Institute for Health Metrics and Evaluation (IHME) approach

The approach to malaria mortality estimates employed by IHME in their recently published paper in the Lancet can be described as risk based. They use identified VR and verbal autopsy (VA) studies, corrected for misclassification due to so called "garbage codes", to derive cause fractions of deaths. These are then modeled for missing place and time for 8 region/sex/age categories. They include three measures of risk, the Lysenko map of endemicity zones, the MAP PfP based map and WHO populations at risk, and covariates for other factors, including rain, health care access, drug resistance, ITN, IRS, income and education. The resulting models are ranked by an out of sample predicted validity method and all included in an ensemble model with varying weights based on their rank. By this method, IHME estimates 1.2 million (929,000-1,685,000) malaria deaths worldwide, compared to WHO's estimate of 655,000 (537,000-907,000). Given the large uncertainty bounds, the only true difference in the two estimates is for deaths in ages 5 years and over Africa (307,000-658,000 for IHME compared to 42,000-75,000 for WHO).

The discussion on the IHME estimates noted the difficulty in following the description of methods put forth in the paper. In addition the ratio of adult to child malaria deaths indicated in the IHME study was not consistent with clinical experience, or other studies, and calls into question the validity of the results. It was noted that most sites in IHME's validation study were either free of malaria or had low levels of transmission, and therefore not a good basis for validation. In the one site with significant amounts of malaria transmission previous studies had suggested that the quality of laboratory diagnosis was poor, which could lead to over-diagnosis of malaria in the validation study and to overestimates of the total number of malaria deaths.

Methods for malaria mortality estimation: the WHO approach

Outside of Africa, WHO uses the adjusted malaria case count multiplied by a fixed CFR (0.3%). The CFR is based on a single study from Burma 1998. For Africa, WHO starts with a risk map to delineate transmission level into two categories, "high" or "low". A mortality rate for children

<5 years is derived from longitudinal studies for each level of transmission, and by urban or rural area. Deaths in those >5 years are derived from modeled relations of malaria transmission intensity (entomological inoculation rate) and age specific malaria death rates. The numbers of deaths are then estimated by multiplying the population at different levels of risk by the derived malaria death rate for each age, urban-rural category. Death rates are reduced 0.5% for each 1% increase in percentage of households owning at least one ITN. The Child Health Epidemiology Reference Group (CHERG) index for child deaths is entered into the model as a covariate so that the estimated malaria deaths fit into the estimates of deaths for all causes.

Discussion noted that other data may be available to refine the fixed CFR applied to adjusted case reports for countries outside Africa and for the mortality rate by level of transmission for countries in Africa. India has embarked on a study to estimate malaria deaths using a modified WHO approach with alternate values for SPR and CFR.

Other possibilities for burden estimation

Other measures to assess malaria control were reviewed. These include entomologic (mosquito abundance and age), parasitologic (prevalence, in convenience sample populations), clinical (severe cases and admissions, malaria specific mortality in confirmed cases), and indirect ones (birth weight). The availability of these measures would be dependent on multiple groups, including academia, ministries of health operational research and routine information systems. Discussion noted that as their work proceeds, the MBE-ERG will need to think more about how these measures could be translated into high level burden estimates.

The group was also provided with a draft paper describing how not taking into account the effects of malaria treatment could lead to underestimates of malaria burden in both risk based and case report based approaches. For risk based approaches, treatment of cases in longitudinal studies, at a higher rate than usually observed in the community, likely lowers overall transmission, and, therefore, these studies may underestimate the true incidence-prevalence relationships. Similarly, treatment seeking for fever may be overestimated in surveys, since fevers for which treatment was sought are more likely to be recalled, and therefore the adjustment of case reports for care seeking may be inadequate. The paper proposes a new approach for estimating malaria burden based on the point prevalence of malaria-attributable disease.

<u>The way forward</u>

Plans for this year's WMR

The question was raised what to do for this year's World Malaria Report while longer term recommendations were being formulated by the ERG. Options discussed for this year include: producing new global and regional estimates for this year's WMR (with same method as used in the past); not producing any new estimates for this year's WMR; reporting country level estimates for 2010 (country clearance for these should be complete in time for the WMR 2012).

The group noted that all estimation methods for both cases and deaths were highly problematic and different methods had both weaknesses and strengths. Methods that use real current data are attractive, but are challenging currently in areas where the burden is greatest. A hybrid approach could be explored, combining the different methods in some way. The group noted the challenge in presenting uncertainty in the estimates and acknowledged the pressure to produce a single number – particularly for deaths.

Preparations for the next meeting

The group considered they had had a useful introduction to the current burden estimation methods but recognized that more details on current methodologies would be helpful. In accordance with the terms of reference for the MBE-ERG developed by GMP and MPAC, the process for inviting other groups who have worked on malaria burden estimates (MAP, IHME) to the next meeting was discussed. The invitation should be specific regarding presentation of methods—i.e. variables used, assumptions made, limitations—and also their willingness to collaborate on future burden estimate efforts. In particular, the group would wish to enquire of the modelers:

1. What are the main assumptions in your model?
2. What are your estimates most sensitive to in terms of assumptions or absence of data?
3. What data/information that could be collected relatively easily would be most useful in improving your model
4. How could your modeling methods be integrated with other modeling methods to produce (better) consistent estimates?
5. How good is your method at measuring trends in addition to absolute numbers?
6. How willing are you to share your basic data with other groups?

Examples from burden estimation approaches for other diseases may be relevant, for instance, what has been done by UNAIDS, and, therefore, UNAIDS modelers could also be invited to the next meeting. Input would also be useful from a country which has recently improved its data quality in surveillance and vital registration.

Time between meetings

The suggestion was made that the complex issue of improving malaria burden estimation may be best approached by breaking it down into smaller parts. For example, the group could focus on important smaller issues identified so far, such as age distribution of malaria deaths, case fatality rates, converting prevalence to incidence, and suggest specific studies to be done and groups that would be engaged.

Accordingly, three pieces of group work were identified that group members will be called upon to complete before the next MBE-ERG meeting, to be held during the first quarter of 2013.

1) Different group members would be asked to review each modeling method in order to lead the discussion at the next meeting to:
    - Identify the most important assumptions
    - Identify the most sensitive assumptions
    - Identify what data/information (easily collected) would improve model estimates.

2) Group members would seek to outline new approaches to estimating absolute numbers and/or trends – especially methods that would involve collecting data at national or sub-national levels.

3) Related to 2), group members would liaise with national malaria control programme staff and others to work out what data it might be possible to collect at national level (and assess its value to the national control programme).

The final meeting of the group was planned to be around June/July 2013.

REVIEW OF MALARIA BURDEN ESTIMATES - REFERENCE LIST

MALARIA CASES

MAP

Gething et al. A new world malaria map: *Plasmodium falciparum* endemicity in 2010. *Malaria Journal* 2011, 10:378
http://www.malariajournal.com/content/10/1/378

Patil, et al. Defining the relationship between *Plasmodium falciparum* parasite rate and clinical disease: statistical models for disease burden estimation *Malaria Journal* 2009, **8**:186
http://www.malariajournal.com/content/8/1/186

Hay, et al. Estimating the Global Clinical Burden of *Plasmodium falciparum* Malaria in 2007. PLoS
Med 7(6): e1000290.
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000290

WHO

Cibulskis et al. Worldwide Incidence of Malaria in 2009: Estimates, Time Trends, and a Critique of Methods PLoS Med 8(12): e1001142.
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001142

WHO. World Malaria Report 2008, Annex 1.
http://www.who.int/malaria/publications/atoz/9789241563697/en/index.html

World Malaria Report 2011, pg 72-75
http://www.who.int/malaria/world_malaria_report_2011/en/index.html

MALARIA DEATHS

WHO/CHERG/MERG

Liu et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012; 379: 2151–61
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60549-1/abstract#

WHO. World Malaria Report 2008, Annex 1.
http://www.who.int/malaria/publications/atoz/9789241563697/en/index.html

WHO. World Malaria Report 2011, pg 72-75
http://www.who.int/malaria/world_malaria_report_2011/en/index.html

IHME

Murray et al. Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet* 2012; 379: 413–31. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60034-8/abstract
WebAnnex http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60034-8/fulltext

Lynch et al. New global estimates of malaria deaths (letter). *Lancet,* submitted 5 April 2012. [subsequently published citation: Lynch et al. New global estimates of malaria deaths. *Lancet,* 2012 Aug 11;380(9841):559. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)61320-8/fulltext]

Malaria Burden Estimation - Evidence Review Group (MBE-ERG)

GLOBAL MALARIA PROGRAMME

Peter Smith (Chair MBE-ERG)

Richard Cibulskis (WHO)

MPAC meeting
September 11, 2012

World Health Organization

MBE-ERG: Terms of Reference

To review approaches to burden estimation and make recommendations to MPAC on:

1. **Approaches WHO should use to:**
    a) estimate the number of malaria cases and deaths in order to prioritize countries for resource allocation
    b) understand trends over time to assess impact of global strategies
    c) prioritize malaria in comparison with other health conditions
2. **Approaches endemic countries should use to:**
    a) estimate the number of malaria cases and deaths nationally and sub-nationally
    b) understand which populations are most affected
    c) improve the quality of input data for malaria burden estimation

MBE-ERG: Membership

- **Salim Abdulla** (Tanzania)
- John Aponte (Spain)
- Zulfiqar Bhutta (Pakistan)
- Peter Byass (UK)
- Azra Ghani (UK)
- **Brian Greenwood** (UK)
- Patrick Kachur (CDC-US)
- Aswan Kumar (India)
- SETH Owusu-Agyei (Ghana)
- Ana Carolina Santelli (Brazil)
- Peter Smith (UK)
- Richard Steketee (PATH)
- Jane Thomason (HMN)
- **Nicholas White** (Thailand)

MPAC Members

MBE-ERG: Timetable

Meeting 1: (June 27-28, 2012):

Initial review of estimation methods, identify issues, and determine key questions

Meeting 2: (First quarter 2013):

Individuals representing major groups involved in malaria burden estimation will present their approaches to the ERG and answer questions on their methods

Meeting 3: (June/July 2013)

Review evidence gathered and formulate recommendations to MPAC that address questions posed.

MBE-ERG first meeting progress: Use of burden estimates

1. Global advocacy for malaria control;
2. Global reporting to targets, such as for Millennium Development goals (MDGs);
3. Global burden of disease analysis and the prioritization of malaria in relation to other conditions;
4. Prioritization of countries for resource allocation (e.g. Global Fund) – it was noted to be problematic for prioritization when different burden estimates were derived for a country.
5. Some countries made little use of the WHO estimates and used their own data, others used WHO data for Global Fund applications.
6. WHO follows a country consultative process for clearing estimates by country that takes several months. By the time this is complete new global and regional estimates are prepared. Consequently, country level estimates for the previous year are out of date and global and country level estimates have not been released together.

MBE-ERG first meeting summary: Review of recently published estimates

- All estimation methods are quite crude and problematic, all with weaknesses and strengths and high levels of uncertainty
- Methods using real current data attractive but challenging where malaria burden is greatest
- Possibility of a hybrid approach to be explored; certain components of each approach could be improved
- Presenting uncertainty is a challenge and there is much focus on a single number (especially for deaths)
- In the short to medium term, whatever estimation method is used is likely to be subject to considerable uncertainty. ERG aim is to suggest way forward in the short-term and explore longer-term approaches, possibly involving collection of new data.

MBE-ERG first meeting summary: Review of recent case estimates

- **MAP: risk-based approach for countries with stable malaria , fixed incidence for unstable areas, national reporting for selected countries. Parasite prevalence (PfP) surveys (1985-2008) converted to malaria incidence using modelled relationship from survey data.**
  - PfP surveys used may be old and not representative - biased in time and place.
  - All-age clinical incidence is modeled from malaria incidence surveys matched by time and place to age-standardized PfP surveys - large uncertainty range in the prevalence to incidence conversion. May also result in underestimate of clinical incidence because cases in longitudinal surveillance offered treatment.

- **WHO: case-based approach (adjusted for estimated under-reporting) for countries with reliable reporting and risk-based (MARA map) in high transmission countries, with adjustment for ITN use.**
  - Treatment-seeking and health facility reporting rates could be overestimated in estimates outside of Africa.
  - For Africa better alternatives to the MARA map probably exist. All-age clinical incidence may also be underestimated because cases in longitudinal surveillance offered treatment.

MBE-ERG first meeting summary: Review of recent death estimates

- **IHME: used modeling approach based on vital registration and verbal autopsy data**
  - difficulty in following the description of methods put forth in the paper.
  - ratio of adult to child malaria deaths is not consistent with clinical experience or in other studies and calls into question the validity of the results.
  - higher number of deaths among African adults is likely driven by use of VA data, which may overestimate adult deaths due to over diagnosis of malaria.

- **WHO: uses malaria estimated case count and CFR of 0.3% outside Africa and Risk map and age-specific mortality rates according to transmission level and urban or rural – adjusted for ITN use.**
  - other data may be available to refine the fixed CFR applied to adjusted case reports for countries outside Africa and for the mortality rate by level of transmission for countries in Africa.
  - India has embarked on a study to estimate malaria deaths using a modified WHO approach with alternate values for CFR.

MBE-ERG first meeting summary: Discussions on way forward

1. Inviting other groups producing burden estimates (MAP, IHME, Swiss Tropical) to meet as per Terms of Reference for the ERG, with specific questions to be addressed:
    a) What are the main assumptions in your model?
    b) What are your estimates most sensitive to in terms of assumptions or absence of data?
    c) What data/ information that could be collected relatively easily/ would be most useful in improving your model?
    d) How could you're your modeling methods be integrated with other modeling methods to produce (better) consistent estimates?
    e) How good is your method at measuring trends in addition to absolute numbers?
    f) How willing are you to share your basic data with other groups?

