World Health Organization

Malaria Policy Advisory Committee (MPAC) Meeting Agenda
Dates: 13-15 March 2013. Location: Salle A, WHO HQ, Geneva

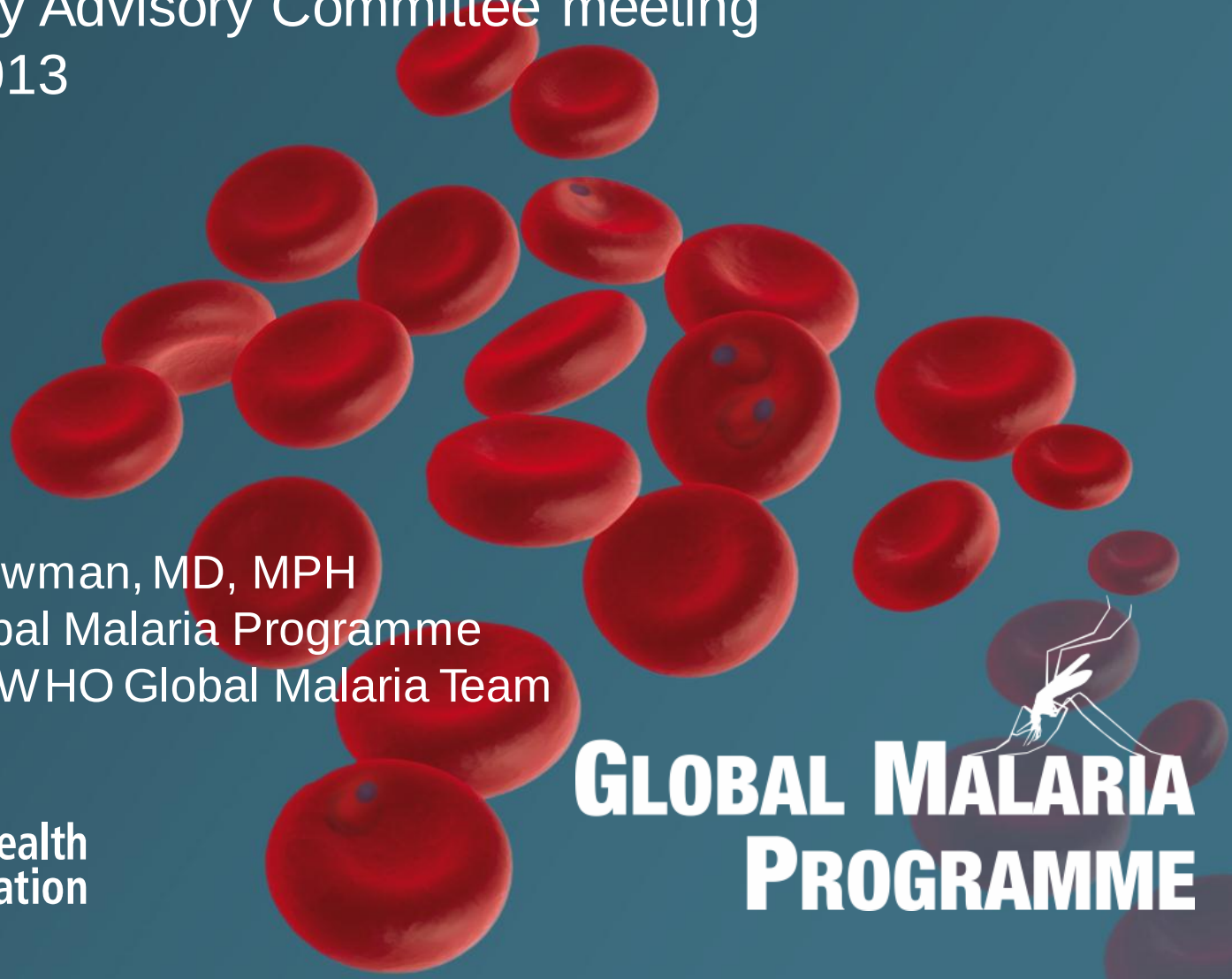
Wednesday, 13 March 2013

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
11:15	Drug Resistance outside Asia **(P Ringwald/K Carter)**	For discussion and statement	
12:30	**Lunch (but first, MPAC group photo at 12:30)**		
	Session 3		open
13:30	Non Malaria Febrile Illness **(V D'Acremont)** Report from 22-24 January consultation	For discussion and decision of malaria specific recommendations	
14:30	Malaria Burden Estimation **(P Smith)** Report back from second ERG meeting	For discussion and input	
15:30	**Coffee/tea break**		
	Session 4		open
16:00 16:30	Malaria Treatment Guidelines **(N White)** Vector Control TEG and update on sustaining universal coverage of LLINs **(M Renshaw/A Mnzava)**	For information – Update on working group progress For discussion and input	
18:00	**End of day**		

Report from the Director

Malaria Policy Advisory Committee meeting
13 March, 2013

Robert D. Newman, MD, MPH
Director, Global Malaria Programme
On behalf of WHO Global Malaria Team



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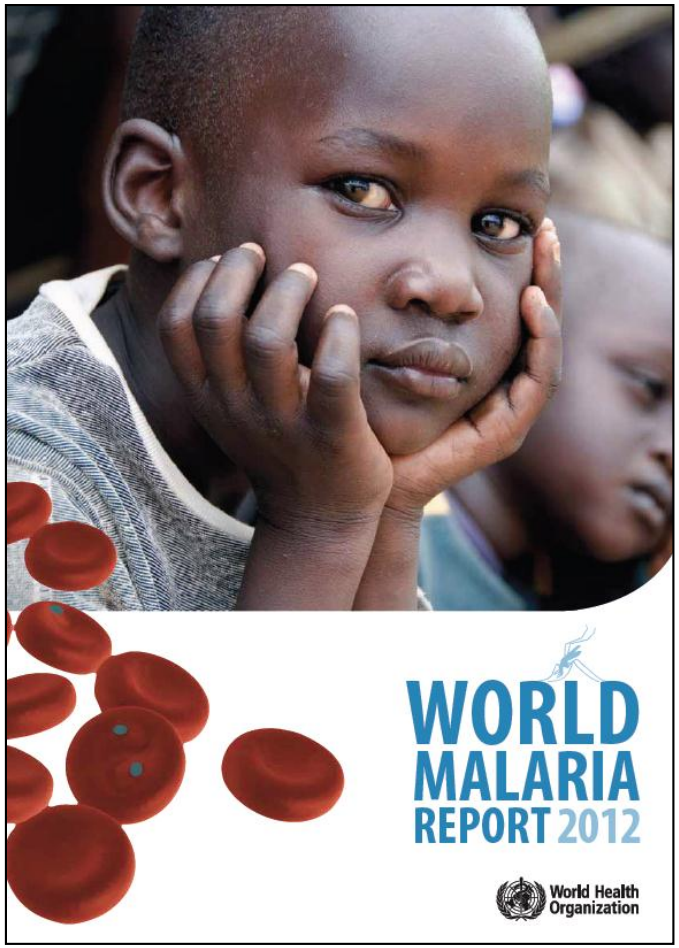
GLOBAL MALARIA PROGRAMME

World Malaria Report 2012



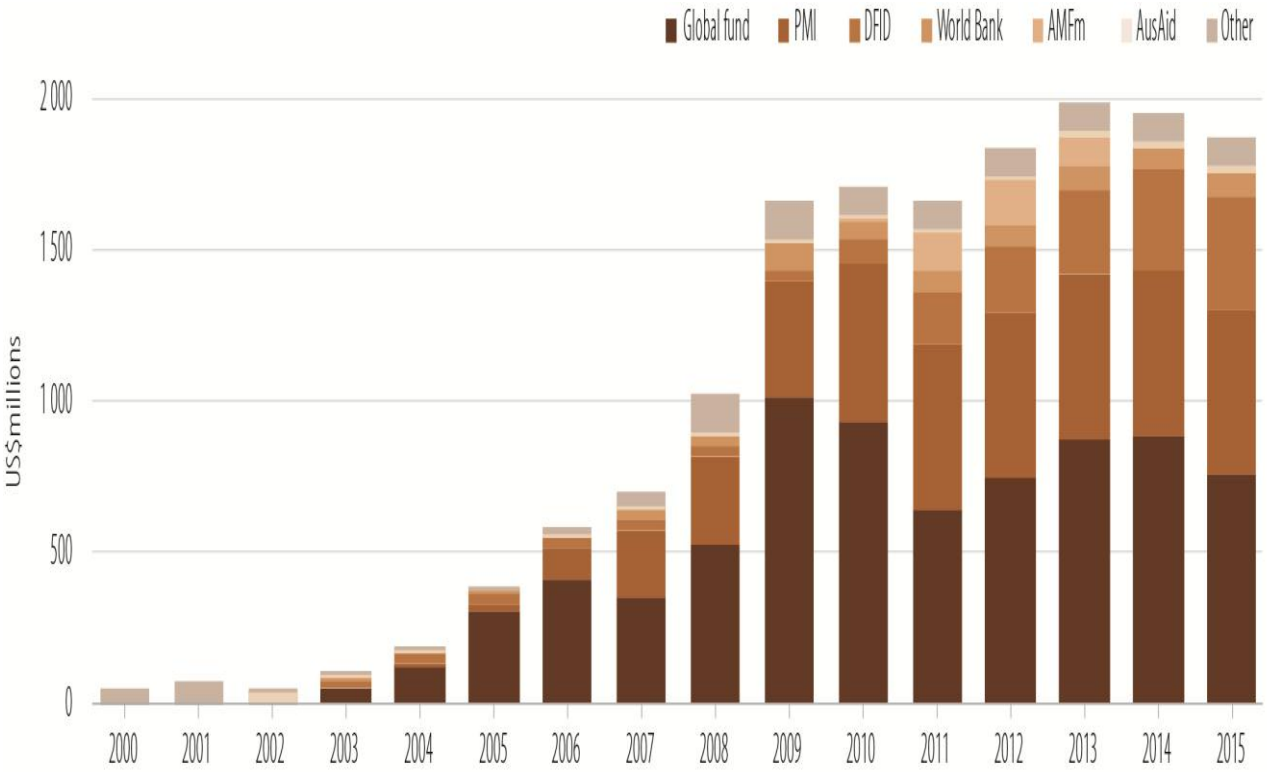
- Released on 17 December 2012 by H.E. President Sirleaf of Liberia
- Annual reference on the status of global malaria control & elimination; data to 2011 and 2012
- Principal data source is national programs in 104 endemic countries with particular support from: WHO Regional offices, ALMA, CDC, Global Fund, IHME, ISGlobal, MAP (Oxford), UNICEF, USAID
- Summarizes key malaria targets & goals
- Documents trends in financing, intervention coverage and malaria cases and deaths
- Profiles for 99 countries and areas with ongoing transmission
- Country level malaria burden estimates for 2010

Past and projected international funding for malaria control

International funding for malaria control rose from <US$ 100 million (2000) to US$ 1.66 billion (2011) and US$ 1.84 billion in 2012

Total funds for malaria control in 2011 estimated at US$ 2.3 billion; short of US$ 5.1 billion required to achieve universal coverage of malaria interventions

Projections indicate that total funding will remain at <US$ 2.7 billion between 2013 and 2015



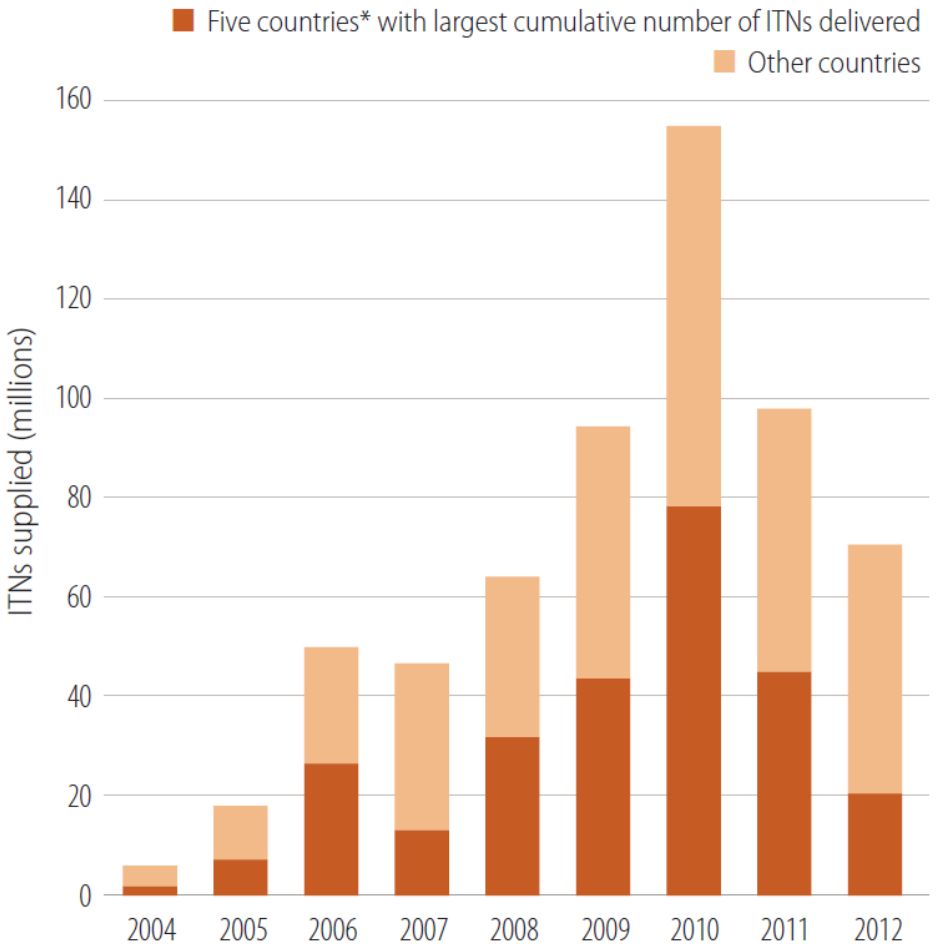
Source: See Box 3.1.

Number of ITNs delivered by manufacturers to countries in sub-Saharan Africa

150 million ITNs needed annually to achieve universal access; number delivered to countries in Saharan Africa was 66 million (2012), down from 145 million (2010)

Without substantial scale-up of vector control in 2013, can expect major resurgences of malaria

Figure 4.1 Number of ITNs delivered by manufacturers to countries in sub-Saharan Africa, 2004–2012



* Democratic Republic of the Congo, Ethiopia, Kenya, Nigeria, United Republic of Tanzania

Source: Alliance for Malaria Prevention. Data for the first three quarters of 2012 have been multiplied by 4/3 to provide an annual estimate.