MBE-ERG first meeting summary: Discussions on way forward

2. Preparatory work by selected group members. Detailed review of a particular method focusing on strengths and weaknesses of particular models.

   - age distribution of malaria deaths

   - case fatality rates

   - converting prevalence to incidence

   and suggesting specific studies to be done and groups that would be engaged.

3. Group members would seek to outline new approaches to estimating absolute numbers and/or trends – especially methods that would involve collecting data at national or sub-national levels (liaising with national malaria control programme staff and others as necessary to assess data availability).

BRIEFING ON RTS,S/AS01 MALARIA VACCINE FOR THE SEPTEMBER 2012 MEETING OF MPAC

Date: 12 August 2012. Author: WHO Secretariat with input from JTEG Chair

Introduction

The most advanced vaccine candidate against *Plasmodium falciparum*, known as RTS,S/AS01, is currently being evaluated in a Pivotal Phase 3 trial. This vaccine is being developed by GSK in partnership with PATH Malaria Vaccine Initiative (MVI) with funds from the Gates Foundation to MVI. There are about 20 other malaria vaccine projects in clinical testing; none of the other approaches have demonstrated proof of concept of efficacy in field settings.

The randomised controlled double-blind Phase 3 efficacy trial started in May 2009 and completed enrolment in January 2011 of 15,460 children in 7 countries in sub-Saharan Africa. These countries are: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania. The children are in two age groups: 1) 5-17 months at first immunization without co-administration and 2) 6-12 weeks at first immunization (which is the target age group for this vaccine) in co-administration with routine infant vaccines. Each child is followed up for at least 30 months following the third dose of RTS,S/AS01. The three doses are given with 1 month intervals followed by an 18 month booster dose in one of the 3 trial arms. The control vaccine is rabies vaccine for 5-17 months olds and meningococcal C vaccine for 6-14 week olds. The trial is occurring in the context of LLIN use by most trial participants. The trial teams liaised with national authorities to maximise LLIN use in the trial settings.

Results available as of Oct 2011

Phase 3 results

The first of three sets of results from the Phase 3 trial were published in Oct 2011 in the *New England Journal of Medicine*. Efficacy against clinical malaria in 6000 infants/toddlers 5-17 months old during the 12 months following administration was about 55% depending on the analysis (95% CIs spanning 45 - 59%), comparable to results obtained in Phase 2 trials. Efficacy against first episode of malaria waned, being substantially higher than 55% at the start of the follow-up period post dose 3 and substantially less than 55% at the 12 month follow-up time point. Variation in efficacy against all episodes of malaria with time has not been presented.

The primary severe malaria analysis included both 5-17 month olds and 6-14 week olds. Here there was a mean follow-up of 11 months from first dose (range 0-22 months) and efficacy was 35% (95% CI 16 - 49%). In the 12 months following vaccination in the 5-17 month age category, the protective effect of the vaccine against severe malaria was estimated to be 47% (95% CI 22 to 64%). The 151 deaths were balanced between malaria vaccine and control groups.

Safety and reactogenicity: In terms of reactogenicity, there was a higher proportion of fever cases (31% vs 13%) in the 7 days after vaccination in the 5-17 months age category, among those receiving RTS,S when compared to controls; and an excess frequency of about 1 in 2000 vaccine doses for febrile seizure was observed within 7 days after RTS,S vaccination. There were also more cases of meningitis (as

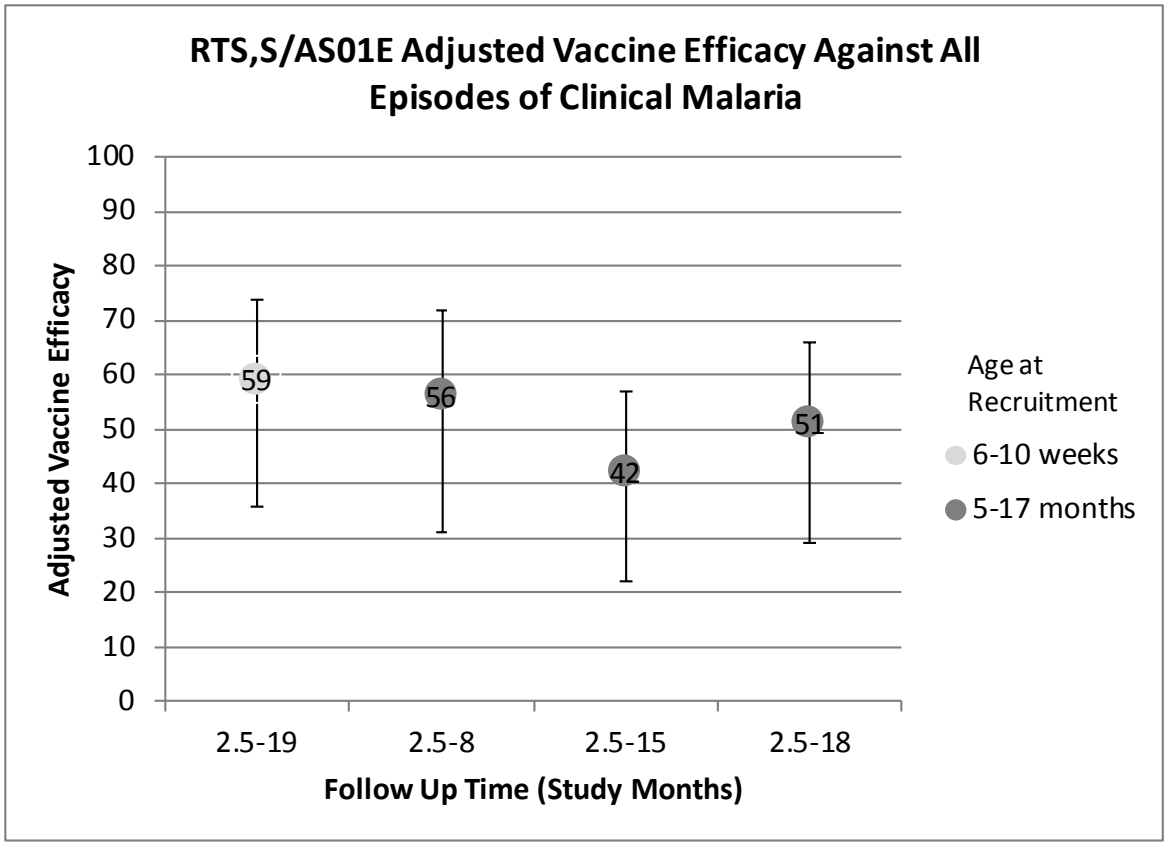
defined by the investigator without proven aetiology) in the RTS,S/AS01 group (19 cases compared to 2 cases in the controls but note 2:1 randomization). No temporal association of meningitis cases with vaccination was observed. The Independent Data Monitoring Committee reviewed these data in an unblinded manner and concluded that there was no evidence of a safety concern at this time.

Phase 2 results

The earlier Phase 2 studies were done using a different adjuvant (AS02, an oil-in-water emulsion containing immunostimulants). Later studies were done with the AS01 adjuvant (a liposomal formulation containing the same immunostimulants) which appeared to give superior IgG and cell-mediated immune responses, as well as improved efficacy in the human challenge model. AS01 is the adjuvant that is being used in the Phase 3 studies.

The longest term efficacy follow-up from Phase 2 available to date is from a RTS,S/AS02 study in Mozambique. Efficacy from this study was 26% (95%CI 12 to 37) for all episodes of clinical malaria over 43 months following administration of the third dose, in children aged 1-4 years at vaccination.

Phase 2 efficacy data against all episodes of clinical malaria for RTS,S/AS01 are summarized in figure 1 (this figure was produced by WHO secretariat). These are per protocol estimates with follow-up starting 2 weeks from the third dose. The first column relates to an exploratory efficacy analysis from a three site safety and immunogenicity study conducted in Gabon, Ghana and Tanzania. The second and third column relate to pooled results from a study conducted in Kilifi, Kenya and Korogwe, Tanzania. The fourth column relates to extended follow-up in the Kilifi site only for the same trial.



Timing of further Phase 3 results

In Q4 2012 the GSK/MVI partnership will announce safety, immunogenicity and efficacy data from infants aged 6-12 weeks at first dose in co-administration with pentavalent vaccine.

In Q4 2014 WHO expects to receive the full 30 month analyses from both age groups, including additional pre-specified analyses requested by WHO including data on all episodes of malaria broken down by time since vaccination.

Intended target population for deployment, and final presentation

GSK has stated that the initial target group for deployment is infants aged 6, 10 and 14 weeks of age in co-administration with routine DTP or pentavalent vaccines. The Phase 3 trial has been conducted with pentavalent DTwP/Hep B/Hib and OPV. Co-administration data has also been generated with measles vaccine. The final presentation will be a 2-dose vial of lyophilized RTS,S antigen clipped to a 2-dose vial of liquid AS01 requiring storage at 2-8 degrees centigrade and to be discarded if the second dose is not used during a 6 hour period after reconstitution.

Other phase III and ancillary studies

An additional phase III co-administration study is underway with pneumococcal conjugate and rotavirus vaccines, powered to evaluate non-inferiority of immunogenicity in co-administration.

A phase III lot to lot consistency and bridging study is underway in Nigeria using anti-circumsporozoite antigen IgG responses in children to bridge the pivotal Phase 3 trial vaccine material (20 L manufacturing scale) with initial commercial scale material (1600 L manufacturing scale), and to demonstrate clinical consistency of 3 different lots produced from 1600-L scale material.

A phase III study in 200 HIV infected children, aged 6 weeks to 17 months, is underway to evaluate safety and immunogenicity in this special population.

A transmission intensity ancillary study is underway to assess the prevalence of asexual *P. falciparum* infection in communities related to each Phase 3 efficacy trial site in various age groups, together with serological exposure studies.

Timing for Policy recommendations

A Joint Technical Expert Group (JTEG) on Malaria Vaccines was first convened in June 2009 by the WHO Global Malaria Programme (GMP) and WHO Department of Immunization, Vaccines & Biologicals (IVB) (www.who.int/vaccine_research/jteg/en/index.html). JTEG determined that there should be sufficient data available to make a draft policy recommendation regarding RTS,S/AS01 in 2015 for subsequent consideration by the policy advisory committees in IVB (SAGE) and GMP (MPAC). The WHO policy recommendation will take into consideration safety and efficacy results from the current Phase 3 efficacy trial after 30-month follow-up of children receiving the malaria vaccine together with routine infant vaccines, as well as site-specific data on efficacy (where there is adequate power), 18 month booster dose efficacy and severe malaria efficacy. Not all sites will be powered for site-specific efficacy, although the highest transmission sites will be well powered for such an analysis.

Reviewing the Oct 2011 results, JTEG has confirmed the previously stated timings of a potential policy recommendation in 2015 depending on the results available to WHO in 2014. JTEG highlighted the essential need for follow-up data beyond 12 months. Given the apparent waning of efficacy reported during the trial, JTEG also highlighted the need for a further exploration of the duration of vaccine protection in the full trial results to be received by WHO in 2014.

Hepatitis B efficacy

The immunogen in the RTS,S/AS01 vaccine is a fusion protein between a malaria antigen and Hepatitis B surface antigen. RTS,S/AS01 may also be submitted for licensure as a Hepatitis B vaccine and it is already clear that RTS,S/AS01 would provide at least equivalent protection against Hepatitis B compared to available Hepatitis B vaccines.

How much longer term follow-up data will be available, and what phase 4 studies are planned?

Five-years of follow-up data has been requested by WHO from at least 3 of the 11 Phase 3 trial sites, with data collection planned for serious adverse events and clinical malaria only during the 30 month extension. The 3 sites were requested to be in different transmission intensity strata. In addition, the GSK/MVI partnership is currently planning to provide post-registration Phase 4 data on safety and effectiveness from both age groups. The Phase 4 safety studies are planned to occur in Senegal, Burkina

Faso, Ghana, Kenya and Tanzania with about 40,000 individuals receiving RTS,S/AS01. The design of the Phase IV studies has been reviewed by JTEG, the WHO Global Advisory Committee on Vaccine Safety and the European Medicines Agency. WHO requested that adequate baseline data is collected on potential adverse events prior to Phase 4 administration of RTS,S/AS01, that Phase 4 studies are planned in close liaison with national authorities, and that studies are conducted in demographic surveillance system sites.

What is the regulatory pathway?

The European Medicines Agency (EMA), under a process known as article 58, will perform a scientific evaluation of this vaccine and issue what is called "a European scientific opinion". The submission timings are currently unknown. This would not result in a European license or registration, but provides a scientific opinion which African regulators may use to help their own regulatory processes. It will be African national regulatory authorities which will consider licensing the vaccine in their jurisdictions. Article 58 is a specific legal basis in the European pharmaceutical legislation, allowing the EMA to perform an evaluation of medicinal products, using the same processes as those used for marketing/registration of European Union (EU) medicinal products, but for medicines to be used outside the EU and intended to prevent or treat diseases of major public health significance in those countries. This evaluation is performed with WHO input and with involvement of the relevant national regulatory authorities as observers.

What has WHO communicated to date about the potential role of RTS,S/AS01 in the context of existing WHO recommended malaria control measures?

There is a detailed WHO "Questions & Answers on Malaria Vaccines" document available here:

http://who.int/entity/vaccine_research/diseases/malaria/WHO_malaria_vaccine_q_and_a_July_2012.pdf

WHO has stated on its website the following: "Contingent on the completion of the on-going phase 3 trial and submission of data supportive of use, WHO will review the evidence for policy recommendation in 2015. The recommendations on RTS,S/AS01 will consider its potential as an addition in some settings to existing preventive measures, such as long-lasting insecticidal nets and indoor residual spraying. The priority need for high quality artemisinin-combination treatments should continue regardless of availability and use of RTS,S vaccine. Based on currently available data the vaccine will be considered as an addition to, not a replacement for, existing preventive and treatment measures."

Depending on the results in Q4 2012, WHO may engage in further communications activities to provide WHO's perspective on the possibility of RTS,S availability in 2015 and later. This would include the implications of an efficacy at around the 50% level including the imperative to continue with preventive, diagnostic and treatment measures, and the fact that vaccinated children cannot be considered to be fully protected from malaria.

For the last 2 years, WHO has been giving presentations at multiple fora including sub-regional malaria programme and EPI meetings in AFRO to present these concepts, and to communicate the potential 2015 policy timings.

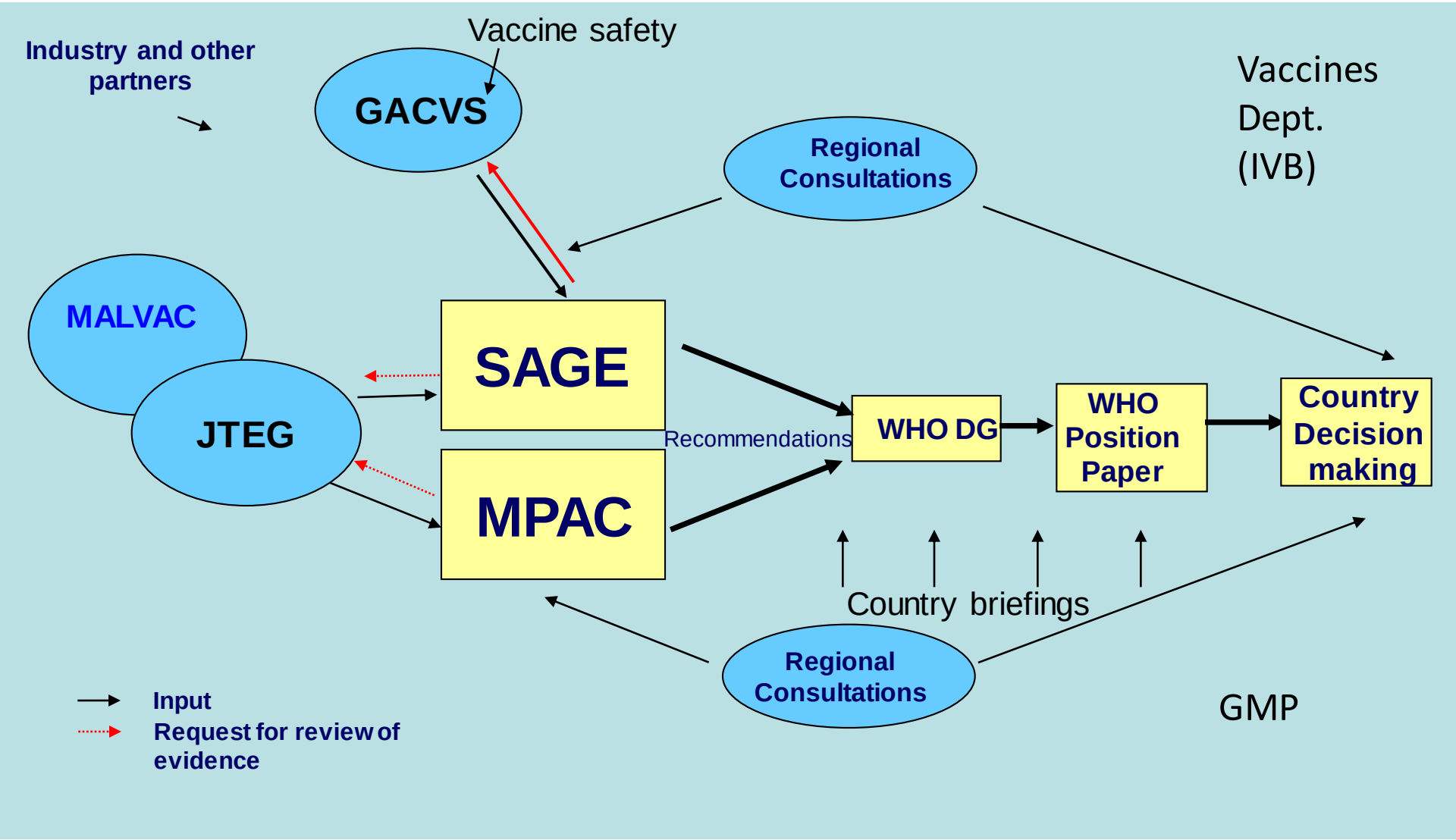
Status of Malaria Vaccines: Update from JTEG Chair and Secretariat

Peter Smith, Chair JTEG

Vasee Moorthy, WHO Secretariat

MPAC
11 Sep 2012

Pathways for WHO Recommendations on Malaria Vaccine Use



www.who.int/vaccine_research/jteg/en/index.html

Process for WHO policy recommendation

- MPAC will have key role for decision on addition to range of malaria prevention measures, on relation to other malaria control measures, and range of transmission settings for recommendation
- SAGE will have key role for decision on addition to routine EPI programmes, for schedule, and ensuring satisfactory co-administration data
- Joint MPAC/SAGE session is agreed at time of possible policy recommendation 1st April 2015

Global Malaria Vaccine Portfolio

Phase 3: One project RTS,S/AS01

Phase 2 field: Three ongoing Pf projects. GMZ2, MSP3, ME-TRAP

Phase 1: One Pv,
One Pf TBV,
20 Pf PEV & Pf BSV

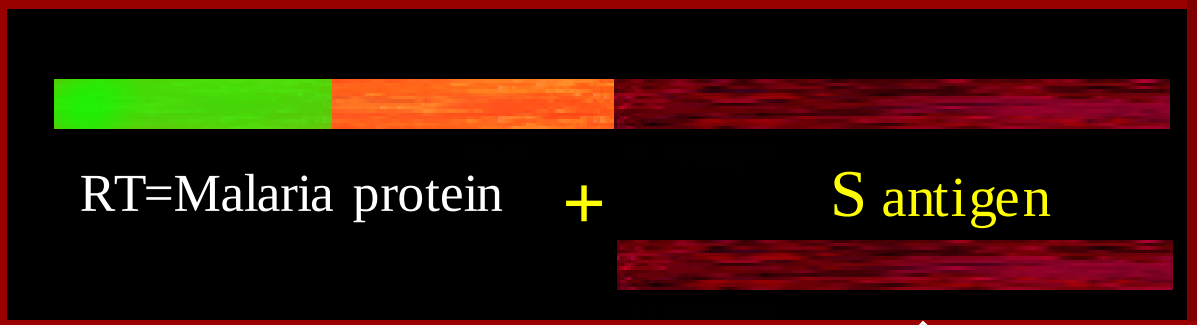
World Health Organization

Introduction to RTS,S

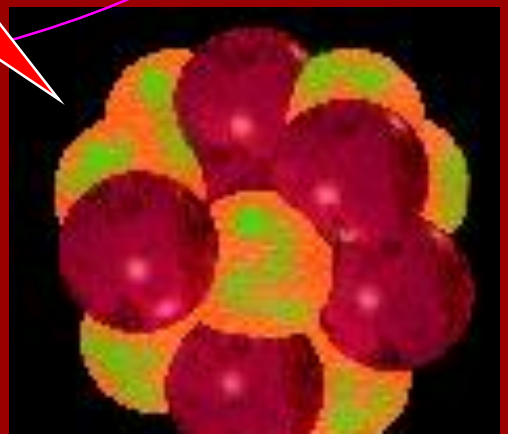
- Development partnership is GSK with PATH Malaria Vaccine Initiative (MVI) with funds from Gates Foundation to MVI
- $200 million funds so far from BMGF and over $200 million from GSK over last 20 years

RTS,S / AS01 Malaria Vaccine

GSK Biologicals/PATH MVI/BMGF



RTS & S co-expressed in *Saccharomyces cerevisiae* – RTS,S VLP



Malaria-Hep BsAg fusion VLP
Lyophilised
Point-of-use reconstitution with AS01 adjuvant: liposomes, MPL, QS21

GMP/ Vaccines Dept.
Joint Technical Expert Group (JTEG) on Malaria Vaccines

Terms of Reference: “Provide recommendations to the secretariat of GMP and IVR on:

1) clinical trial data necessary and desirable for evaluation of public health impact of a malaria vaccine in malaria endemic countries, and

2) the design, conduct, analyses and interpretation of Phase 2, Phase 3 and Phase 4 trials of malaria vaccines.”

World Health Organization

JTEG members

- Chair, Peter Smith
- **Fred Binka (MPAC member)**
- **Kamini Mendis (MPAC member)**
- Malcolm Molyneux
- Paul Milligan
- Kalifa Bojang
- Mahamadou Thera
- Blaise Genton
- Janet Wittes
- Robert Johnson
- Zulfiqar Bhutta (SAGE member)
- Claire-Anne Siegrist (SAGE member)

Observers from NRAs of Kenya, Tanzania, Ghana, Malawi
European Medicines Agency Observer attends

Three Previous JTEG meetings

Meeting 1 Jun 2009: Indicative policy recommendation and PQ timings (2015)

Meeting 2 Nov 2010: Feedback on regulatory submission plans and Phase 4 study design

Meeting 3 23-24 Feb 2012: Review of Phase 3 data to date, planning for first data on target population to be received Q4 2012

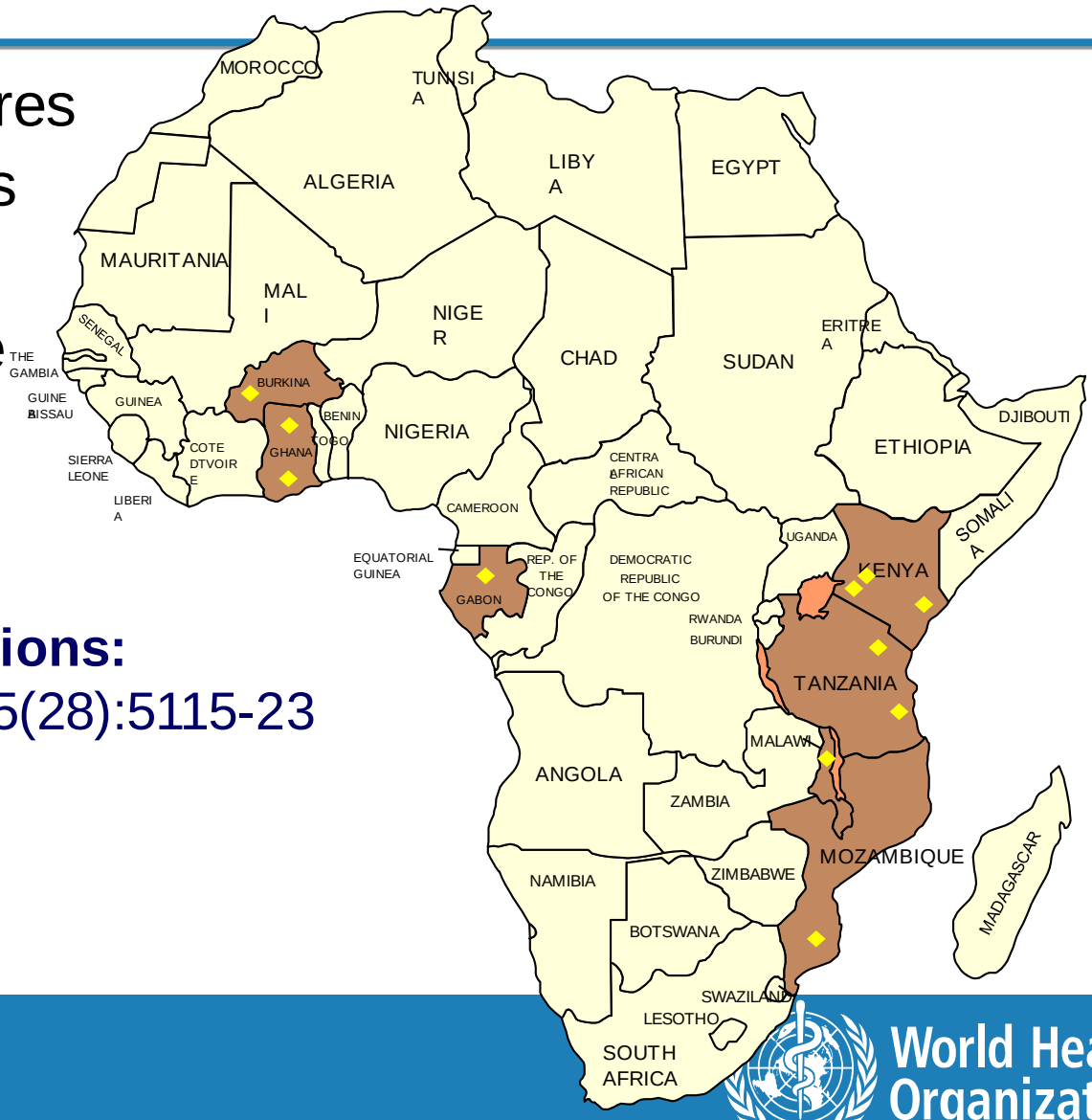
Fourth JTEG

- During Q4 2012
- In confidence meeting, for JTEG to review second set of results