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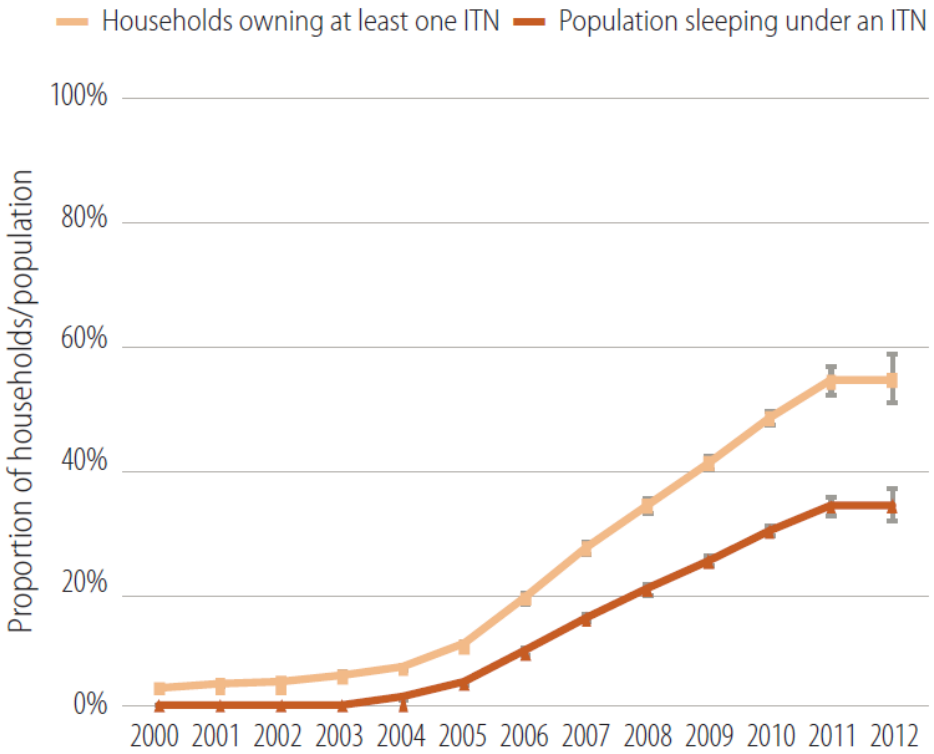
Estimated trends in households owning ≥1 ITN and population sleeping under an ITN in sub-Saharan Africa

Percentage of households in sub-Saharan Africa owning ≥1 ITN rose from 3% (2000) to 53% (2011); remained at 53% in 2012

Proportion of population sleeping under ITN also increased from 2% (2000) to 33% (2011); remained at 33% in 2012

Figure 4.2 Estimated trend in proportion of households with at least one ITN and proportion of the population sleeping under an ITN in sub-Saharan Africa, 2000–2012

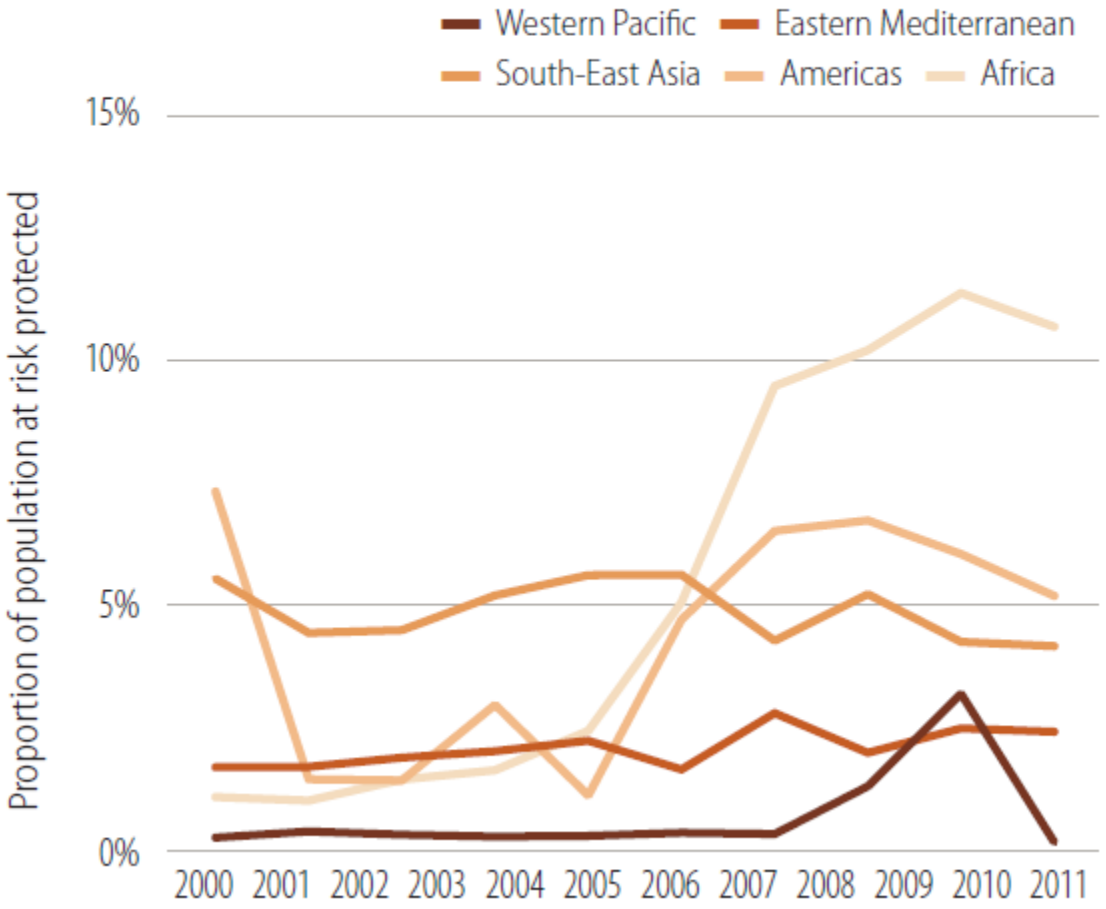


Proportion of population sleeping under an ITN derived from relationship with household ownership of at least one ITN analyzed by linear regression in 48 household surveys 2001-2011, y= 0.67x - 0.03.

Source: ITN coverage model from the Institute for Health Metrics and Evaluation, which takes into account ITNs supplied by manufacturers, ITNs delivered by NMCPs and household survey results (1). Includes Djibouti, Somalia and Sudan which are in the WHO Eastern Mediterranean Region.

Proportion of population at malaria risk protected by IRS, by WHO Region

Figure 4.5 Proportion of population at malaria risk protected by IRS by WHO Region, 2000–2011



Source: NMCP reports

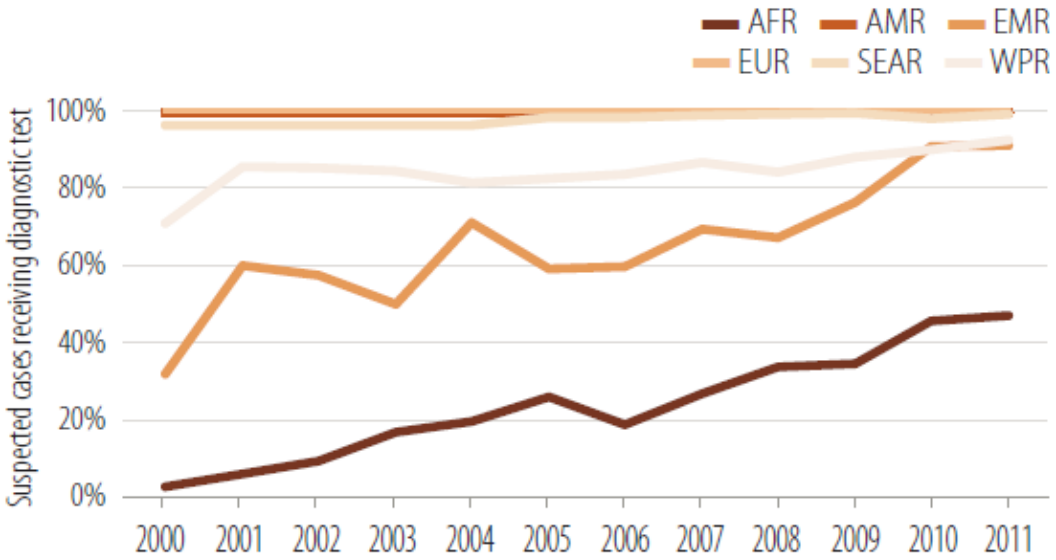
Proportion of suspected malaria cases attending public health facilities that receive a diagnostic test

Number of patients tested by microscopy rose to 171 million in 2011, with India accounting for over 108 million blood slide examinations

Number of RDTs supplied by manufacturers increased from 88 million in 2010 to 155 million in 2011

Proportion of suspected malaria cases receiving a diagnostic test in the public sector increased from 20% in 2005 to 47% in 2011 in the African Region and from 68% to 77% globally

Figure 6.6 Proportion of suspected malaria cases attending public health facilities that receive a diagnostic test, 2000–2011



Source: NMCP reports

Note: Trends are based on reports to WHO which may disproportionately reflect countries with better reporting systems and diagnostic testing rates.

ACT deliveries 2005–2011

ACT treatment courses delivered to public and private sectors increased from 11 million (2005) to 76 million (2006), and reached 278 million in 2011

Increases in ACT procurement in 2011 largely due AMFm. Although AMFm accounts for substantial portion of public sector sales, total number of ACTs procured for public sector decreased between 2010 and 2011

Figure 6.10 ACT deliveries, by health sector and AMFm contribution, 2005–2011

Source: Data provided by 8 manufacturers eligible for procurement from WHO/UNICEF and AMFm reports (as of 30 August 2012). Routine ACT public sector deliveries monitored 2005–2011; AMFm-facilitated public and private sector deliveries through AMFm monitored 2010-2011, in 2010 by AMFm reports and in 2011 by reports of manufacturers. ACT deliveries through non-AMFm private-sector channels are not monitored, but are estimated to be a small fraction (approx. 5-10%) compared to public sector deliveries.

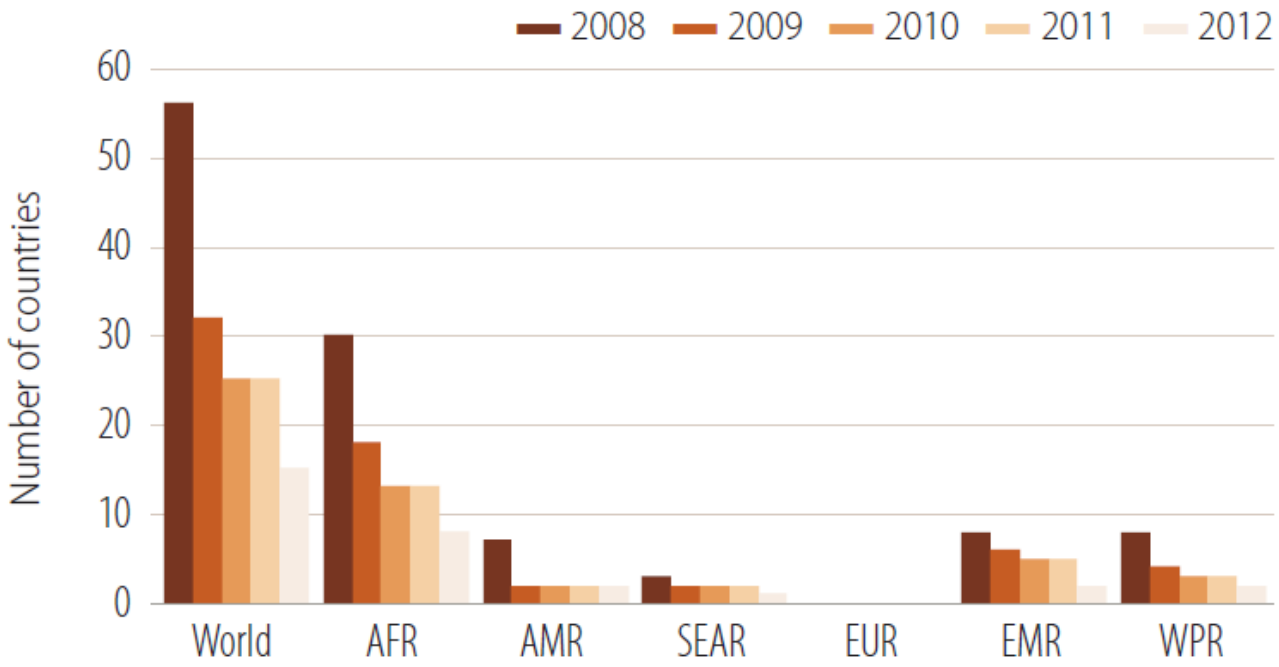
Marketing of oral artemisinin-based monotherapies

WHO recommends oral artemisinin-based monotherapies (oAMT) be withdrawn from market and replaced with ACTs; endorsed by World Health Assembly in 2007

Number of countries marketing oAMTs decreased from 55 (2008) to 16 (2012); 9 are in African Region

Number of pharmaceutical companies marketing oAMTs dropped from 38 in 2010 to 28 in 2011

Figure 6.15 Number of countries allowing marketing of oral artemisinin-based monotherapies, by WHO Region, 2008–2012



Source: http://www.who.int/malaria/monotherapy_NDRAs.pdf

Estimated number of cases and deaths 2010

Table 8.2 WHO estimates of the number of malaria cases and deaths in 2010

Region	Estimated cases ('000s)				Estimated deaths			
	Estimate	Lower	Upper	% *falciparum*	Estimate	Lower	Upper	% <5
African	174 000	110 000	242 000	98%	596 000	429 000	772 000	91%
Region of the Americas	1 100	900	1 300	35%	1 100	700	1 800	29%
Eastern Mediterranean	10 400	6 400	16 600	83%	15 300	7 200	23 500	70%
European	0.2	0.2	0.2	–	0	0	0	–
South-East Asia	32 000	25 900	41 900	53%	43 000	31 100	60 300	32%
Western Pacific	1 700	1 300	2 100	79%	4 000	2 400	6 100	41%
World	**219 000**	**154 000**	**289 000**	**90%**	**660 000**	**490 000**	**836 000**	**86%**