Phase 3 multi-centre efficacy trial

11 participating centres in 7 African countries

Also Nigeria, 2nd site in Malawi



WHO Recommendations:
Vaccine. 2007 Jul 9;25(28):5115-23

World Health Organization

Phase 3 Trial Study design

- Designed to provide both data for filing and to support assessment of public health impact for possible implementation
- 15,460 children in 2 age categories:
  - 6 to 12 weeks in co-administration with infant vaccines
  - 5 to 17 months
  - 0,1, 2 month schedule
- 1:1:1 randomisation to include an arm with booster immunization at 20 months
- Total trial duration per child 32 months

Hum Vaccin. 2010 Jan;6(1):90-6

ESTABLISHED IN 1812 NOVEMBER 17, 2011 VOL. 365 NO. 20

First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership*

Efficacy

First of 3 sets of results from Phase 3 trial published:

12 month follow-up in first 6000 5-17 month olds

CLINICAL MALARIA (per protocol analyses)

First or only episode

VE = 55.8% (97.5% CI 50.6 to 60.4)

All episodes of malaria

VE = 55.1% (95% CI 50.5 to 59.3)

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First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership*

Efficacy

SEVERE MALARIA (per protocol analysis)

Case-driven analysis – both age groups (12961 children) (263 cases)

VE = 34.8% (95% CI 16.2 to 49.2)

Ave. duration of follow-up (5-17mo) 16mo (Range 0-22mo)
(6-14wks) 7mo (Range 0-15mo)

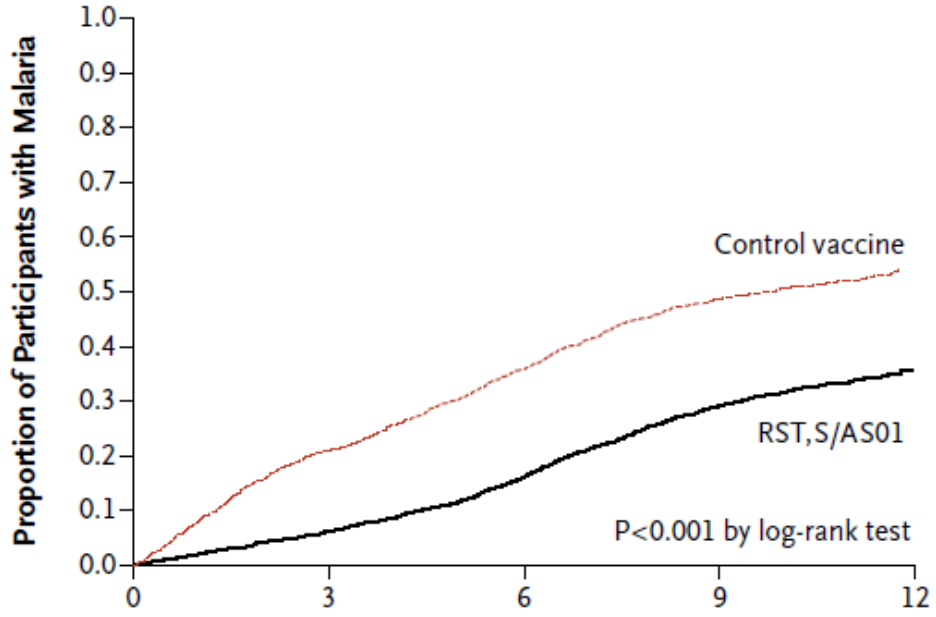
5-17mo followed for 1 year (4296 children) (113 cases)

VE = 47.3% (95% CI 22.4 to 64.2)

DEATHS

151 deaths, balanced between groups (10 deaths attributed to malaria)

A **Per-Protocol Population**



No. at Risk					
RTS,S/AS01	2830	2602	2279	1885	698
Control vaccine	1466	1137	909	712	274

Variation in efficacy with time

- Analyses performed by trial team support waning of efficacy during the first year in the 5-17 month age group for first or only episode of malaria

- In work by Paul Milligan (JTEG member) and others, under many scenarios heterogeneity of risk will tend to lead to underestimates of vaccine efficacy over time

- Efficacy against all episodes of malaria with time is more relevant to public health, but has not been presented

Efficacy with time for all episodes of malaria

Time period	Vaccine group			Control group		
	Malaria episodes	PYAR	Rate	Malaria episodes	PYAR	Rate
(0-6 months)						
(6-12 months)						
(12-18 months)						
(0-18 months)						

This additional analysis requested by JTEG will be provided with month 32 analyses in late 2014

World Health Organization

ESTABLISHED IN 1812 NOVEMBER 17, 2011 VOL. 365 NO. 20

First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership*

Safety

A reactogenic vaccine with 31% vs 13% fever cases within the 7 days after vaccination in the 5-17 month age category in those receiving RTSS compared to controls

Excess frequency of about 1 in 2000 vaccine doses for febrile seizure was observed in 7 days after vaccination

ESTABLISHED IN 1812 NOVEMBER 17, 2011 VOL. 365 NO. 20

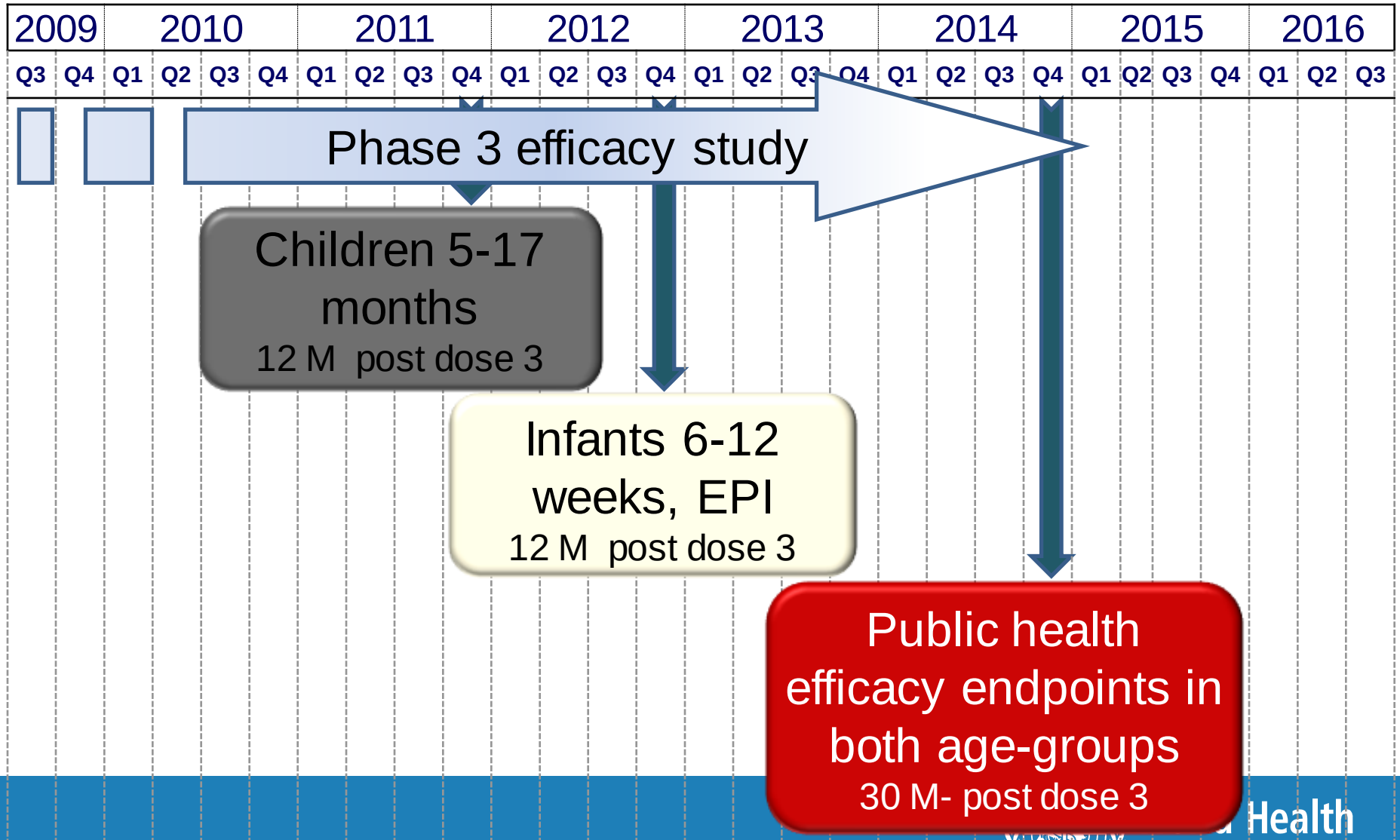
First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership*

Safety

- 19 cases of meningitis versus 2 in controls (but note 2:1 randomization)
- Investigator defined, some with no microbiological confirmation.
- No temporal association of meningitis cases with vaccination.
- IDMC assessment: no safety concern at this time

RTS,S : Availability of Further Phase 3 results



Reporting and Analysis

- GSK/MVI have provided statistical analysis plans for the 12-month analyses in the two age groups
- GSK/MVI have agreed to perform additional analyses at the request of WHO, in late 2014 at the time of the 32 month analyses
- JTEG will provide guidance to WHO on the nature of these additional analyses including all episodes of malaria broken down by time period, by site and seasonality

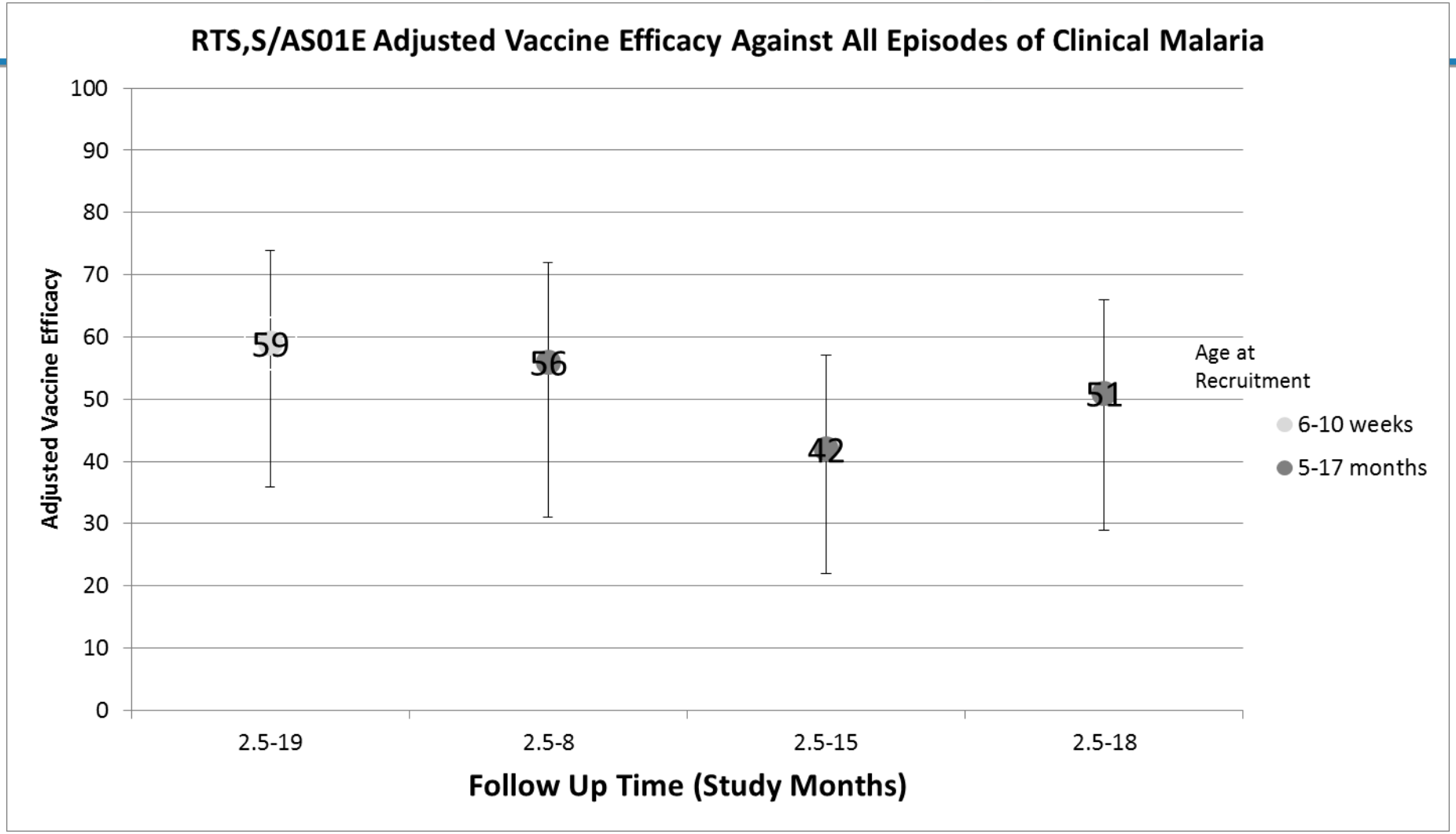
Reporting and Analysis

- The details of GSK/MVI's plans for the analyses at month 32 have not yet been presented to WHO
- An additional set of analyses at month 20 (18 months post dose 3) in both age groups will occur if a protocol amendment passes all ethics committees. Application in process.

Phase 2 results

- Earlier studies done with different adjuvant, AS02.
- Phase 3 studies with RTS,S/AS01 giving superior efficacy in human challenge model, and higher antibody and cell-mediated immune responses
- Longest term efficacy follow-up from Phase 2 studies is from Mozambique with RTS,S/AS02
- Efficacy from this study was 26% (95%CI 12 to 37) for all episodes of malaria over 43 months following 3 doses in children aged 1-4 years at vaccination

Phase 2 Efficacy



Intended target population

- GSK have stated that the initial target group is infants aged 6,10,14 weeks
- The Phase 3 trial conducted in this age group in co-administration with DTwP/HepB/Hib and OPV
- Measles and yellow fever co-administration data has also been generated

GSK/MVI Responses to Requests

- GSK/MVI have responded to multiple areas of guidance from WHO
  - Phase 4 design: include DSS sites, liaison with national authorities, and baseline data
  - Information-sharing: JTEG meeting held in-confidence prior to public release of infant data. Phase 3 Trial Protocol and Study Report shared with WHO.
  - Published methods papers at WHO's request

Messages from WHO

- Detailed Q&A available on website
- Key message: the WHO policy decision in 2015 will reflect data available up to 2014
- Key message: RTS,S will be considered as an addition to, not a replacement for, existing preventive and treatment measures
- WHO presentations at AFRO subregional and national meetings for last 2 years on these issues

Further communications

- Plans to increase intensity of communications work depending on Q4 2012 data to include the following
- Meaning of 50% efficacy in this context: many vaccinated children would still experience clinical malaria, must use other preventive measures, consider malaria diagnosis when febrile and seek treatment
- Communities will need to understand meaning of 50% efficacy

Timing for policy recommendations

- JTEG advised that 32 month analyses are required prior to possible policy recommendation
- Following review of these analyses in late 2014, JTEG will draft candidate policy recommendation for review by MPAC and SAGE in early 2015
- Given apparent waning of efficacy for first or only episode of malaria JTEG has highlighted the need for further analyses to explore duration of protection in the full trial results to be received in 2014.

Discussion, Questions and Comments

WHO Evidence Review Group: Intermittent Preventive Treatment of malaria in pregnancy (IPTp) with Sulfadoxine-Pyrimethamine (SP)

WHO Headquarters, Geneva, 9-11 July 2012

Meeting Report

Background

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the neonate. The World Health Organization (WHO) currently recommends a package of interventions for controlling malaria during pregnancy in areas with stable transmission of *Plasmodium falciparum*, which includes the use of insecticide treated nets (ITNs), the administration during pregnancy of at least 2 doses of intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) after quickening and effective case management of malaria[1].

Preliminary data from recent observational studies have suggested reduced effectiveness of SP for IPTp in Malawi, the first country where IPTp-SP was implemented in 1993[2]. In addition, there is growing concern over the decreasing effectiveness of the 2-dose regimen of SP for IPTp in other countries with a high level of resistance to SP, especially in Eastern and Southern Africa, regions that also carry the highest incidence of HIV in the world[3]. Even in the absence of resistance to SP, HIV positive women require more doses of SP to achieve effective protection against malaria in pregnancy than women who are HIV negative[4].

In order to review the WHO policy on IPTp with SP, the Global Malaria Programme (GMP), as part of its new policy making process, convened an Evidence Review Group (ERG) to review evidence from published literature and unpublished studies on the current efficacy and effectiveness of IPTp with SP[5]. The aim of the ERG was to formulate recommendations to the Malaria Policy Advisory Committee (MPAC) for an interim policy statement on IPTp with SP for dissemination to national health authorities of malaria endemic countries where IPTp is implemented.

Objectives

The specific objectives of the meeting of the Evidence Review Group were to:

- Review new evidence emerging from published literature (since the last WHO recommendations on IPTp with SP were made in 2007[6]) as well as unpublished studies completed more recently.
- Develop draft responses to key questions identified by the WHO secretariat and the MPAC on IPTp with SP.
- Formulate recommendations for an interim policy statement on IPTp with SP for dissemination to Ministries of Health (MoH) of countries where IPTp is implemented.

- Identify the critical gaps in knowledge and priority research agenda that need to be addressed in relation to IPTp with SP.

Evidence reviewed

A series of published articles[2,7-13] describing studies which had evaluated the efficacy and effectiveness of IPTp with SP and patterns of SP drug resistance in Malawi, Mozambique and Tanzania were provided as meeting pre-reads. A recent overview paper on the coverage of IPTp and ITNs among pregnant women in 47 African countries was also included [13].

An additional background paper for the ERG meeting reviewed studies published since 2007 on IPTp-SP efficacy and effectiveness in relation to the current WHO recommendations on IPTp with SP (González *et al,* unpublished[*]).

Two unpublished studies were considered, one of which the ERG reviewed in detail. This was a meta-analysis of 7 trials which had compared 3 or more doses of IPTp-SP with the standard 2-dose regimen in preventing low birth weight (LBW) (Kayentao *et al*, unpublished[†]).

In addition, preliminary results of ongoing IPTp-SP effectiveness monitoring studies conducted in HIV negative pregnant women from Burkina Faso, Kenya, Malawi, Mali, Uganda and Zambia were presented and reviewed by the ERG.

The list of pre-reads for the meeting and of the principal studies reviewed is shown in Annex 1.

[*] *González et al. Review on IPTp-SP efficacy, effectiveness and its effects on maternal and infant's health. Unpublished.*

[†] *Kayentao et al. Effect on low birth weight of monthly dosing versus the standard two- dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished*

Draft Interim Policy Statement on IPTp with SP
(for dissemination to MoH of countries where IPTp is implemented)

The ERG proposed the following Interim Policy Statement on intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) for consideration by the Malaria Policy Advisory Committee (MPAC):

- IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry quintuple mutations associated with *in vivo* therapeutic failure to SP [‡]; therefore, IPTp with SP should still be administered to women in such areas.

- In areas of stable (moderate-to-high) malaria transmission, IPTp with SP is recommended for all pregnant women **at each scheduled antenatal care visit**. In particular:
  - The first IPTp-SP dose should be administered as early as possible during the 2nd trimester[§] of gestation
  - Each SP dose should be given at least 1 month apart from the other and up to the time of delivery
  - The last dose of IPTp with SP can be administered late (after 36 weeks) in the 3rd trimester of gestation without safety concerns
  - IPTp should be administered as directly observed therapy (DOT)
  - SP can be given on an empty stomach
  - Folic acid at a daily dose equal or above 5 mg should not be given concomitantly with SP as this counteracts its efficacy as an antimalarial
  - SP is contraindicated in women receiving cotrimoxazole prophylaxis

- Currently, there is no established threshold level of malaria transmission below which IPTp-SP is no longer cost-effective and should therefore be suspended[**].

- There is insufficient evidence to support a general recommendation for the use of IPTp-SP outside Africa.

- Monitoring of IPTp-SP effectiveness is essential and should continue. Research is ongoing to define the best methodology, and this will be shared when available.

[‡] *The findings of an observational study in Tanzanian women in an area where the parasite dhps resistance mutation of codon 581 was present showed increased placental parasite density and inflammatory changes in women reporting IPTp with SP use. This needs further investigation although it is important to note that this specific dhps resistance mutation is not common.*

[§] *IPTp administration should be avoided during the 1st trimester of gestation but should start as soon as possible in the 2nd trimester. The fact a woman has entered the second trimester can be determined by the onset of quickening or by measurement of fundal height by ANC health personnel.*

[**] *Cost-effectiveness modelling studies are ongoing to address this question. Risk-benefit of SP administration needs also to be taken into account when considering recommendations on IPTp implementation.*

Summary of the discussions and main findings

The review of recent evidence suggests that in sub-Saharan Africa, in spite of the increased prevalence in *Plasmodium falciparum* of molecular markers associated with resistance to SP (based on quintuple mutant *dhps*/*dhfr* haplotypes prevalence), IPTp-SP remains effective at preventing peripheral parasitemia, maternal anemia, and clinical malaria during pregnancy and is associated with reduced neonatal mortality[14-18].

An ongoing series of facility-based observational studies evaluating IPTp effectiveness in areas with high prevalence of molecular markers of SP resistance (quintuple mutations) in Kenya, Malawi and Zambia also indicate that IPTp remains safe, and is not associated with worse pregnancy outcomes. The data also suggest a generally beneficial dose dependent effect of SP on maternal and neonatal outcomes when administered on 1, 2 or 3 occasions. The limitations of these facility-based observational studies were acknowledged as women who receive fewer IPTp doses may also receive less antenatal care.

Overall, most studies suggested that IPTp with SP remains effective, or at least it is not associated with any harm, in areas with high prevalence of quintuple mutant *P. falciparum* parasites. The significance of the additional mutation at codon 581, which was particularly prevalent in the Tanzanian study, needs further investigation. This retrospective cross sectional study conducted among 104 women at delivery in an area of Tanzania where the fraction of parasites carrying the resistance allele at *dhps* codon 581 is relatively high (36%) found an increased placental parasite density and inflammatory changes in women who reported taking IPTp with SP[8]. However, these findings have not been confirmed in a larger study conducted in Malawi[12] or in a randomized controlled trial (RCT) comparing IPTp-SP with placebo in Mozambique, where the protective efficacy of IPTp-SP was shown and no association was found between infections with parasites carrying quintuple resistance markers and increased parasite density or malaria-related morbidity in mothers and children[10]. However, the mutation at codon 581 was only detected in low frequencies in samples from these two studies and, furthermore, it cannot be assumed that all parasites carrying the 581 mutation have the same genetic background and biological characteristics.

The number of IPTp doses that need to be administered during pregnancy to achieve the maximal beneficial effects of IPTp was examined in the unpublished meta-analysis by Kayentao *et al*. The meta-analysis, which included 7 controlled trials conducted in 5 sub-Saharan countries from 1994 to 2008, showed that 3 or more doses (median of 4 doses) of IPTp with SP was superior to the standard 2 dose regimen in preventing LBW rates (relative risk reduction of 21% [95% CI 8-32]) both in HIV infected and uninfected pregnant women and in all gravidity groups. Furthermore, women who received a median of 4 doses of IPTp-SP compared to those on the 2-dose regimen also had a lower risk of moderate-severe maternal anemia, maternal malaria at delivery, and placental malaria. The meta-analysis, which included two trials in areas of Burkina Faso and Mali where the efficacy of SP remains high, showed that even in areas of high SP efficacy, 3 doses of SP were more effective than 2 doses. Ongoing observational studies monitoring IPTp effectiveness in Burkina Faso and Mali also show that even in areas with low levels of SP resistance, there is a dose-dependent association with beneficial maternal and fetal outcomes.

The programmatic challenges of implementation of IPTp and achieving high coverage were also raised and discussed briefly. It is estimated that in 2007, 25% of pregnant women received at least 1 dose of IPTp[13]. The importance of providing IPTp under direct observation, as directly observed treatment, was stressed.

It was also suggested that WHO recommendations should state that all possible efforts should be made to avoid SP use as monotherapy for malaria treatment in order to protect its efficacy for IPTp.

The lack of studies on the cost-effectiveness of IPTp-SP in areas with low transmission was noted; cost-effectiveness analysis should be considered to guide health policies for such areas. IPTp-SP has recently been shown to be highly cost-effective for both prevention of maternal malaria and reduction of neonatal mortality in areas with moderate or high malaria transmission[19]. Studies on the cost-effectiveness analysis of 2 dose of IPTp-SP *versus* 3 or more doses are ongoing. The results of modeling cost-effectiveness and risk-benefit analysis could also inform decisions for consideration of suspension of IPTp-SP in areas where the malaria transmission intensity has been reduced to low levels over a sustained period of time.

Recommendations

The ERG addressed the following key questions and made the recommendations below.

1. **What are the key determinants and potential confounders of reduced effectiveness of IPTp with SP emerging from the recent trials?**

   The ERG identified the following key determinants and potential confounders of IPTp-SP effectiveness:

   - Maternal:
     i. Compliance with antenatal care (including number of ANC visits attended)
     ii. HIV infection
     iii. Age
     iv. Gravidity
   - Health system
     i. Quality of/access to care
     ii. Directly observed therapy (DOT)
     iii. SP quality
     iv. High concomitant dose of folic acid (≥ 5 mg/day)
   - Other
     i. Malaria transmission intensity (high transmission is expected to be associated with a higher effectiveness of IPTp)
     ii. Number and timing of SP doses in relation to gestational age
     iii. SP resistance
     iv. ITN use
     v. Pharmacokinetic changes in pregnancy

2. **Which levels of transmission intensity and SP resistance (monitored using molecular markers) are associated with loss of effectiveness of IPTp with SP?**

   Currently there is insufficient evidence on the level of malaria transmission below which IPTp with SP would no longer be cost-effective and could be suspended.

   There is also not enough evidence yet to establish a threshold prevalence of quintuple mutant *dhfr*, *dfps* haplotypes, nor *dhps* 581, *dhps* 540, nor *dhfr* 164 point mutations above which there is a clear loss of IPTp-SP cost-effectiveness.

3. **Is there evidence of harm with the implementation of IPTp with SP in areas with high level of resistance to SP?**

   There is currently no consistent evidence of harm associated with administration of IPTp-SP in areas with high levels of resistance to SP. There is good evidence supporting the benefits of IPTp-SP even in areas with a high prevalence of quintuple mutations, which are associated with high levels of therapeutic failures to SP *in vivo* [12,17]. The findings of retrospective observational studies[7,8] in Tanzanian women in an area with a high prevalence of parasites carrying the *dhps* resistant mutation at codon 581 which suggested increased placental parasitemia among those reporting use of SP for IPTp needs further investigation. Of note, this same study[7] found a

generally protective effect against other maternal and infant outcomes among those who reported use of SP, but the findings did not reach statistical significance. A subsequent serial cross sectional analysis in Malawi[12] where the *dhps* 581 mutation was detected in one isolate, indicated that women who received 2 dose IPTp-SP had lower peripheral and placental parasite densities compared to women who received < 2 doses IPTp.