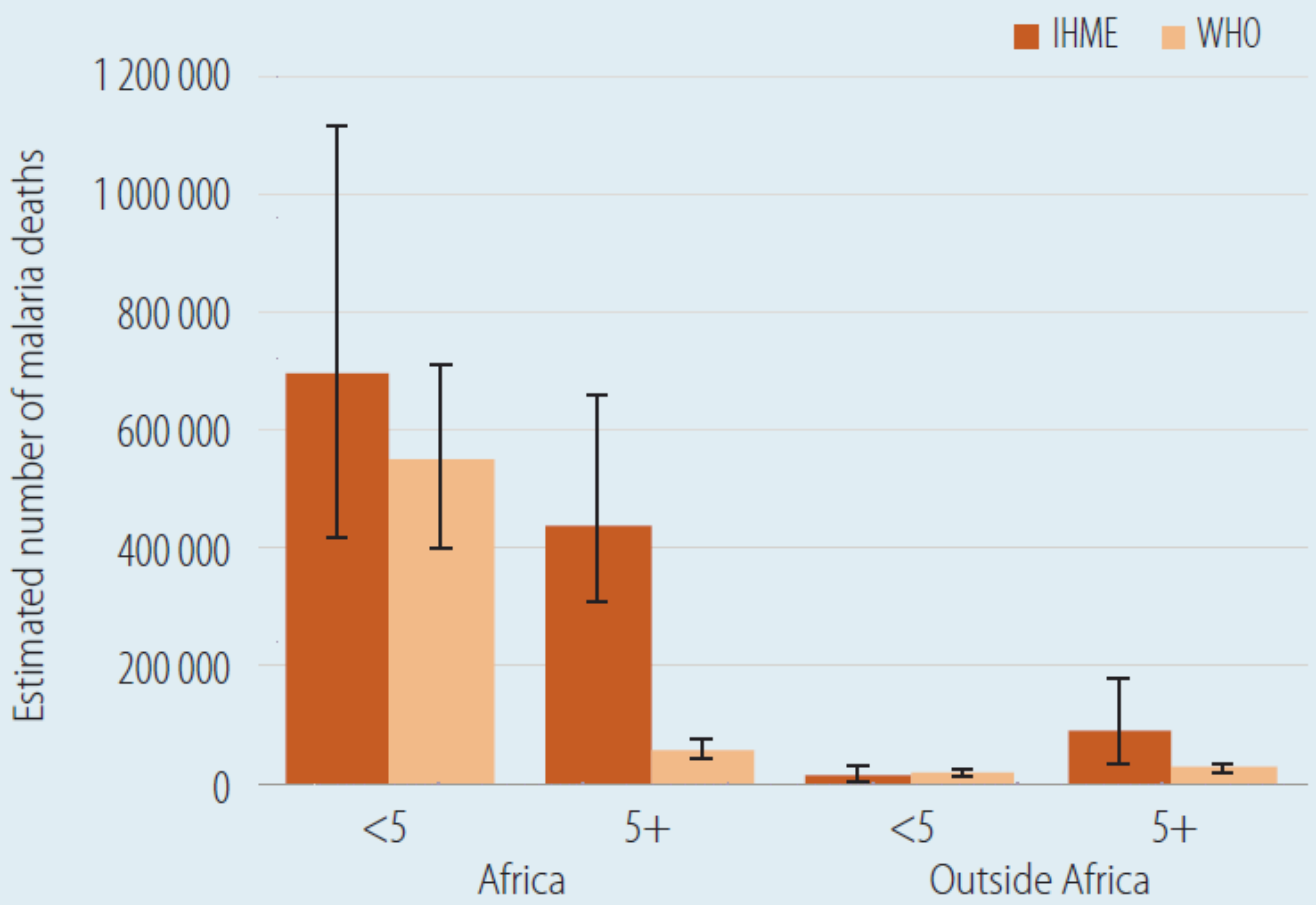
Source: WHO estimates

An estimated 219 million cases of malaria occurred in 2010, with a wide uncertainty interval. Approximately 80%, or 174 million cases, were in the African Region, with the South-East Asian Region accounting for another 15%.

There were an estimated 660 000 malaria deaths in 2010, of which 90% were in the African Region. Approximately 86% of global malaria deaths were of children under 5 years of age.

Comparison of WHO and IHME estimates 2010

Figure Box 8.2 Estimates of number of malaria deaths in 2010, by age group and geographical region (*1,2*)



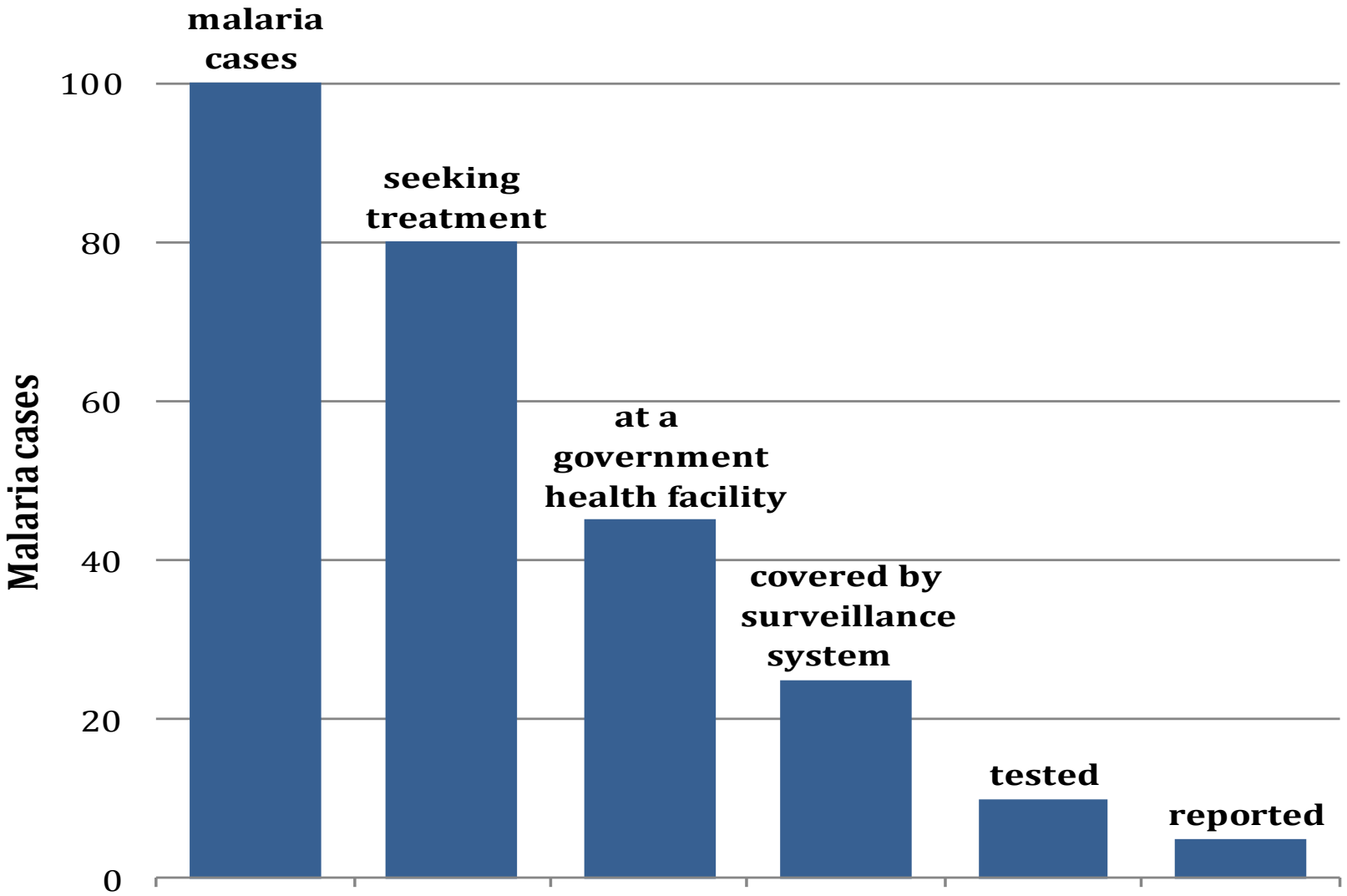
Source: IHME and WHO estimates

Proportion of cases detected by surveillance systems

Region	Estimated number of cases 2010	Reported number of cases 2010	Reported/ estimated
Africa	174 000	18 000	11%
Americas	1 100	700	59%
Eastern Mediterranean	10 400	1 000	10%
Europe	0.2	0.2	87%
South-East Asia	32 000	2 400	9%
Western Pacific	1 700	260	13%
World	219 000	22 500	10%

Malaria surveillance systems detect only 10% of cases estimated to occur annually

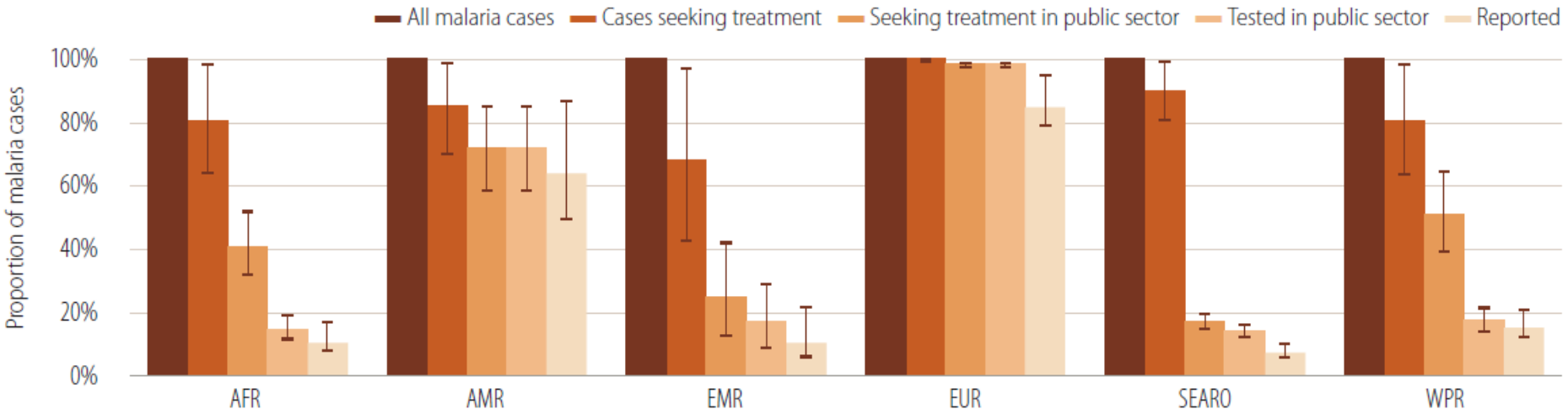
Bottlenecks in case detection



Bottlenecks in case detection by WHO region

Figure 7.5 Bottlenecks in case detection, by WHO Region

Public sector includes cases in the private sector that are reported through the public sector



Source: *NMCP reports, WHO estimates*

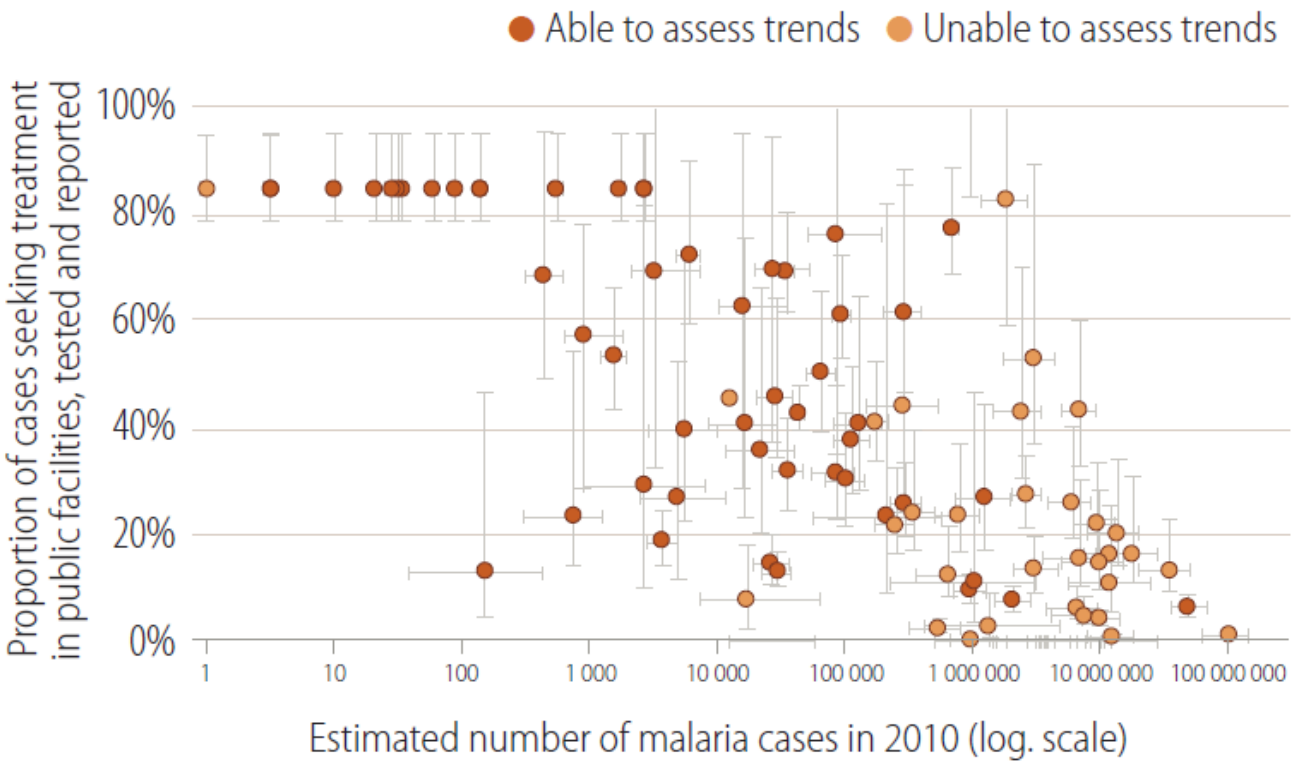
Assessing trends in malaria through surveillance systems

Case detection rates are lowest in countries with the highest number of malaria cases.

A reliable assessment of trends can be made in 58 countries out of 99 with ongoing transmission using data submitted to WHO.

These countries account for only 34 million or 15% of total estimated cases in 2010.