4. **Should 3-doses or monthly doses of SP for IPTp be recommended in all countries with stable malaria transmission, replacing the current practice of 2-dose SP regimen?**

   Results of an unpublished meta-analysis[††] that compared 3 or more doses of IPTp-SP (median of 4 doses) with the standard 2 dose-regimen in 7 randomized trials demonstrated the benefit of more doses.

   In addition, preliminary results of ongoing monitoring studies of IPTp-SP effectiveness suggest that IPTp-SP effectiveness could be improved with the administration of a 3 dose regimen.

   Thus, in areas of stable (moderate-to- high) malaria transmission, IPTp with SP is recommended for all pregnant women at each scheduled ANC visit. IPTp-SP should be given as early as possible during the second trimester of gestation, with each dose at least 1 month apart from any other and continuing up to the time of delivery.

5. **Should the policy of IPTp with SP be limited to Africa only or should it be extended to all areas with stable transmission (also outside Africa)?**

   There is currently insufficient evidence to support a general recommendation for the use of IPTp-SP outside Africa. Issues requiring additional evidence include: the effectiveness of IPTp-SP in preventing the adverse consequences of *P. vivax* infection during pregnancy; the burden of malaria during pregnancy in different transmission settings; and current data regarding *P. falciparum* resistance to SP outside Africa.

   Policy decisions could be based on modelling studies including cost-effectiveness at different levels of transmission.

6. **What are the core elements and methods of a simplified protocol to monitor the effectiveness of SP for IPTp?**

   Potential core elements of monitoring studies include:
   - Review of ANC (number and timing of IPTp-SP doses) and birth weight data through routine health system records

[††] *Kayentao et al. Effect on low birth weight of monthly dosing versus the standard two- dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished.*

- Use of data on trends of birth weight and neonatal mortality and their association with IPTp-SP coverage (adjusting for other potential confounders routinely collected during ANC visits)
- Specific studies to evaluate IPTp-SP effectiveness controlling for multiple factors (age, gravidity, HIV status, ANC visits, number of SP doses received, etc) such as:
    i. Cross-sectional studies at delivery units
    ii. Case-control studies of women delivering LBW babies or with maternal anemia
- Monitoring of prevalence of SP molecular resistance markers, preferably at first ANC (pre-SP administration) although the association of resistance markers with SP effectiveness requires further investigation
- Collection of dried blood spots for analysis of molecular markers of SP resistance
- Assessment of *in vitro* SP efficacy
- Assessment of 42 day *in vivo* SP efficacy in asymptomatic parasitaemic pregnant women

The methods to monitor the effectiveness of IPTp-SP are under study and, based on these findings, will need to be improved and enhanced. Therefore, the ERG suggested establishing a working group to specifically address this question and to develop a simplified protocol template to monitor IPTp-SP effectiveness.

7. What are the minimum requirements (technical expertise, personnel, laboratory equipment etc) to monitor the effectiveness of SP for IPTp?

Research is ongoing to define the best methodology of monitoring the effectiveness of IPTp and the minimum requirements to monitor effectiveness of IPTp with SP will be specified once the template monitoring protocol has been developed.

8. What data need to be available for review in order to consider a policy of IPTp with an alternative antimalarial medicine (other than SP)?

To consider an alternative antimalarial drug for IPTp, data from carefully designed superiority RCTs including efficacy, safety, acceptability/tolerability, feasibility and cost-effectiveness are needed.

In addition, baseline data on *P. falciparum* resistance to the alternative drug, together with information on how commonly this drug is used for other indications (e.g. as first line therapy) are needed to inform where this alternative could be implemented as IPTp policy.

9. What data are needed to decide if an IPTp policy should be stopped when transmission has been reduced to a certain level?

Results from modeling studies of cost-effectiveness analyses (including costs, benefits, side effects of SP in the model) together with data from IPTp trials from different levels of malaria endemicity when available, will be needed to determine the level of malaria transmission below which IPTp with SP is no longer cost effective. In areas where transmission has recently been substantially reduced, the likelihood that this low transmission will be sustained should also be considered.

10. Based on the review of the evidence available should the current WHO policy recommendations on IPTp be updated?

The ERG advises that an update to the WHO policy on IPTp is needed and recommends that all pregnant women in areas of stable (high or moderate) malaria transmission should receive SP at each scheduled ANC visit. IPTp-SP doses should be administered as early as possible during the 2nd trimester[‡‡] of gestation, with each dose given at least 1 month apart from any other and continuing up to the time of delivery.

Please refer to Annex 2 for a detailed description of the suggested changes in the WHO recommendations.

11. What core messages should be addressed by a WHO interim position statement on IPTp with SP to the MoH of malaria endemic countries?

- IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry a quintuple mutation associated with *in vivo* therapeutic failure to SP [§§]; therefore, IPTp with SP should still be administered to women in such areas.
- In areas of stable (moderate-to-high) malaria transmission, IPTp with SP is recommended for all pregnant women **<u>at each scheduled antenatal care visit</u>**. In addition:
    i. The first IPTp-SP dose should be administered as early as possible during the 2nd trimester[***] of gestation
    ii. Each SP dose should be given at least 1 month apart from the other and up to the time of delivery
    iii. The last dose of IPTp with SP can be administered late (after 36 weeks) in the 3rd trimester of gestation without safety concerns
    iv. IPTp should be administered as directly observed therapy (DOT)
    v. SP can be given on an empty stomach
    vi. Folic acid at a daily dose equal or above 5 mg should not be given concomitantly with SP as this counteracts its efficacy as an antimalarial.
    vii. SP is contraindicated in women receiving cotrimoxazole prophylaxis
- Currently, there is no established threshold level of malaria transmission below which IPTp-SP is no longer cost-effective and should therefore be suspended[†††].

[‡‡] *IPTp administration should be avoided during the 1st trimester of gestation but should start as soon as possible in the 2nd trimester. The fact a woman has entered the second trimester can be determined by the onset of quickening or by measurement of fundal height by ANC health personnel.*

[§§] *The findings of an observational study in Tanzanian women in an area where the parasite dhps resistance mutation of codon 581 was present showed increased placental parasite density and inflammatory changes in women reporting IPTp with SP use. This needs further investigation although it is important to note that this specific dhps resistance mutation is not common.*

[***] *IPTp administration should be avoided during the 1st trimester of gestation but should start as soon as possible in the 2nd trimester. The fact a woman has entered the second trimester can be determined by the onset of quickening or by measurement of fundal height by ANC health personnel.*

[†††] *Cost-effectiveness modelling studies are ongoing to address this question. Risk-benefit of SP administration needs also to be taken into account when considering recommendations on IPTp implementation.*

- There is currently insufficient evidence to support a general recommendation for the use of IPTp-SP outside of Africa.
- Monitoring of IPTp-SP effectiveness is essential and should continue. Research is ongoing to define the best methodology, and will be shared when available.

Furthermore, the ERG suggested the following additional recommendations/messages regarding IPTp with SP:

- In order to preserve SP effectiveness for IPTp, increased efforts should be made to avoid SP use as monotherapy for malaria treatment of clinical cases of malaria.
- Preliminary results of observational studies on IPTp effectiveness also show that even in areas with low levels of SP resistance, the efficacy of IPTp-SP is greater when more than 2 doses are administered.

12. Based on the review of available evidence, including unpublished reports, which key recommendations (if any) could be proposed for a GRADE assessment?

The following recommendations were proposed for a GRADE assessment:

- Effectiveness of 2-dose IPTp-SP *versus* IPTp-SP at every scheduled ANC visit on birth weight and LBW, placental infection, clinical malaria, maternal anemia and fetal anemia
- Impact of IPTp-SP on neonatal mortality

13. What are the current knowledge gaps (scientific and operational) for effective implementation of IPTp with SP?

The following gaps in knowledge and research key areas were identified:

- The safety of IPTp-SP when given 5 times or more during pregnancy
- Interactions between antimalarials and antiretrovirals in HIV infected individuals
- The effect of sustained malaria transmission reduction on IPTp effectiveness
- Relationship between malaria transmission intensity level and IPTp-SP effectiveness (risk-benefit and cost-effectiveness analysis based on modeling data)
- Effectiveness of IPTp-SP against *P. vivax* infection in pregnancy
- The effect of the presence of the *dhps* 581 codon mutation on IPTp effectiveness
- Monitoring protocol for IPTp-SP effectiveness
- Innovative strategies to improve the delivery of IPTp-SP and malaria case management among pregnant women at the primary health center level
- Innovative community strategies that simultaneously do not detract from ANC services to increase IPTp coverage (such as community-based ANC outreach, promotion or distribution of IPTp)
- Methods for using health system information systems for routine monitoring of IPTp-SP implementation and effectiveness
- Operational interventions to improve delivery and use of ITNs to women before they conceive

References

1. WHO. A strategic framework for malaria prevention and control during pregnancy in the African region. *World Health Organization. Geneva* 2004;**AFR/MAL/04/01**.
2. Feng G, Simpson JA, Chaluluka E, Molyneux ME, Rogerson SJ. Decreasing burden of malaria in pregnancy in Malawian women and its relationship to use of intermittent preventive therapy or bed nets. *PLoS One* 2010;**5**(8)**:**e12012.
3. UNAIDS/WHO. Global report: UNAIDS report on the global AIDS Epidemic 2010. *Joint United Nations Programme on HIV/AIDS* 2010;**UNAIDS/10.11E** (JC1958E).
4. Filler SJ, Kazembe P, Thigpen M, et al. Randomized trial of 2-dose versus monthly sulfadoxine-pyrimethamine intermittent preventive treatment for malaria in HIV-positive and HIV-negative pregnant women in Malawi. *J Infect Dis* 2006;**194**(3)**:**286-93.
5. WHO. Inaugural meeting of the malaria policy advisory committee to the WHO: conclusions and recommendations. *Malar J* 2012;**11:**137.
6. WHO. Technical Expert Group meeting on intermittent preventive treatment in pregnancy (IPTp). *World Health Organization* 2008;**Geneva 11-17 July 2007**.
7. Harrington WE, Mutabingwa TK, Kabyemela E, Fried M, Duffy PE. Intermittent treatment to prevent pregnancy malaria does not confer benefit in an area of widespread drug resistance. *Clin Infect Dis* 2011;**53**(3)**:**224-30.
8. Harrington WE, Mutabingwa TK, Muehlenbachs A, et al. Competitive facilitation of drug-resistant Plasmodium falciparum malaria parasites in pregnant women who receive preventive treatment. *Proc Natl Acad Sci U S A* 2009;**106**(22)**:**9027-32.
9. Mayor A, Moro L, Aguilar R, et al. How Hidden Can Malaria Be in Pregnant Women? Diagnosis by Microscopy, Placental Histology, Polymerase Chain Reaction and Detection of Histidine-Rich Protein 2 in Plasma. *Clin Infect Dis* 2012;**54**(11)**:**1561-8.
10. Menendez C, Serra-Casas E, Scahill MD, et al. HIV and placental infection modulate the appearance of drug-resistant Plasmodium falciparum in pregnant women who receive intermittent preventive treatment. *Clin Infect Dis* 2011;**52**(1)**:**41-8.
11. Taylor SM, Antonia A, Feng G, et al. Adaptive evolution and fixation of drug-resistant Plasmodium falciparum genotypes in pregnancy-associated malaria: 9-year results from the QuEERPAM study. *Infect Genet Evol* 2012;**12**(2)**:**282-90.
12. Taylor SM, Antonia AL, Chaluluka E, et al. Antenatal Receipt of Sulfadoxine-Pyrimethamine Does Not Exacerbate Pregnancy-Associated Malaria Despite the Expansion of Drug-Resistant Plasmodium falciparum: Clinical Outcomes From the QuEERPAM Study. *Clin Infect Dis* 2012;**55**(1)**:**42-50.
13. van Eijk AM, Hill J, Alegana VA, et al. Coverage of malaria protection in pregnant women in sub-Saharan Africa: a synthesis and analysis of national survey data. *Lancet Infect Dis* 2011;**11**(3)**:**190-207.
14. Kapito-Tembo A, Meshnick SR, van Hensbroek MB, Phiri K, Fitzgerald M, Mwapasa V. Marked reduction in prevalence of malaria parasitemia and anemia in HIV-infected pregnant women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventive therapy during pregnancy in Malawi. *J Infect Dis* 2011;**203**(4)**:**464-72.
15. Wilson NO, Ceesay FK, Obed SA, et al. Intermittent preventive treatment with sulfadoxine-pyrimethamine against malaria and anemia in pregnant women. *Am J Trop Med Hyg* 2011;**85**(1)**:**12-21.
16. Mockenhaupt FP, Bedu-Addo G, Eggelte TA, et al. Rapid increase in the prevalence of sulfadoxine-pyrimethamine resistance among Plasmodium falciparum isolated from pregnant women in Ghana. *J Infect Dis* 2008;**198**(10)**:**1545-9.
17. Menendez C, Bardaji A, Sigauque B, et al. A randomized placebo-controlled trial of intermittent preventive treatment in pregnant women in the context of insecticide treated nets delivered through the antenatal clinic. *PLoS One* 2008;**3**(4)**:**e1934.
18. Menendez C, Bardaji A, Sigauque B, et al. Malaria prevention with IPTp during pregnancy reduces neonatal mortality. *PLoS One* 2010;**5**(2)**:**e9438.
19. Sicuri E, Bardaji A, Nhampossa T, et al. Cost-effectiveness of intermittent preventive treatment of malaria in pregnancy in southern Mozambique. *PLoS One* 2010;**5**(10)**:**e13407.

Annex 1
List of the pre-read meeting documentation and principal studies reviewed

Publications	Country/ies	Study description
Mayor *et al*, 2012[9]	Mozambique	Evaluation of the performance of microscopy, placental histology and HRP2-based plasma methods for the diagnosis of malaria in pregnant women and the clinical relevance of undetected infections.
Taylor *et al*, 2012[12]	Malawi	Serial cross sectional analysis of the relationship between IPTp-SP, SP resistant *P. falciparum* and pregnancy associated malaria during a period of 9 years.
Taylor *et al*, 2012[11]	Malawi	Cross-sectional molecular analysis of samples collected between 1997 and 2006 investigating changes in SP resistant *P. falciparum* among women at delivery.
Harrington *et al*, 2011[7]	Tanzania	Cross-sectional study evaluating the reported use of IPTp and its effects on maternal and fetal outcomes in an area of high SP resistance.
van Eijk *et al*, 2011[13]	47 African countries	Analysis of extracted data on malaria control strategies in pregnancy from national policies including an assessment of coverage with ITNs and IPTp.
Menéndez *et al*, 2011[10]	Mozambique	Molecular analysis of samples obtained from women at delivery during a RCT of IPTp SP vs placebo, evaluating the impact of IPTp and HIV on molecular markers of SP resistance and its clinical relevance.
Feng *et al*, 2010[2]	Malawi	Analysis of longitudinal data from women at delivery collected over 9 years investigating the changes in malaria prevalence and the association between pregnancy outcomes and use of IPTp with SP.
Harrington *et al*, 2009[8]	Tanzania	Molecular analysis of resistant parasites obtained from samples of women at delivery and its association with reported use of IPTp.
Manuscript/ presentations	**Country/ies**	**Study description**
González *et al*, unpublished[‡‡‡]	Studies from over 11 sub-Saharan countries where IPTp-SP is implemented	Comprehensive literature review of published studies evaluating IPTp-SP efficacy and effectiveness and its effects on maternal and infant's health since 2007, in relation to the current WHO recommendations on IPTp.
Kayentao *et al*, unpublished[§§§]	Kenya, Zambia, Malawi, Tanzania, Mali, Burkina Faso	Meta-analysis of 7 trials to determine whether regimens containing 3 or more doses of IPTp-SP are more effective than standard 2-dose regimens in preventing LBW.
van Eijk *et al*, unpublished[****]	47 African countries	Updated analysis of data from national household cluster-sample surveys assessing ITN and IPTp coverage in pregnancy from 2009-2011.
MiP consortium monitoring studies	Kenya, Malawi, Zambia, Uganda, Mali	Series of ongoing observational facility-based studies evaluating the relationship between SP resistance and the effectiveness of IPTp-SP.

RCT: Randomized Controlled Trial; MiP: Malaria in Pregnancy

[‡‡‡] *González et al. Review on IPTp-SP efficacy, effectiveness and its effects on maternal and infant's health. Unpublished.*

[§§§] *Kayentao et al. Effect on low birth weight of monthly dosing versus the standard two- dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished.*

[****] *van EijK et al. Prevention of malaria in pregnancy in sub-Saharan Africa: a synthesis and ecological analysis of national survey data. Unpublished.*

Annex 2

Suggested modifications of current WHO text recommendations on IPTp-SP

Current WHO recommendations related to ~~combined benefits of IPTp and ITN use~~ [1] Malaria in Pregnancy Prevention and Control

- *WHO promotes a three-pronged approach for all pregnant women living in stable malaria transmission areas.* The policy for malaria prevention and control during pregnancy in areas of stable transmission should emphasize a package of intermittent preventive treatment (IPTp) and insecticide-treated nets (ITNs) and ensure effective case management of malaria illness and anaemia.
- ITNs should be provided to pregnant women as early in pregnancy as possible. Their use should be encouraged for women throughout pregnancy and during the postpartum period.
- ITNs can be provided through the antenatal clinic or other sources in the private and public sectors.

Current WHO recommendations related to the number and timing of IPTp doses

Current scientific evidence suggests that d~~At least two IPT doses during~~ the second and third trimester IPTp is beneficial to the pregnant woman and her unborn baby.~~are required to achieve optimal benefit in most women~~ ~~One study of intermittent preventive treatment in HIV-infected pregnant women showed that monthly dosing (most women receiving 3–4 doses) was necessary to achieve optimal benefit.~~ In areas of stable transmission, give IPTp-SP, at every scheduled ANC visit, following quickening and at least one month apart. A review of 7 clinical trials conducted in Africa in areas of stable transmission and different levels of SP resistance revealed that 3 or more doses of IPTp-SP yielded better clinical outcomes for the mother and the newborn than the standard two doses of IPTp-SP in all gravidae and HIV groups††††

The World Health Organization recommends a schedule of four antenatal clinic visits, with three visits after quickening. ~~The delivery of IPT-SP at each scheduled visit after quickening will assure that a high proportion of women receive at least two doses.~~

~~*In settings with an HIV prevalence among pregnant women greater than 10%, it is more cost-effective to treat all women with a 3-dose regimen than to screen for HIV and provide the regimen only to HIV-infected women.*~~

~~*IPTp-SP doses should not be given more frequently than monthly [1].*~~

~~***Current WHO recommendations related to the timing of IPTp-SP doses [1]***~~

~~All pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening.~~

~~The World Health Organisation recommends a schedule of four antenatal clinic visits, with three visits after quickening. The delivery of IPT-SP at each scheduled visit after quickening will assure that a high proportion of women receive at least two doses.~~

†††† *Kayentao et al. Effect on low birth weight of monthly dosing versus the standard two- dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished*

Current WHO recommendations related to IPTp and SP resistance

IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry a quintuple mutation associated with in vivo therapeutic failure to SP. The effect of high level of SP resistance on IPTp effectiveness including the significance of the *dhps* 581 codon mutation should be further investigated

~~SP-IPTp is threatened by the spread of SP-resistant parasites. Although there must be a relationship between the level of parasite resistance to SP and the benefit provided by SP-IPTp, data on in vivo therapeutic efficacy of SP in young children with symptomatic malaria cannot be extrapolated to protective efficacy of IPTp in pregnant women because of differences in therapeutic efficacy between young children, and pregnant women-related immunity and possibly pharmacokinetics.~~

~~However, in vivo therapeutic efficacy[b] and protective efficacy[c] of SP (and antimalarials in general) used for IPTp need to be determined specifically in pregnant women[17,18].~~

Current WHO recommendations related to IPTp and HIV

Current scientific evidence suggests:

~~One study of intermittent preventive treatment in HIV-infected pregnant women showed that monthly dosing (most women receiving 3–4 doses) was necessary to achieve optimal benefit.~~

~~In settings with HIV prevalence among pregnant women greater than 10%, it is more cost-effective to treat all women with a 3-dose regimen than to screen for HIV and provide the regimen only to HIV-infected women.~~

~~Intermittent preventive treatment with sulphadoxine-pyrimethamine~~IPTp-SP should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.

Annex 3
List of Participants

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INTERMITTENT PREVENTIVE TREATMENT OF MALARIA

IN PREGNANCY WITH SULPHADOXINE/PYRIMETHAMINE

WHO EVIDENCE REVIEW GROUP

WHO, Geneva,

July 9th – 11th 2012

MPAC MEETING
September 11th- 13th 2012

CURRENT WHO RECOMMENDATIONS ON THE COMBINED USE OF IPTp AND ITNs IN PREGNANCY

Overall recommendation

- **The policy for malaria prevention and control during pregnancy in areas of stable transmission includes intermittent preventive treatment (IPTp) and insecticide-treated nets (ITNs) and ensure effective case management of malaria illness and anaemia.**

- **ITNs should be provided to pregnant women as early in pregnancy as possible. Their use should be encouraged for women throughout pregnancy and during the postpartum period.**

CURRENT WHO RECOMMENDATIONS RELATED TO THE NUMBER AND TIMING OF IPTP-SP DOSES

- **All pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening.**

- **WHO recommends a schedule of four antenatal clinic visits, with three visits after quickening. The delivery of IPT-SP at each scheduled visit after quickening will assure that a high proportion of women receive at least two doses.**

CURRENT WHO RECOMMENDATIONS RELATED TO IPTp AND HIV

- One study of intermittent preventive treatment in HIV-infected pregnant women showed that monthly dosing (most women receiving 3–4 doses) was necessary to achieve optimal benefit.

- In settings with HIV prevalence among pregnant women greater than 10%, it is more cost-effective to treat all women with a 3-dose regimen than to screen for HIV and provide the regimen only to HIV-infected women.

- Intermittent preventive treatment with sulphadoxine-pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.

TASK OF THE EVIDENCE REVIEW GROUP

To review the current WHO recommendations on SP IPTp and to make recommendations on any changes that are needed related to –

a. The number of treatments with SP that should be given,

b. The effectiveness of SP IPTp in areas of high SP resistance,

c. The level of transmission below which SP IPTp is no longer cost effective.

d. To identify the critical gaps in knowledge and a priority research agenda *for* IPTp with SP.

FORMAT OF THE CONSULTATION

Pre-meeting

- **Discussions between WHO secretariat and co-chairs on the scope and format of the meeting and preparation of a set of questions for review by the ERG members.**
- **Preparation of a background paper summarising the results ofSP IPTp studies published since 2007 (Raquel Gonzáles).**
- **Preparation of a manuscript on meta-analysis of 2 vs 3 or more doses of SP for IPTp (Kayentao et al.).**

FORMAT OF THE CONSULTATION

Meeting

July 9th – 11th 2012

- **Presentation at the meeting by members of the MIP consortium on programmatic evaluation of 2 vs 3 or more doses of SP IPTp in high SP resistance areas.**
- **Wide ranging discussions by two working groups on a common set of issues/questions related to SP IPTp.**
- **Formulation of new policy recommendations by ERG members for consideration by MPAC.**

PARTICIPANTS TO THE IPTp-SP ERG MEETING

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Jenny Hill
Jayne Webster

* Co-chairs ** Rapporteur *** Unable to attend

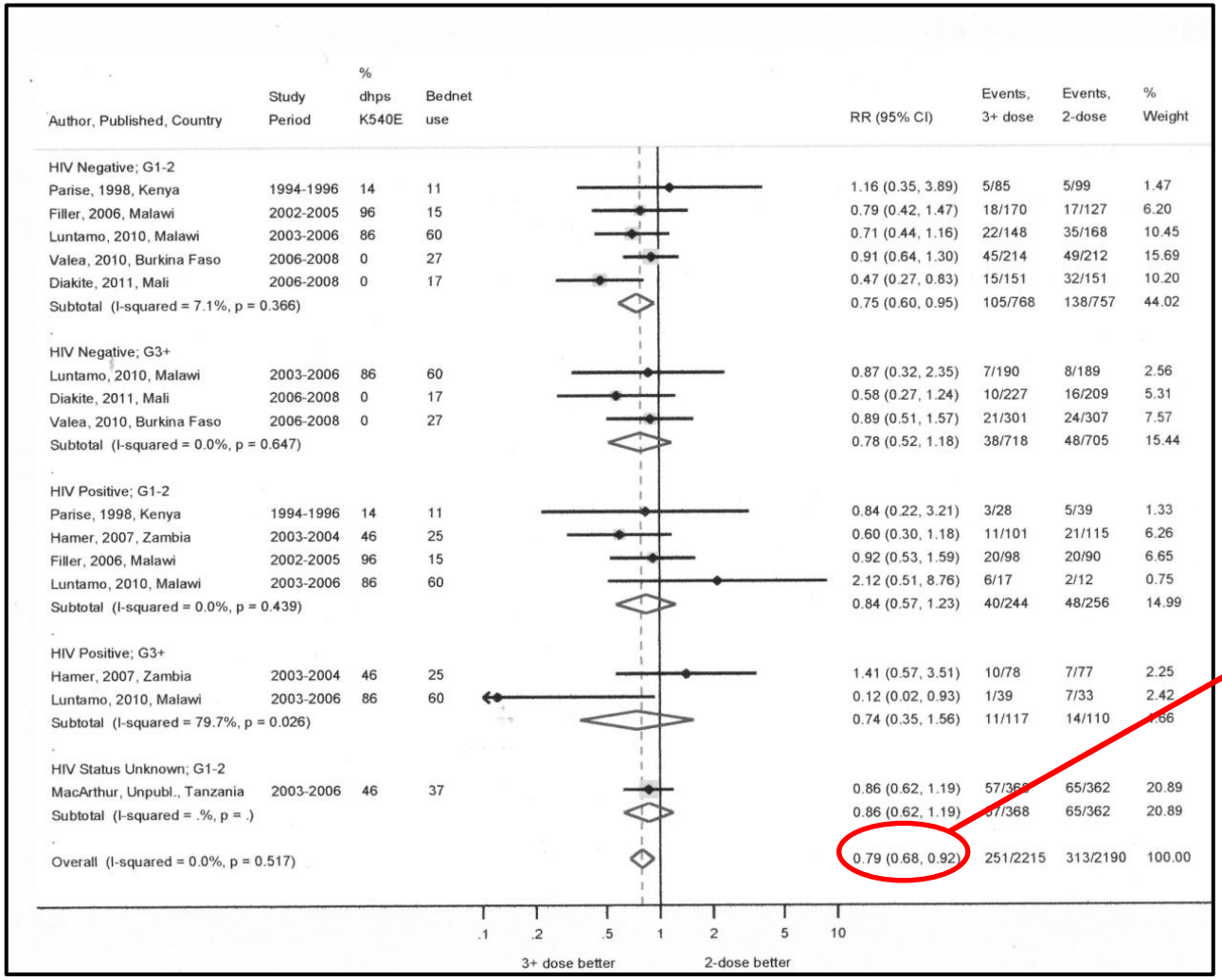
EVIDENCE OF EFFICACY OF MORE FREQUENT DOSES OF SP IPTp IN REDUCING LOW BIRTHWEIGHT