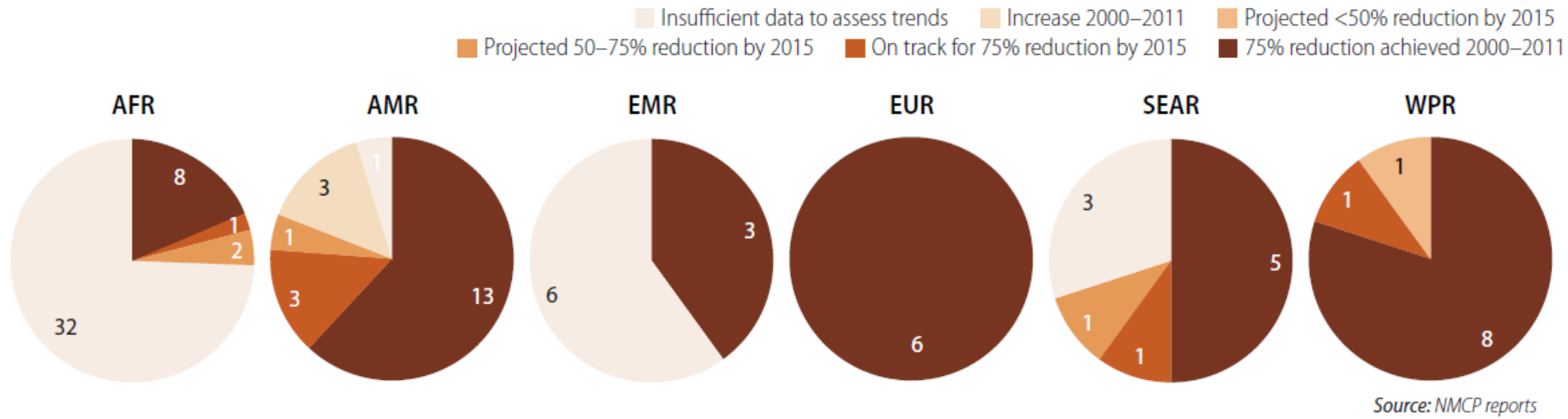
Figure 7.6 Proportion of malaria cases captured by surveillance systems, in relation to total estimated number of cases and whether trends over time can be assessed



Source: NMCP reports, WHO estimates

Progress towards 2015 target of 75% reduction in malaria case incidence

Figure 8.2 Decreases in reported malaria case incidence rates 2000–2011, by WHO Region
The number of countries in each category is shown in each pie slice



Source: NMCP reports

50 countries are on track to reduce malaria case incidence by 75% by 2015: these account for only 3% of total estimated cases

Progress in reducing cases and in relation to initial burden

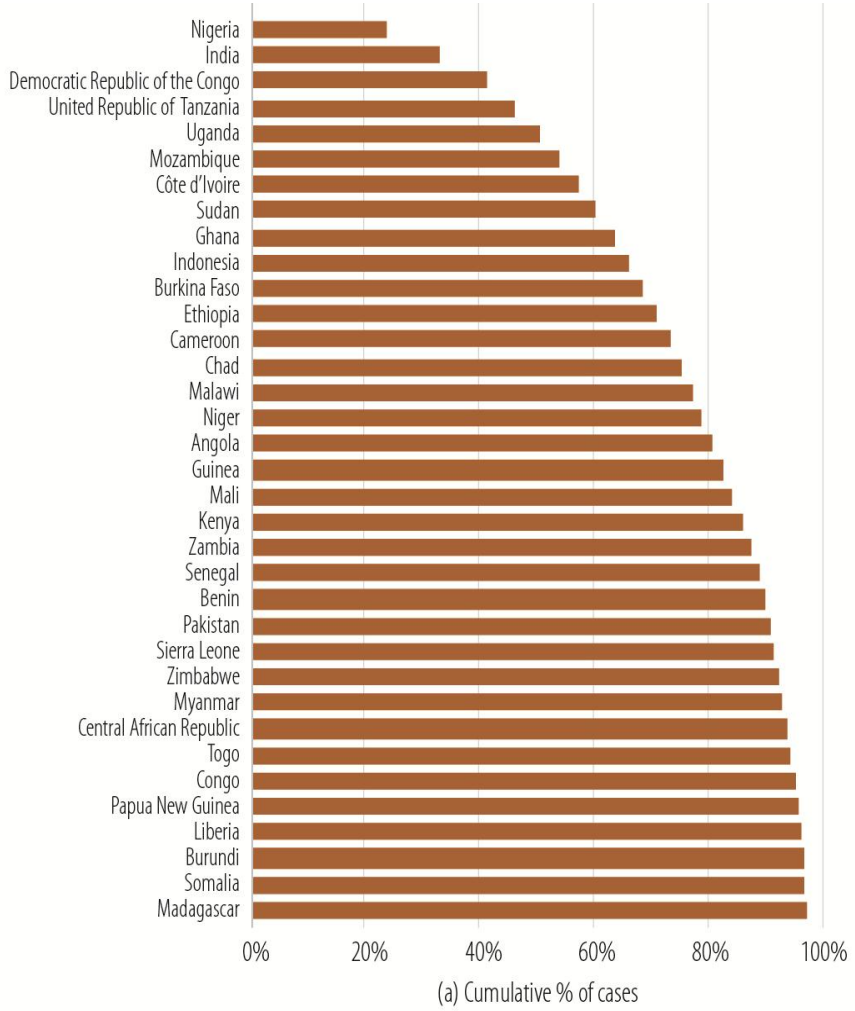
For the 58 countries in which it is possible to assess trends, greater reductions in cases have been seen in countries with smaller reported case loads

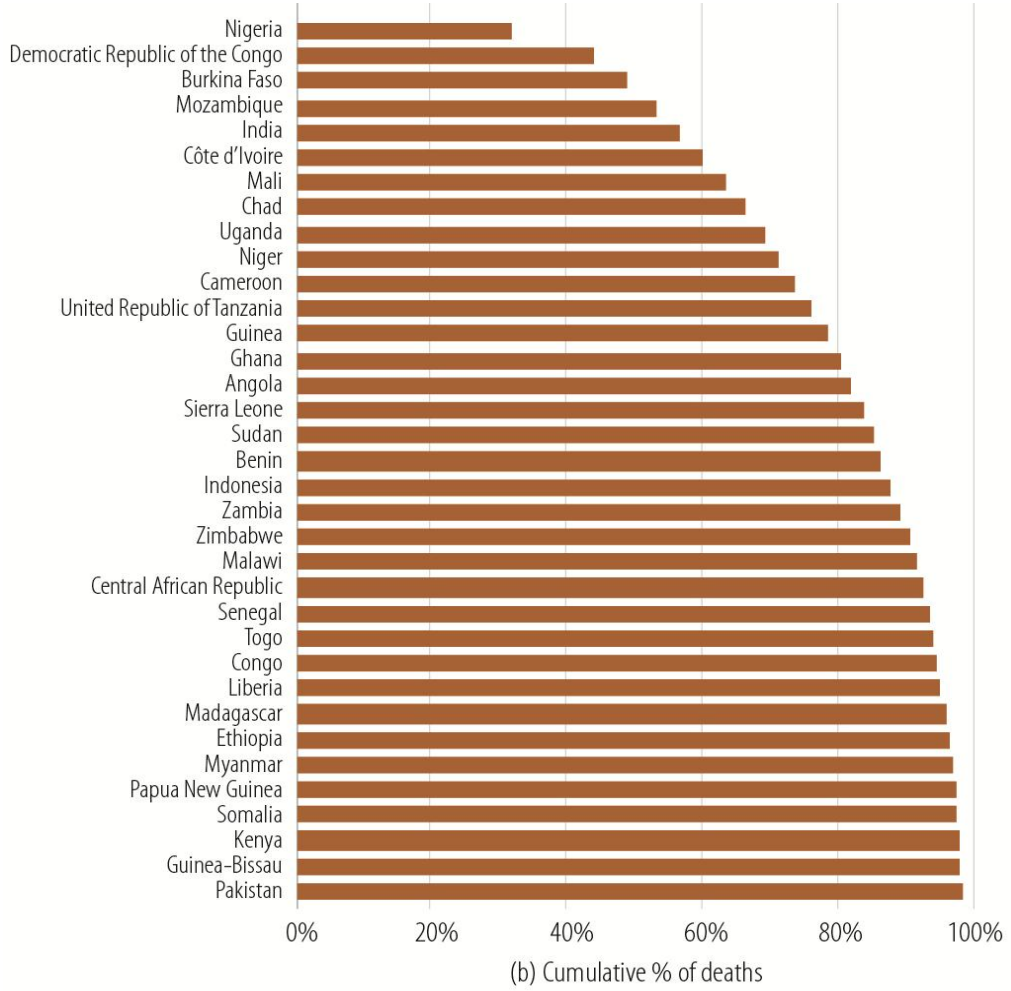
Figure 8.3 Percentage change in reported case incidence versus reported cases in 2000

Countries reporting a smaller number of cases in 2000 achieved larger rates of decrease in malaria incidence. There are a few outliers from this general pattern, in particular 3 countries in the Region of the Americas which have recorded an increase in malaria case incidence since 2000.

Source: NMCP reports

Cumulative proportion of cases and deaths





17 countries account for 80% of estimated cases and 14 countries account for 80% of estimated deaths in 2010

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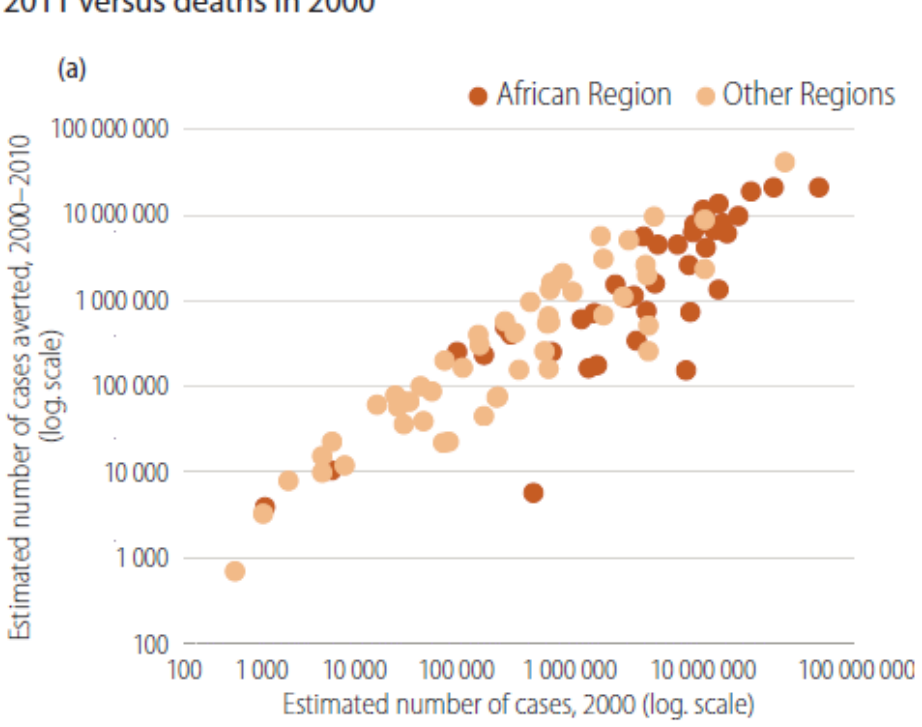
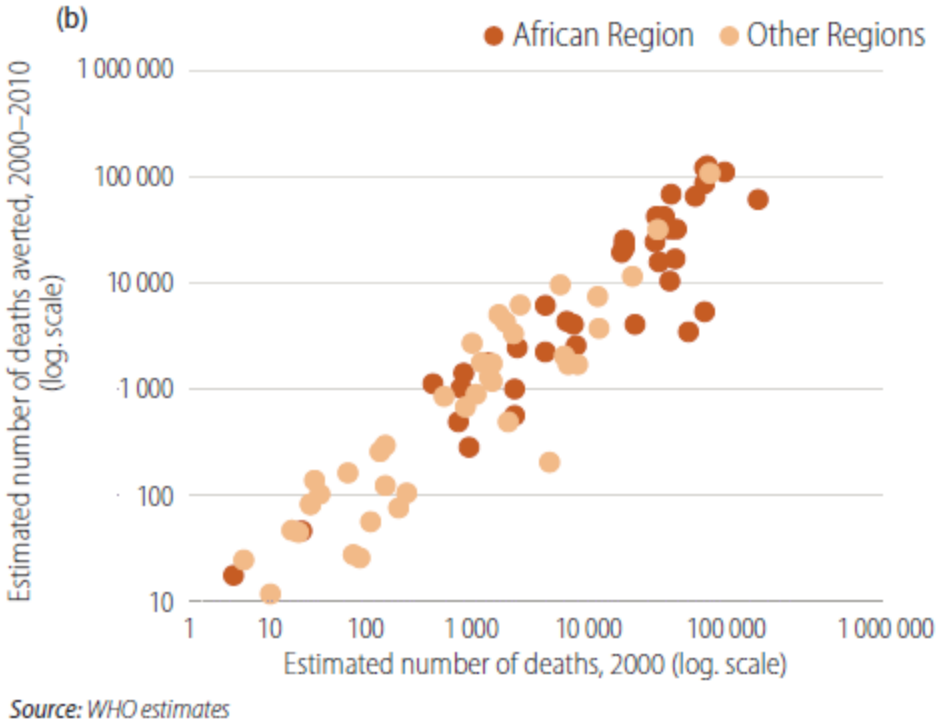
Progress faster in smaller countries; greater number of cases and deaths averted in highest burden countries

Figure 8.8 Estimated numbers of (a) cases averted in 2000–2011 versus cases in 2000 and (b) number of deaths averted in 2000–2011 versus deaths in 2000





Source: WHO estimates

If malaria case incidence and mortality rates witnessed in 2000 had continued there would have been 274 million more malaria cases and 1.1 million more malaria deaths between 2001-2010

The majority of cases averted (52%) and lives saved (58%) are in the 10 countries with the highest estimated malaria burdens i.e. malaria programmes are having their greatest impact where the burden is highest.

Elimination status of countries, as of December 2012

Table 8.1. Classification of countries by stage of elimination, as of December 2012

Region	Pre-elimination	Elimination	Prevention of re-introduction	Recently certified as malaria free
African	Cape Verde	Algeria		
Region of the Americas	Argentina Costa Rica Ecuador El Salvador Mexico Paraguay			
Eastern Mediterranean		Iran (Islamic Republic of) Saudi Arabia	Egypt Iraq Oman Syrian Arab Republic	Morocco - 2010 United Arab Emirates – 2007
European		Azerbaijan Kyrgyzstan Tajikistan Turkey Uzbekistan	Georgia	Armenia - 2011 Turkmenistan – 2010
South-East Asia	Bhutan Democratic People's Republic of Korea	Sri Lanka		
Western Pacific	Malaysia	Republic of Korea		

Source: NMCP reports

Of 104 endemic countries in 2012, 79 countries classified as being in control phase, 10 in pre-elimination, 10 in elimination, and 5 in prevention of introduction phase. Elimination of malaria in the European Region appears attainable by 2015.

Regional Updates

AFRO Update 1 – Scale up, SME/OR

Background

- Parasitological diagnosis of malaria still low in most countries including high burden countries (Angola, Burkina Faso, Côte d'Ivoire, DRC, Malawi, Mozambique, Nigeria, Tanzania, Uganda)
- Compliance of health workers to RDTs vs. microscopy
- Scaling up RDTs and development of implementation manuals for QA/QC.
- Strengthening capacity for laboratory diagnosis as part of larger effort of strengthening surveillance for accelerated malaria control and pre-elimination.