HIV - ve G1-2

HIV -ve G3 or >

HIV +ve G1,2

HIV +ve G3 or >



RR = 0.79 (0.68, 0.92)

3+ doses better **2 doses better**

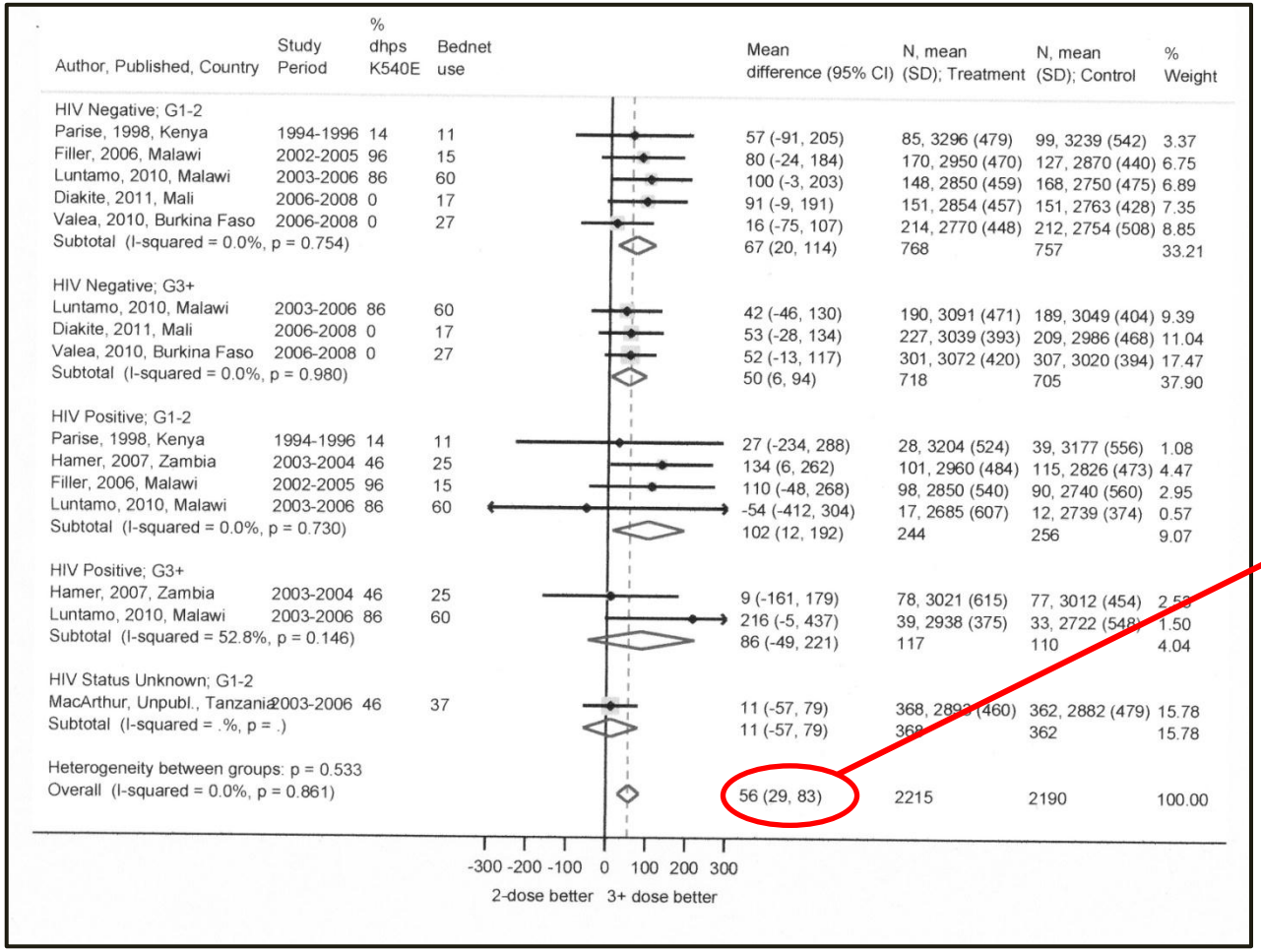
EVIDENCE OF EFFICACY OF MORE FREQUENT DOSES OF SP IPTp ON BIRTHWEIGHT

HIV - ve G1-2

HIV -ve G3 or >

HIV +ve G1,2

HIV +ve G3 or >



56 (29, 83) g

2 doses better **3+ doses better**

NUMBER OF DOSES OF SP FOR SP IPTp

Conclusions

Three or more doses are more effective than two

EVIDENCE OF THE EFFICACY OF SP IPTp IN AREAS WITH SP RESISTANCE

- **Results from a retrospective study in an area of Tanzania with a high level of SP resistance (including a 36% prevalence of 581 *dhfr* mutation) indicated damage to the placenta in women who received SP.**

- **Results from a randomised, placebo-controlled trial in an area of Mozambique with a high level of quintuple mutation (not at codon 581) showed protective efficacy of SP IPT and no association between the presence of quintuple mutant parasites and increased parasite densities or malaria-related morbidity in mothers or children.**

- **Longitudinal studies in Malawi showed a waning over time in the efficacy of SP IPT in the prevention of peripheral and placental parasitaemia and low birth weight in association with a scale up in ITN use and an increasing prevalence in SP resistance markers.**

- **Observational studies in Kenya, Malawi, and Zambia, where there is significant SP resistance, have shown an increase in birth weight and a reduction in maternal anaemia with increasing number of doses of SP, however, their observational design limits the ability to control for potential confounders.**

USE OF SP IPTp IN AREAS OF SP RESISTANCE

Conclusions

- There is some evidence of benefit from SP IPTp in areas of high prevalence of quintuple mutant *P. falciparum* parasites.

- There is no evidence of harm from SP IPTp in areas with a high level of resistance to SP. The findings of increased parasite density and inflammatory changes in women reporting use of IPTp with SP, from an observational stydy in Tazanian women need further investigation.

EVIDENCE OF THE EFFECTIVENESS OF SP IPTp AT DIFFERENT LEVELS OF MALARIA TRANSMISSION

- **There are insufficient data on which to make a decision as to the level of malaria transmission below which SP IPTp is no longer a cost effective intervention.**

- **There is insufficient evidence on which to decide on the usefulness of SP IPT outside Africa.**

EVIDENCE OF THE EFFECTIVENESS OF SP IPTp AT DIFFERENT LEVELS OF MALARIA TRANSMISSION

Conclusion

There are insufficient data to make a recommendation on the level of malaria transmission below which implementation of SP IPTp is no longer cost effective.

SUGGESTED AMENDMENTS TO THE CURRENT WHO RECOMMENDATIONS

1. Number and timing of IPTp treatments

In areas of stable (moderate-to-high) malaria transmission, IPTp with SP is recommended for all pregnant women **at each scheduled antenatal care visit**.

- The first IPTp-SP dose should be administered as early as possible during the 2nd trimester of gestation.
- Each SP dose should be given at least 1 month apart from the other and up to the time of delivery.
- The last dose of IPTp with SP can be administered late (after 36 weeks) in the 3rd trimester of gestation without safety concerns.
- IPTp should be administered as directly observed therapy (DOT).
- SP can be given on an empty stomach.
- Folic acid at a daily dose equal or above 5 mg should not be given concomitantly with SP as this counteracts its efficacy as an antimalarial.
- SP is contraindicated in women receiving cotrimoxazole prophylaxis.

SUGGESTED AMENDMENTS TO THE CURRENT WHO ECOMMENDATIONS

2. SP IPTp in areas of SP resistance

IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry quintuple mutations associated with *in vivo* therapeutic failure to SP; therefore, IPTp with SP should still be administered to women in such areas.

RECOMMENDATIONS FOR FURTHER RESEARCH

Implementation of SP IPTp

- Innovative community strategies to increase IPTp coverage that do not detract from ANC services.
- Operational interventions to improve delivery and use of ITNs to women before they conceive.

Efficacy

- Effectiveness of IPTp-SP against *P. vivax* infection in pregnancy.
- The effect of the presence of the *dhps* 581 codon mutation on IPTp-SP effectiveness.

Safety

- The safety of IPTp-SP when given 5 times or more during pregnancy.
- Interactions between antimalarials and antiretrovirals in HIV infected individual.

Monitoring

- Monitoring protocol for IPTp-SP effectiveness.
- Methods for using health system information systems for routine monitoring of IPTp-SP implementation and effectiveness.

Epidemiology

- Relationship between malaria transmission intensity level and IPTp-SP effectiveness (risk-benefit and cost-effectiveness analysis based on modeling data).
- The effect of sustained malaria transmission reduction on IPTp effectiveness.

CONCLUSIONS

- **SP IPTp remains an effective strategy for the prevention of malaria in pregnancy in Africa, even in the majority of areas of moderate to high SP resistance, provided that it is given at least three times during pregnancy.**

- **Currently, there is no established threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.**

Timelines of upcoming MiP studies of potential relevance to ERG and MPAC

2013

	J	F	M	A	M	J	J	A	S	O	N	D
Meta-analysis of IPTp-SP effectiveness trials	x	x	x	x								
Protocol to monitor IPTp-SP effectiveness	x	x	x	x								
IPTp mefloquine vs SP RCT	x	x										
IPTp with SP+AZ ° in PNG	x	x	x	x	x	x						
Multicenter IST trial § in West Africa	x	x	x	x	x	x	x	x	x			

° CQ + AZ multicenter trial in Africa will be completed in 2014

§ IST trials in Malawi and India will be completed in 2014

World Health Organization

GLOBAL MALARIA PROGRAMME

Updated WHO Policy Recommendation (October 2012)

Intermittent Preventive Treatment of malaria in pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP)

During the last few years, WHO has observed a slowing of efforts to scale-up intermittent preventive treatment of pregnant women (IPTp) for malaria with Sulfadoxine-Pyrimethamine (SP) in a number of countries in Africa. While there are several reasons for this, confusion among health workers about SP administration for IPTp may also be playing a role. For this reason, WHO is clarifying its recommendations, and urging national health authorities to disseminate these recommendations widely and ensure their correct application.

In several countries in Africa, some *Plasmodium falciparum* parasites carry quintuple mutations linked to SP resistance which are associated with *in vivo* therapeutic failure to SP. IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry these quintuple mutations[1] . Therefore, IPTp with SP should still be administered to women in such areas.

All possible efforts should be made to increase access to IPTp with SP in all areas with moderate-to-high transmission in Africa, as part of antenatal care services. Based on a recent WHO evidence review[2], the following updated recommendations are provided:

- In areas of moderate-to-high malaria transmission, IPTp with SP is recommended for all pregnant women **at each scheduled antenatal care visit**. WHO recommends a schedule of four antenatal care visits.
  - The first IPTp-SP dose should be administered as early as possible during the 2nd trimester[3] of gestation
  - Each SP dose should be given at least 1 month apart
  - The last dose of IPTp with SP can be administered up to the time of delivery, without safety concerns

[1] The findings of an observational study in Tanzanian women in an area with high levels of quintuple mutation strongly associated with drug resistance and where the parasite dhps resistance mutation of codon 581 was also present showed increased placental parasite density and inflammatory changes in women reporting IPTp with SP use. This needs further investigation although it is important to note that this specific dhps resistance mutation is currently not common.

[2] Report available on the WHO-GMP website at the following URL:
http://www.who.int/malaria/mpac/sep2012/iptp_sp_erg_meeting_report_july2012.pdf

[3] IPTp administration should be avoided during the 1st trimester of gestation but should start as soon as possible in the 2nd trimester. The fact that a woman has entered the second trimester can be determined by the onset of quickening or by measurement of fundal height by ANC health personnel.

- IPTp should ideally be administered as directly observed therapy (DOT)
- SP can be given either on an empty stomach or with food
- Folic acid at a daily dose equal or above 5 mg should not be given together with SP as this counteracts its efficacy as an antimalarial[4]
- SP should not be administered to women receiving co-trimoxazole prophylaxis

- In some countries where IPTp with SP is currently being implemented, transmission of malaria has been reduced substantially. In the absence of information on the level of malaria transmission below which IPTp-SP is no longer cost-effective, such countries should not stop IPTp.[5]

- There is currently insufficient evidence to support a general recommendation for the use of IPTp-SP outside Africa.

- Monitoring of IPTp-SP effectiveness and safety of multiple doses is essential and should continue. Research is ongoing to define the best methodology for such monitoring; this will be shared when available.

[4] WHO recommends daily iron and folic acid supplementation in pregnant women at the dose of 30-60 mg of elemental iron and 0.4 mg of folic acid, to reduce the risk of low birth weight infants, maternal anaemia and iron deficiency at term.

[5] Cost-effectiveness modelling studies are on-going to address this question. Risk-benefit of SP administration needs also to be taken into account when considering recommendations on IPTp implementation.