Discussion

- Robust plan for continuous supply of RDT and microscopy reagents in high burden counties
- BCC/IEC to improve adherence of health workers to diagnostic test result and clear direction on management of non-malaria fevers
- QA/QC of malaria diagnosis (Microscopy & RDT)
- Strengthening pharmacovigilance system at country/Regional level with collaborating centers and networks of experts

Action or Next Steps

- Support countries in planning for supply of laboratory reagents and QC/QA system
- Operational research

AFRO Update 2 – Scale up, SME/OR

Background

- Botswana, Eritrea, Namibia, South Africa, Swaziland and United Republic of Tanzania-Zanzibar moving towards pre-elimination phase.
- Cross-Border/Island pre-elimination initiatives (moving to phase: Mauritania, Senegal, The Gambia, Cape Verde, Bioko, Madagascar, Comoros, Sierra Leone).
- WHO East & Southern Africa Intercountry Support Team developed handbook on vector control to help countries to address current challenges of moving from very strong VC programmes to next phase towards elimination;

Discussion

- Inadequate surveillance data to guiding phase-out of some activities
- Community engagement to better target VC interventions
- Global and Regional support to cross-border initiatives

Action or Next Steps

- Alignment of vector control interventions with surveillance in control & elimination
- Community awareness and engagement
- Regional cooperation and cross-border vector control activities
- Support to countries for implementation of GPIRM: ANVR, Collaborating Centers

EMRO Update 1 - Malaria diagnosis

Background

- In 2011, only 37% of reported malaria cases confirmed with parasitological testing

Discussion

- Defects in recording and reporting systems – example: not all cases confirmed by RDTs are captured (e.g., s- Sudan)
- No national resources secured for RDTs - all from donor funding
- Lack of confidence in RDT results in some areas and microscopy in other areas (both clients & health workers)

Action or Next Steps

- Advocate for mobilizing financial resources at national and international levels to scale up quality diagnostic testing and ensure sustainability
- Need for position statement on use of RDTs (where and when) for malaria free countries including for routine diagnostic testing and screening
- More advocacy for standardization of RDT format
- Develop roster of experts and standard tools for diagnostic system assessment including QC/QA

EMRO Update 2 - Prevention of re-establishment of malaria transmission

Background

- 14 EMR countries free of malaria, of which 2 are certified, 3 (Egypt, Syria, Iraq) reported no cases >3 years, but did not request certification. Oman had local outbreaks in past years after importation
- Risk of local malaria transmission is increasing: high vulnerability and receptivity (huge population movement, new water projects)

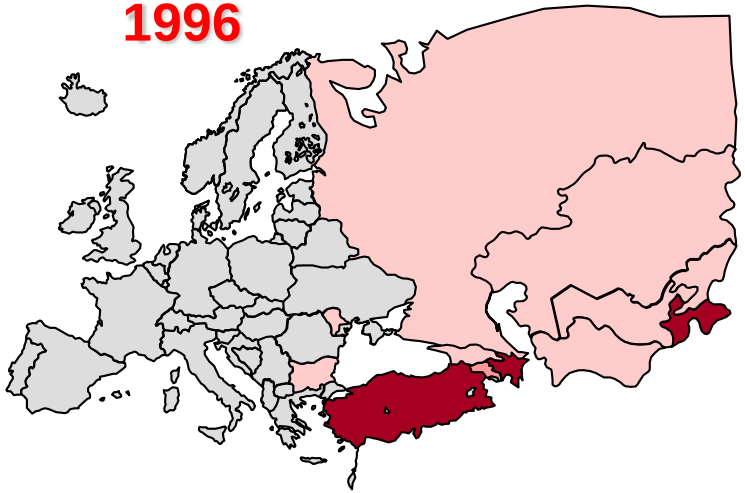
Discussion

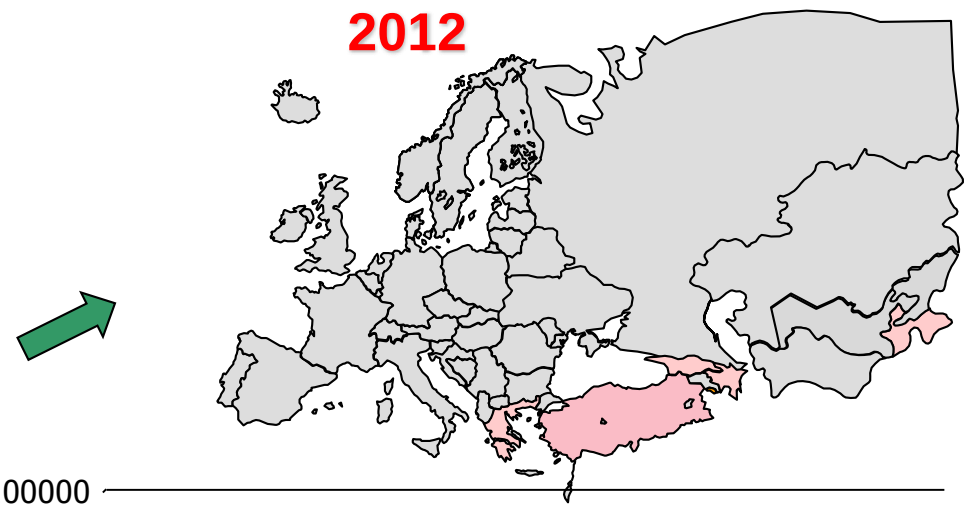
- Imported cases from Pakistan are increasing
- Loss of expert technicians and workers of MCP without adequate replacement
- Collapse of the malaria programme in some countries (Syria and Libya)
- Malaria and VBDs are not considered a priority health problem in many countries

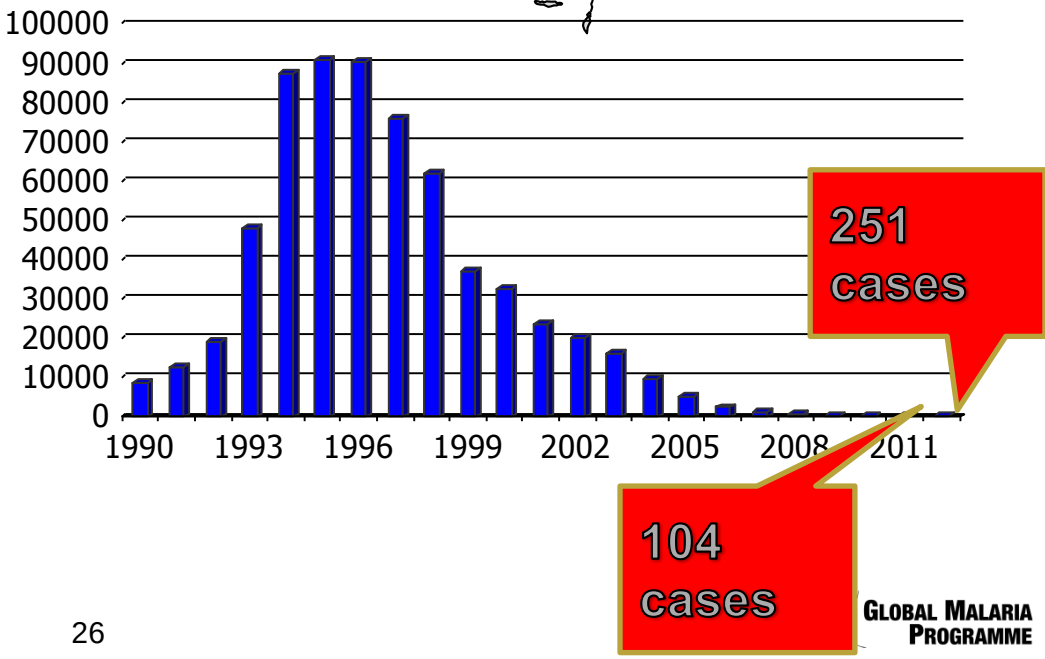
Actions or next steps

- Develop briefs for high level political and economic fora to sustain appropriate programme funding for eliminating and malaria free countries
- Advocacy document for national parliaments and equivalent, as the Arab League summit and the Organization of Islamic Countries, support programme review and strategy update
- Sustain regional stock of ACT and support capacity building

EURO Update 1 – Locally acquired cases







EURO Update 2 - Priority issues 2013

- Malaria Elimination (WHO/Europe, GMP/HQ, Global Fund, B&MGF and countries)
- Prevention of malaria re-introduction and certification of malaria elimination (WHO/Europe, GMP/HQ, Global Fund, B&MGF, ECDC, MSF and countries)
- Capacity building on malaria elimination (WHO/Europe, GMP/HQ, the Russian Federation, Global Fund and countries)
- Cross-border collaboration on malaria elimination (WHO/Europe, EMRO/WHO, GMP/HQ, Global Fund, B&MGF and countries)
- Promotion of integrated vector management approach (WHO/Europe, NTD/HQ, Global Fund, UNEP, GEF, Green Cross International, MKI and countries)

PAHO Update 1 - Situation & Impact 2000-2011

- Approx. 23 million people live in areas at high or moderate risk for malaria
- 489,610 confirmed cases; 113 malaria deaths (2011)
- **59% reduction cases; 70% decline deaths** since 2000
- **69% *P. vivax*; 30% *P. falciparum***; <1% *P. malariae* (reported Brazil, Colombia, F. Guiana, Guyana, Peru, Suriname, Venezuela)
- **Reduced Incidence in 18 of 21 endemic countries** (2000 and 2010 - achievement Roll Back Malaria goal 50% reduction). Non-achievement: Dominican Republic, Haiti and Venezuela
- Increased cases Guyana (2011): now four countries compared with 2000; but downward trend in Dominican Republic since 2005
- Non-endemic countries: average 2,000 malaria cases (imported or introduced) per year
- **WHO-GMP criteria, six in pre-elimination phase** (Argentina, Costa Rica, Ecuador, El Salvador, Mexico and Paraguay); elimination also considered feasible in Hispaniola

PAHO Update 2 - Targets and Challenges

- **Continue efforts to reduce incidence and prevent malaria related deaths vis a vis increased mining, population movement, accessibility to health providers, availability and adherence to appropriate treatment**

- **Elimination of *P. falciparum* (susceptibility to CQ – Mexico, Central America, Hispaniola)**
- **Elimination of *P. vivax* (Argentina, Paraguay)**
- **Request certification elimination - Argentina**

- **Suspected emergence reduced efficacy – Artemisinin (SUR, GUY); Amazon efficacy monitoring**
- **Global Program Artemisinin Resistance Containment**

- **Elimination of *P. vivax (greater challenge)* ~ 70% cases in Region**
- **Global Strategy and Plan - Control and Elimination of *P. vivax***

- **Global Program Insecticide Resistance Management**

- **AMI/RAVREDA – *new additional* network focus on elimination? – lessons other Regions**

- **Prevent re-establishment of transmission where interrupted -** Bahamas and Jamaica: outbreaks 2006. Lessons for other non-endemic countries. Surveillance and Quality Diagnosis

- **Recent announcement Global Fund financing - Elimination malaria from Mesoamerica and Hispaniola – program reorientation**

SEARO Update 1 - Control of malaria among high risk groups

Background

- High risk groups include migrant workers, ethnic communities, settlers in forest fringes
- Pockets of high endemicity in remote hard to reach areas, including international borders, populated by ethnic communities

Discussion

- Delivery mechanisms to reach the hard to reach high risk groups
- Additional tools needed to control outdoor transmission
-

Action or Next Steps

- Situation analyses – forest related malaria, malaria along international borders, malaria among tribal communities
- Operational research (including MDA in isolated/remote villages? – Bangladesh is proposing)
- Research to develop tools to control of outdoor transmission

SEARO Update 2 - Prevention of resurgence

Background

- Several countries are eliminating malaria

Discussion

- Receptivity and vulnerability is high; resurgence of transmission is always a threat
- Several areas need to be strengthened (e.g., surveillance and response, staff capacity, SOPs, delimitation of risk areas, etc)

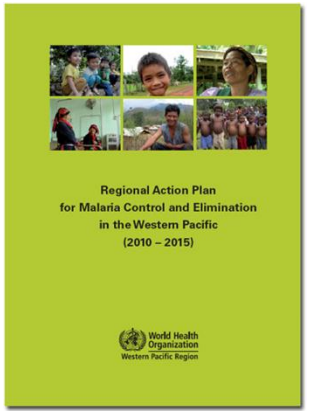
Action or Next Steps

- Training (e.g., malaria elimination; surveillance)
- Stratification and mapping of risk areas
- Practical guide for malaria elimination and prevention of resurgence
- Advocacy (to sustain financing; multi-sectoral support)

WPRO Update 1- Reaching Targets

Background

- WHA 58.2: 75% reduction in malaria morbidity and mortality by 2015 (2000 baseline).
- Regional Action Plan (RAP) for Malaria Control and Elimination in the Western Pacific (2010-2015), endorsed by WP RCM 2009: 50% reduction in malaria morbidity and mortality (2007 baseline)
- Sydney Malaria 2012 *Saving Lives in Asia-Pacific* Consensus supports and expands WHA 58.2 targets
- 2012 ASEAN and East Asia Summit strongly commit to malaria



Discussion

- Progress towards WHA 58.2 targets made, to varying degrees
- Progress towards Regional Action Plan targets not encouraging
- Sustainability of efforts needs to be considered
- Resurgence of malaria in some countries

Action or Next Steps

- Country malaria program reviews, followed by review of national strategic plans
- Gap analysis by country and the entire region
- Intensive resource mobilization
- Intensify WHO TA in some countries
- Follow up and capitalize on political commitment (e.g. APLMA, task forces)

WPRO Update 2 - Drug Resistance

Background

- Four/six Greater Mekong Subregion (GMS) countries affected by artemisinin resistance, containment operations ongoing
- Resistance to partner drugs emerging (mefloquine, piperaquine, lumefantrine)
- $16M (BMFG/AusAID) to coordinate GMS response, but insufficient funding in countries
- Commitment of development partners and ASEAN increased

Discussion

- WHO has technical leadership for artemisinin resistance containment and response, high expectations
- Emergency Response Plan based on the joint assessment development partners
- Regional Hub to be established in Cambodia with close collaboration the 3 levels of WHO
- "not business as usual approach" is needed

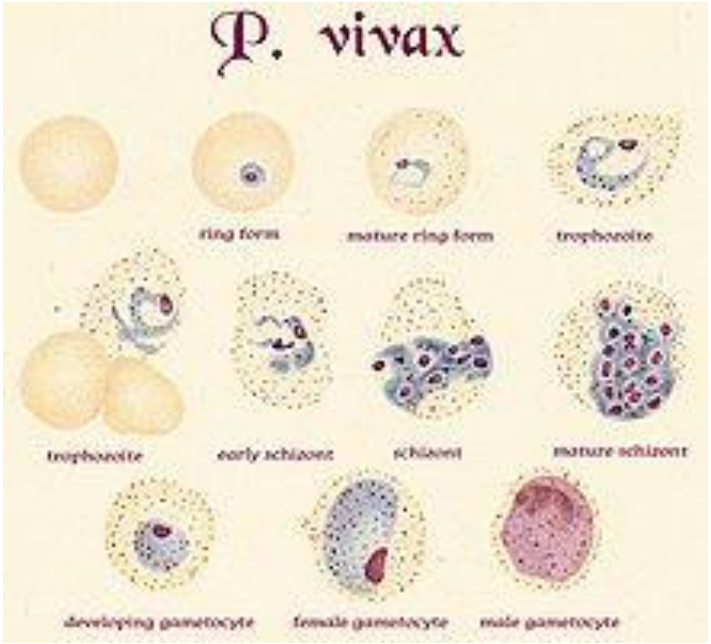
Action or Next Steps

- Launch ERAR Plan on April 25, 2013 in Cambodia with WPR RD and Director GMP; ERAR is on agenda of high-level meeting in August, for further political commitment.
- Finalize staff recruitment, new *modus operandi* approved by RDs, develop workplan
- Intensify TA to countries for NSPs with ERAR activities and gap analysis
- Resource mobilization, including $100M for regional AR initiative from GF
- Intensify antimalarial drug efficacy monitoring
- Expand approach to address antimicrobial resistance more broadly.

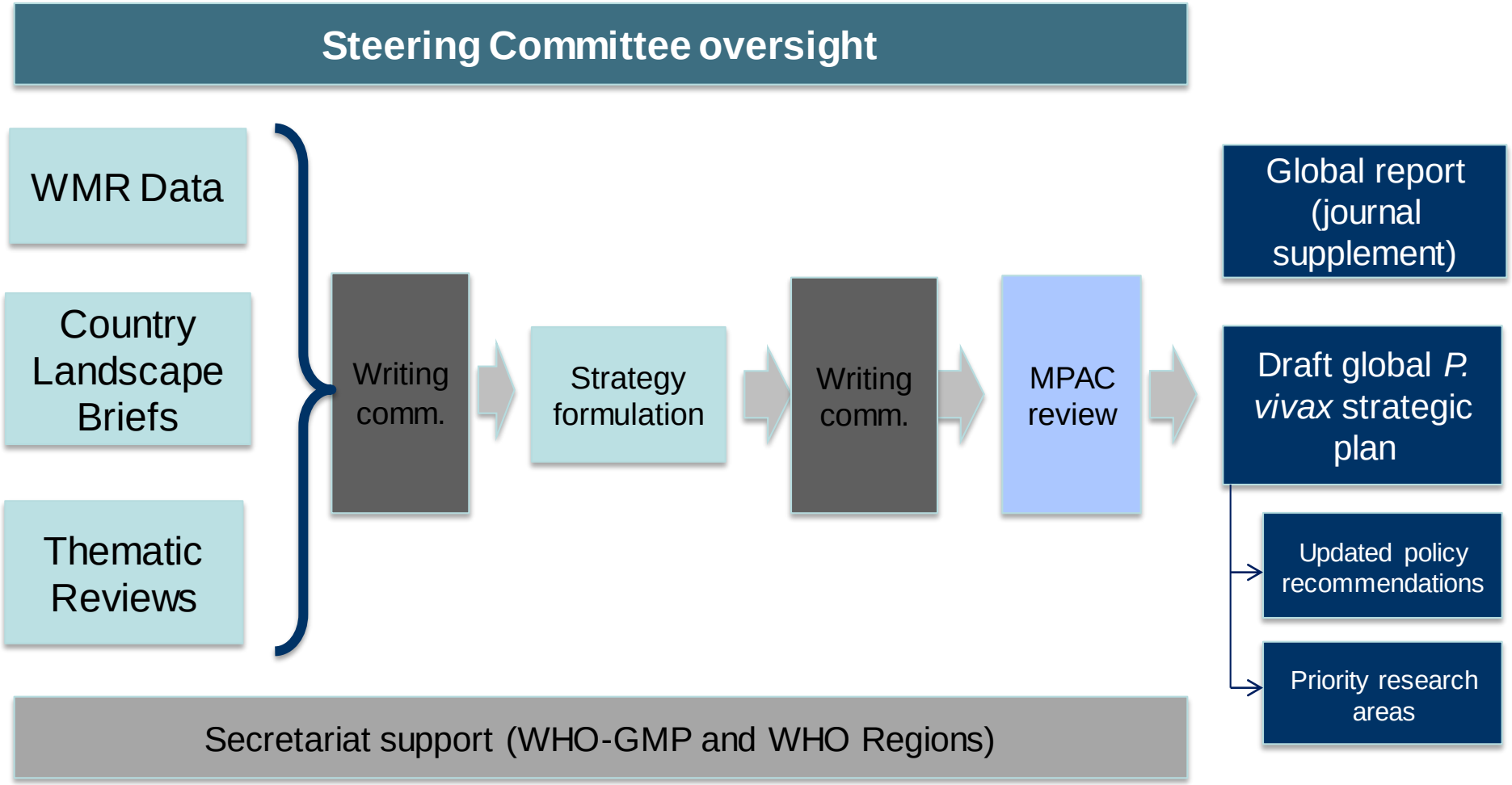
GMP Updates

Global Strategic Plan for *P. vivax* control & elimination

- Because *P. vivax* not perceived to be a major killer compared to *P. falciparum*, often features as an "add-on" to strategies
- 2.6 billion people at risk
- More formidable technical challenge
- In September 2012, MPAC endorsed urgent need to develop a global plan for *P. vivax*
- Although will be included in Global Technical Strategy for Malaria Control and Elimination (2016-2025), recommended that vivax plan be developed first



Structure for developing *P. vivax* plan



Global Strategic Plan for *P. vivax* control & elimination

- Initial Steering Committee meeting in November 2012 at ASTMH
- Writing Committee (includes most of Steering Committee) to be convened in early 2013
- Regional and country stakeholders to be convened in 2013
- Presentation to MPAC in 2014
- Support provided by MMV

Global Strategic Plan for *P. vivax* control & elimination

	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Expert Guidance												
Steering Group meeting												
Evidence Review Group meeting												
Compiling the Evidence Base												
1. World Malaria Report												
Data collection												
Data analysis												
2. Country landscapes/ background papers												
India: 2 states												
Brazil												
PNG												
Other countries												
3. Thematic reviews												
P.vivax epidemiology												
P.vivax biology												
Vector conrol considerations for *P.vivax*												
Diagnosis & treatment (inc G6PD deficiency, resistance)												
Surveillance and elimination												
Health systems responses (policies, financing, IEC etc)												
Cost-effeciveness of interventions and optimal mix												
Research priorities												
Analysis and Formulation of Strategy												
Regional overviews												
Developing strategy												
Developing global report on *P. vivax*												
Finalize database of references												
Finalize Strategy & Report												

Malaria Situation Room - Objectives

- Track financial flow, commodities, intervention coverage and impact, and to proactively identify bottlenecks
- Work with countries to develop solutions for action
- Initially, the Situation Room will track these data in the 10 highest burden countries in Africa (Nigeria, DRC, Tanzania, Uganda, Mozambique, Ghana, Côte d'Ivoire, Burkina Faso, Niger, Cameroon) that account for over 70% of regional and 56% of global malaria burden

Malaria Situation Room - Progress

- WHO secured funding from Bill & Melinda Gates Foundation to cover start-up and three years of operations
- Staffing plan:
  - GMP - one professional and one GS
  - WHO - PSM expert on loan
  - RBM - two professionals
  - ALMA - one professional (seconded)
  - IFRC - one professional (seconded)
  - Consultant-operation manager (recruitment in progress)
  - AFRO - one staff (P3) to assist MSR and RSIS/SHOC will be recruited
- Dedicated space recently created; will be equipped with display and communication facilities
- Steering committee (GMP, RBM, UN-SEO, ALMA) - Teleconference every other week
- Malaria Situation Room team - teleconferences every other week

Situation Room Update – Next Steps

- Informing the 10 member states:
  - RD/AFRO to send letter MoHs
- Launch event (WHA, date and venue TBD):
  - to engage the MoH of the 10 countries and key partners to ensure high level commitment and support
- Populate data (national, subnational, etc)
- Finalize web-based data entry and display tool (14 Apr)

RAcE 2015 – Key elements

Support iCCM in 5 African countries as an integral part of government health services

- 5 year project: April 2012 to 2017
- CAD $74.5M

Objectives:

- Increase access to correct diagnosis, treatment and referrals for malaria, pneumonia and diarrhea at the community level
- Stimulate policy review and regulatory update on disease case management in countries, including adaptation of supply management and surveillance systems

RAcE 2015 – Progress

- 5 countries jointly selected by GMP, MCA and AFRO: Malawi, Mozambique, DRC, Niger, Nigeria

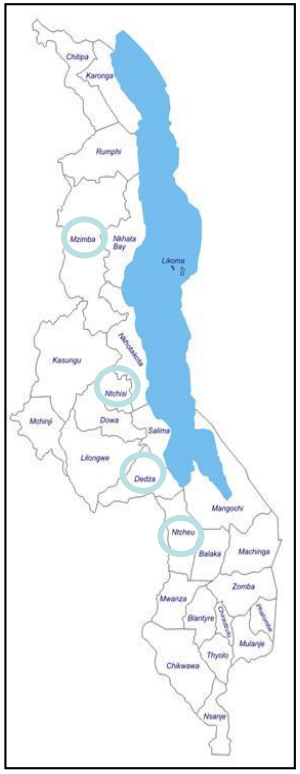
- Implementing partners selected in 4 countries, after guidance workshops, co-facilitated by WHO and MoH's
  - Malawi and Mozambique: Save the Children
  - DRC: International Rescue Committee
  - Niger: World Vision

  Implementation expected to start April-May 2013

- Nigeria: two states (Niger and Abia) selected in collaboration with FMoH

  Implementation expected to start July 2013

RAcE 2015 – Countries

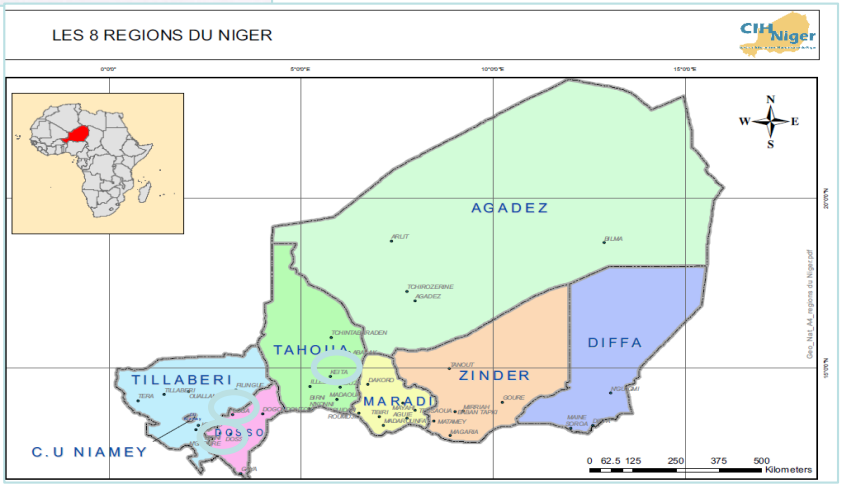


Mozambique: 4 provinces, 308,000 children 2-59 months

DRC: 2 provinces, 150,000 children 2-59 months

Malawi: 4 districts, 160,000 children 2-59 months

Niger: 3 districts, 184,000 children 2-59 months

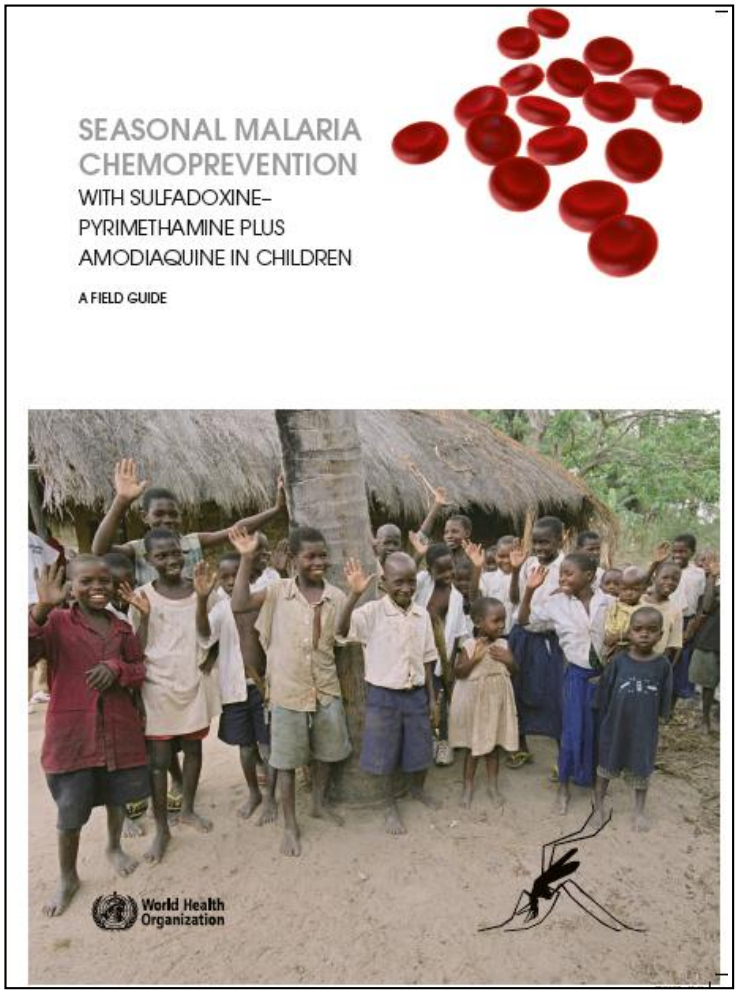


GMP website restructuring

- Website content review and restructuring process began three months ago – almost finished;
- All GMP content has been updated, each technical section expanded, new ones added;
- Content architecture revised to ensure all current priorities are appropriately covered/ linked, with improved navigation and search function;
- 200+ documents have been reviewed for validity (almost half will be labeled 'archived');
- Most changes have been done, but not yet visible to public. New website to go live in April;
- New website will serve as foundation for strengthened knowledge management work, incl. regular digital outreach to partners.

SMC: policy and implementation status

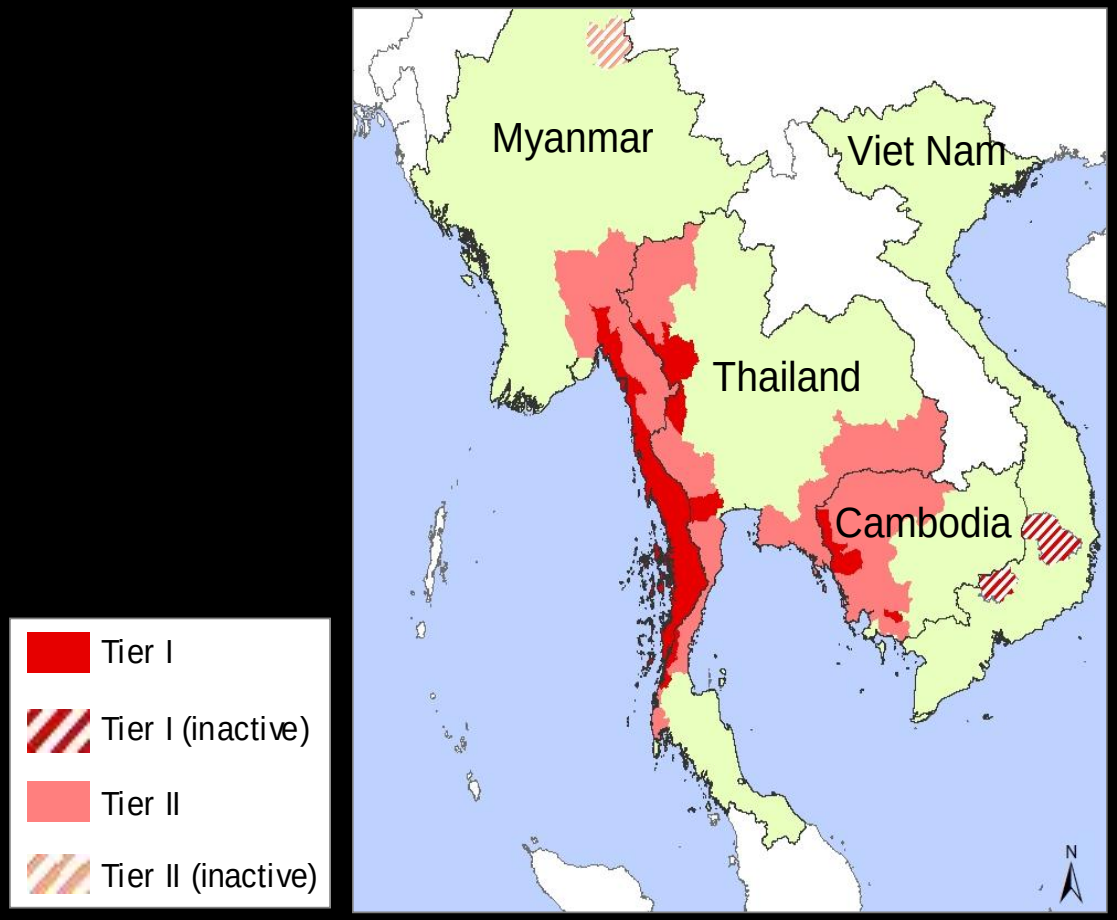
- WHO Policy formulation – (March 2012)
- Development and publication of an Implementation Manual – (November 2012)
- Orientation and training workshop for 10 countries (December 2012)



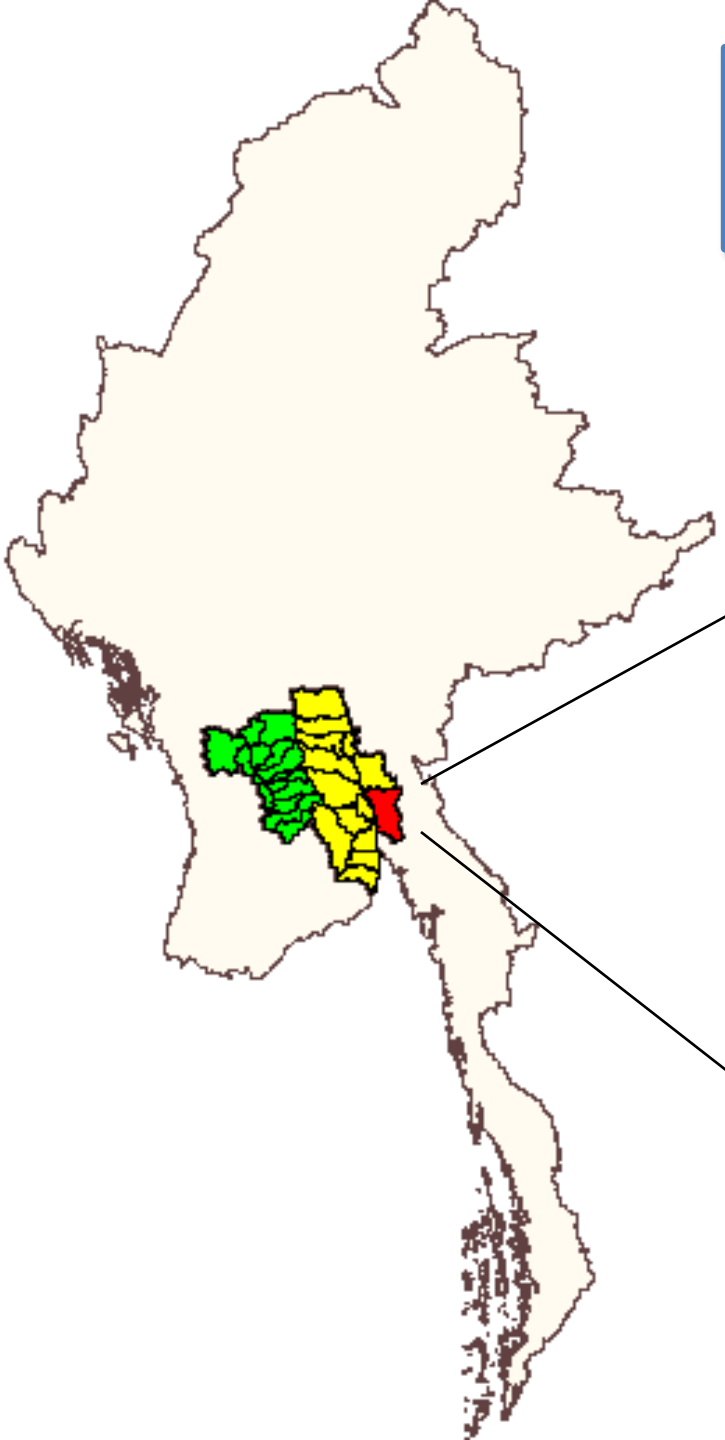
Artemisinin Resistance in Greater Mekong Subregion (GMS) - Updates

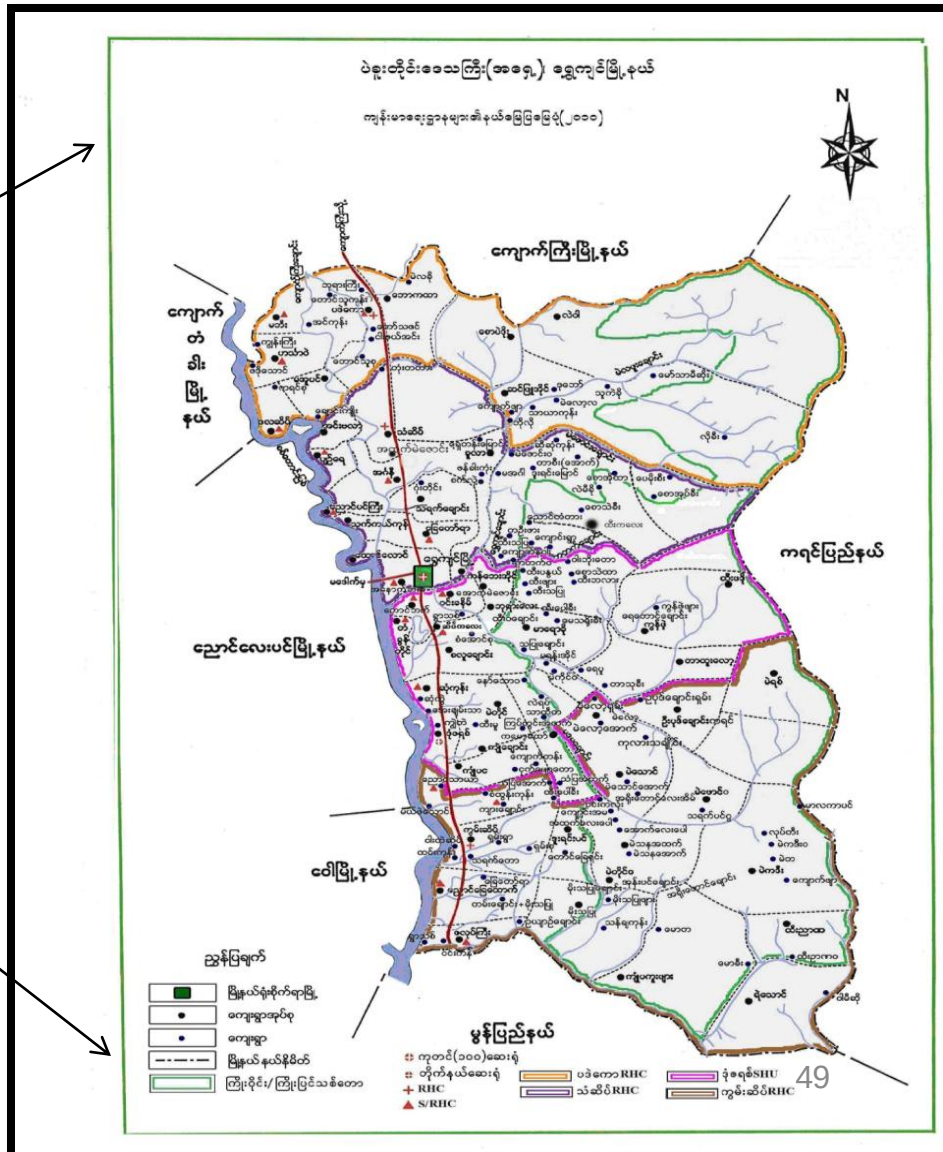
- Scope of problem unchanged since last MPAC meeting
- Activities in Myanmar being scaled up under MARC project
- Emergency Response to Artemisinin Resistance in GMS developed
  - Endorsed by countries in late February 2013
  - Launch planned for World Malaria Day in
- Resources for coordinating the response received from Bill & Melinda Gates Foundation, and expected from AusAid
- WHO Regional Hub being opened in Cambodia
- Global Fund included Regional Proposal for responding to artemisinin resistance in GMS in Early Applicants for New Funding Model: $100 million over 3 years
- Main factor limiting success remains resources
  - Need to do more of what is working

Scope of AR containment activities

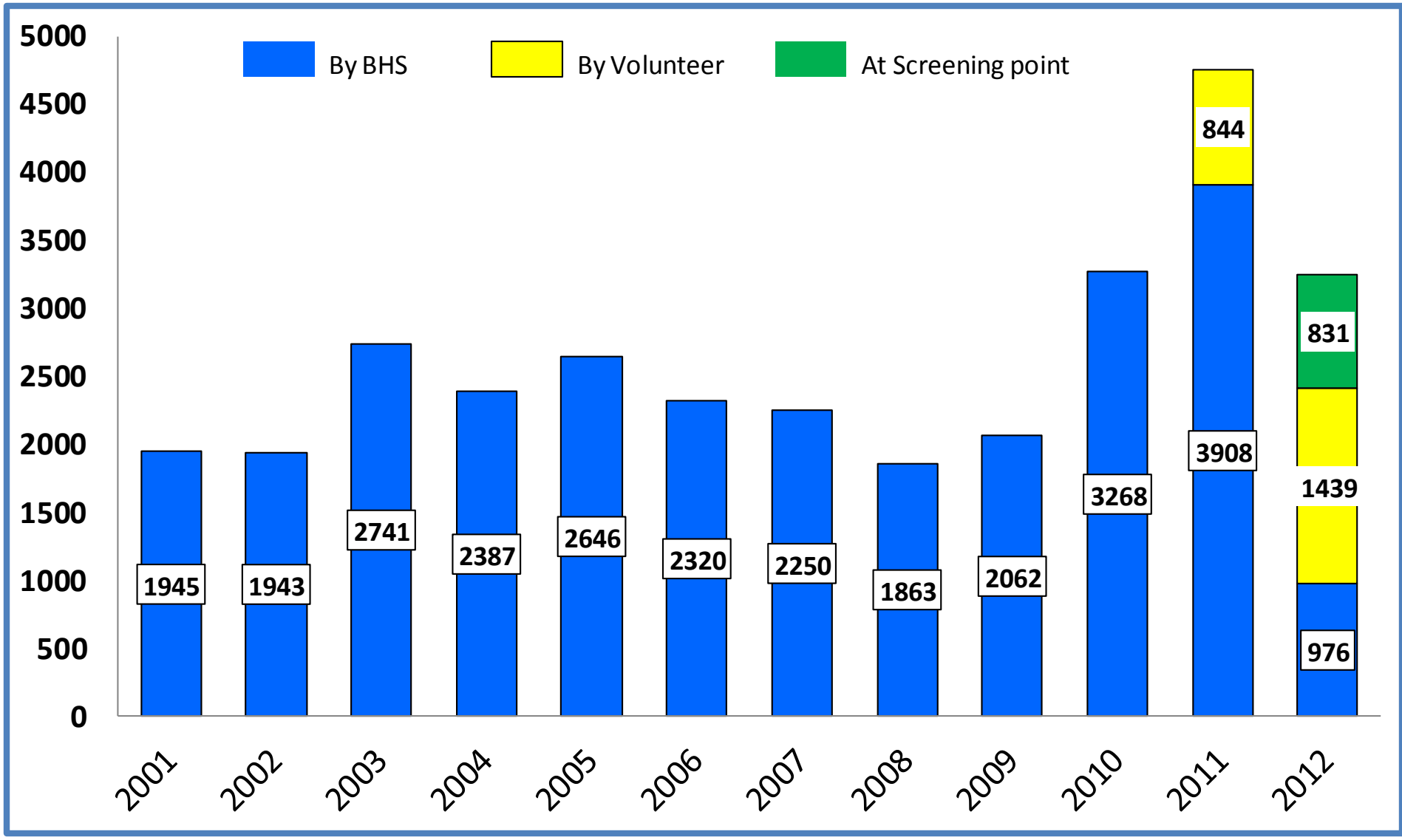


SHWEKYIN TOWNSHIP, Bago State, Myanmar

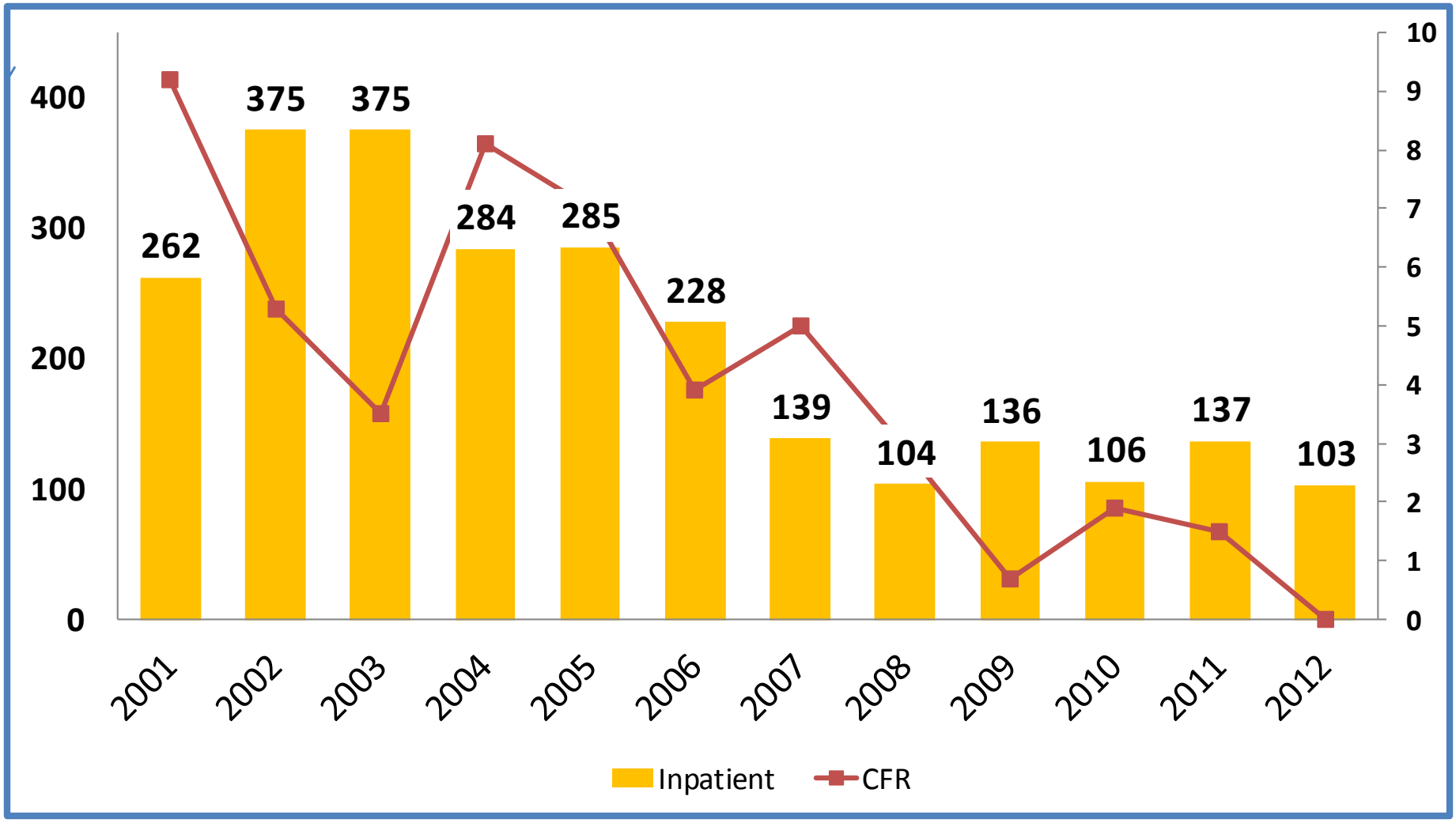




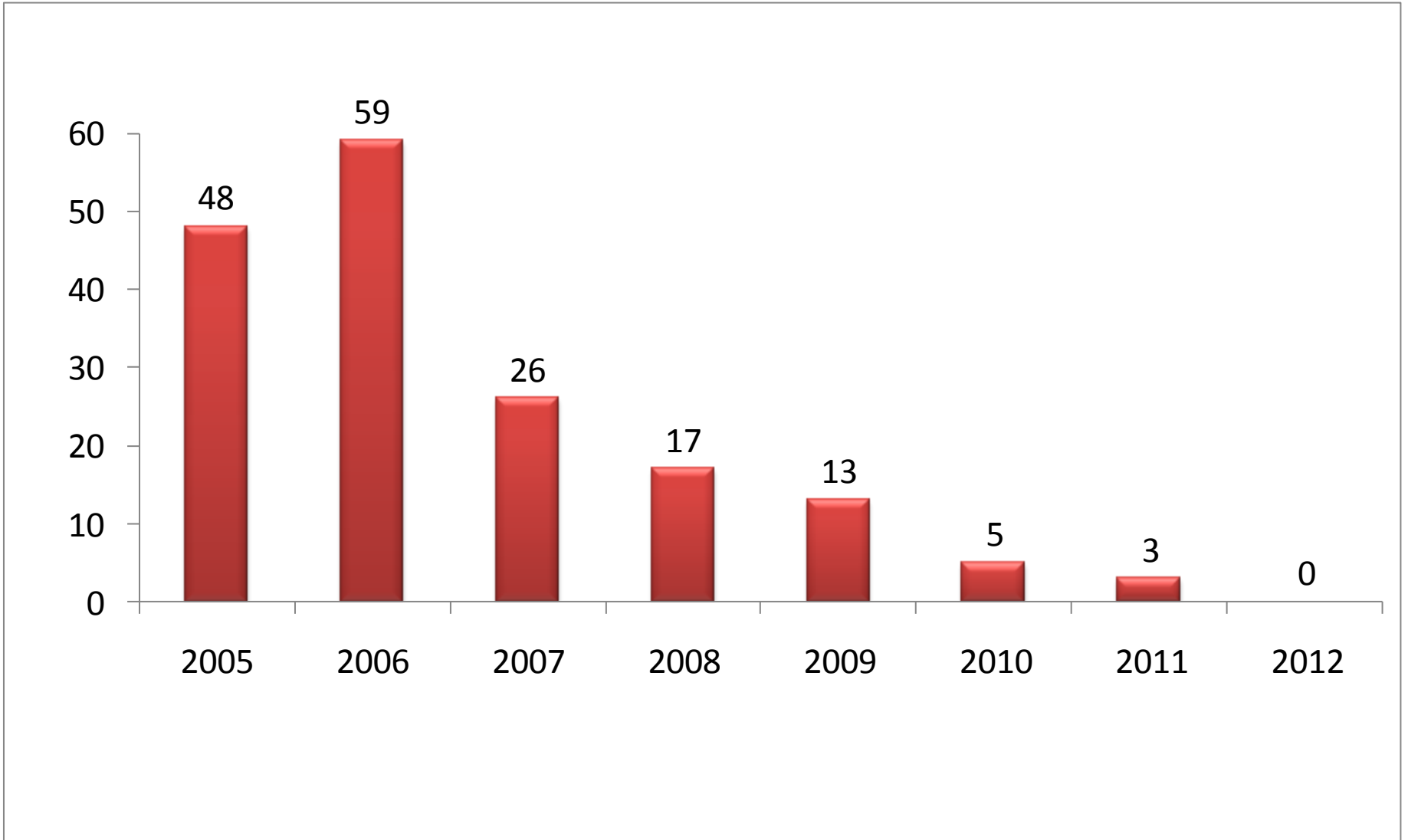
Treated malaria cases by type of service provider (2001 - 2012)



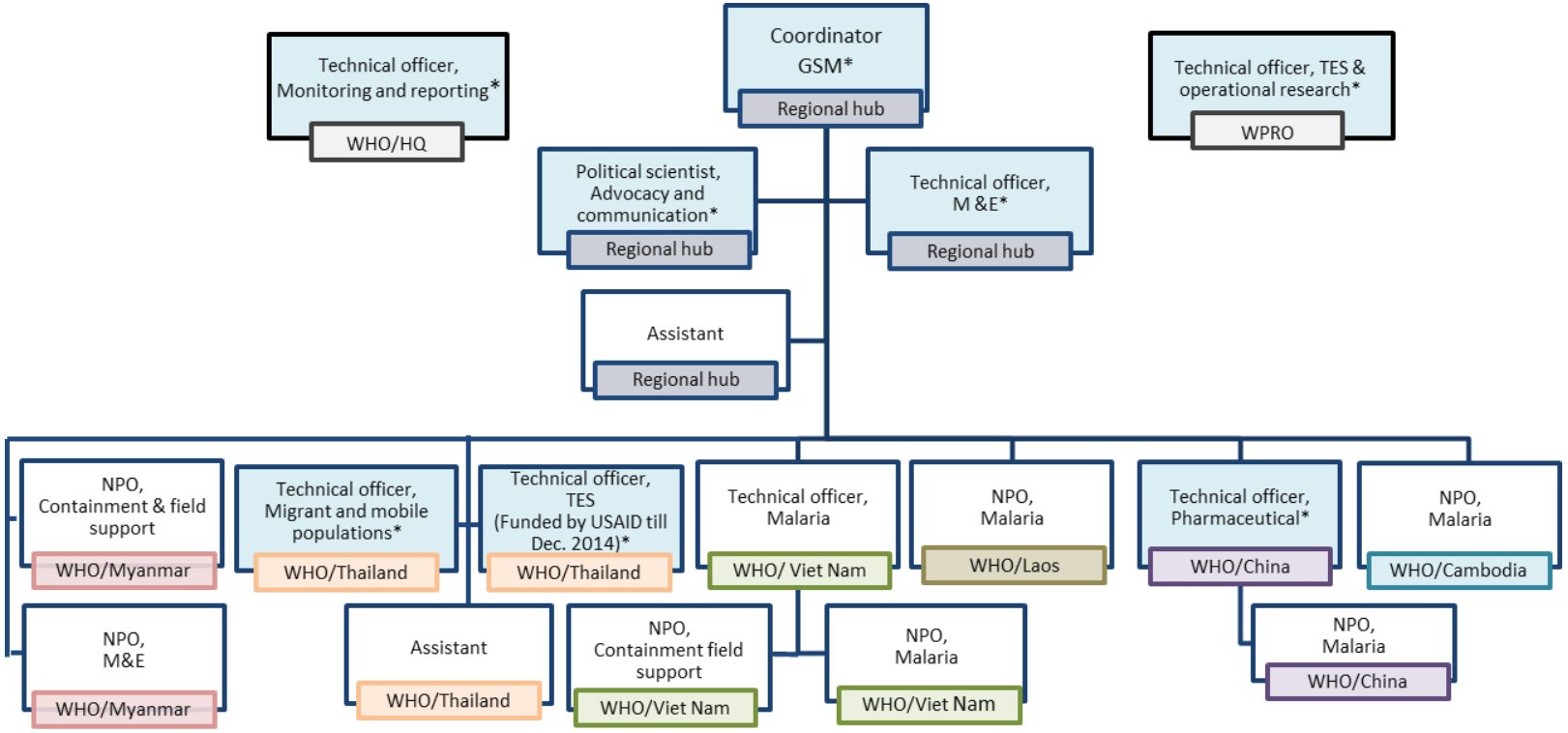
Malaria inpatients & CFR (Shwe Kyin Township) (2001 - 2012)

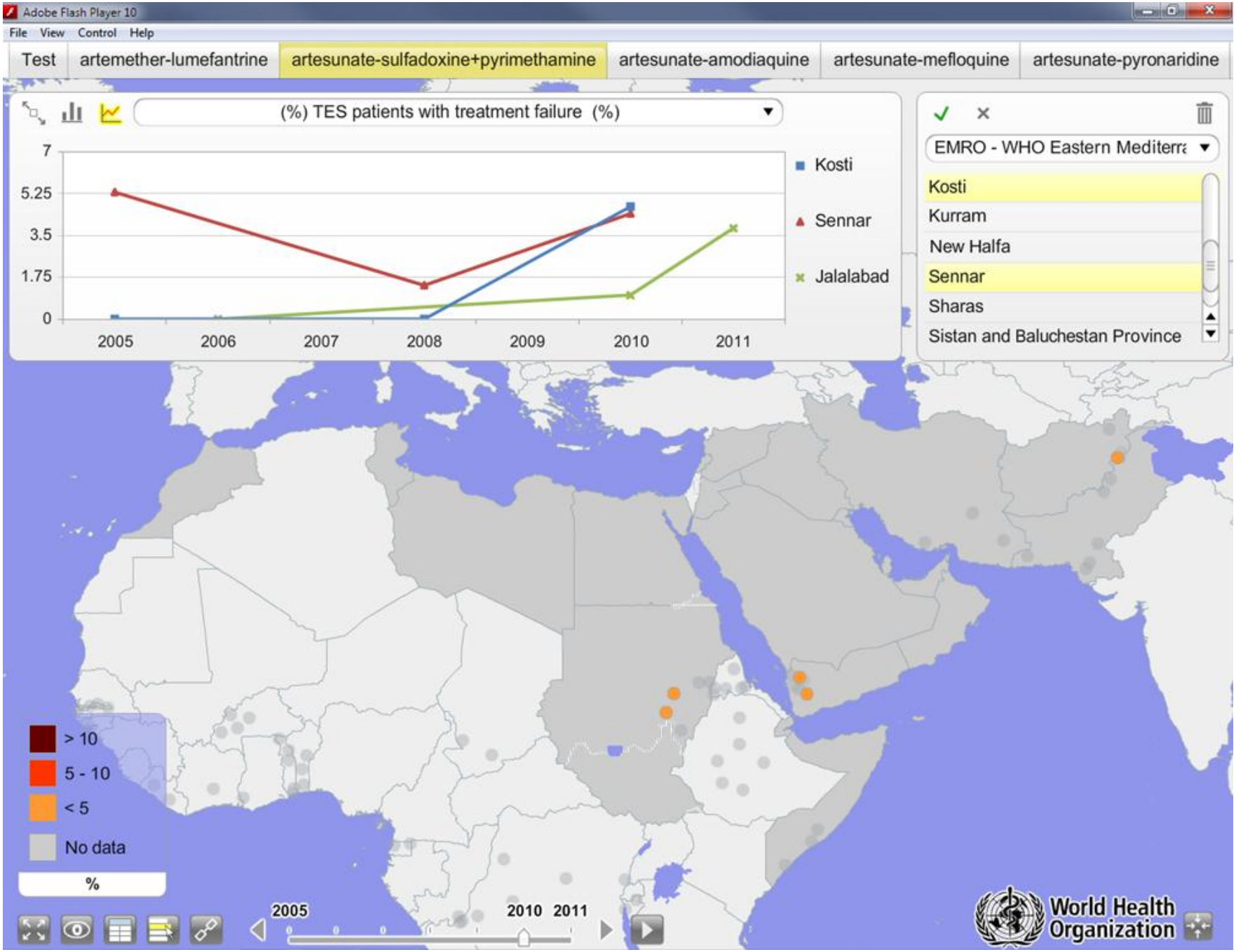


Cerebral malaria cases (Shwe Kyin Township) (2005 - 2012)



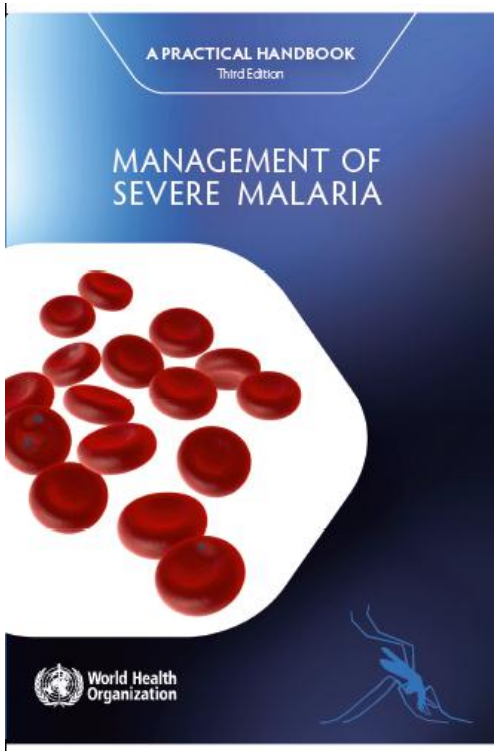
Structure of Emergency Response to Artemisinin Resistance (ERAR)



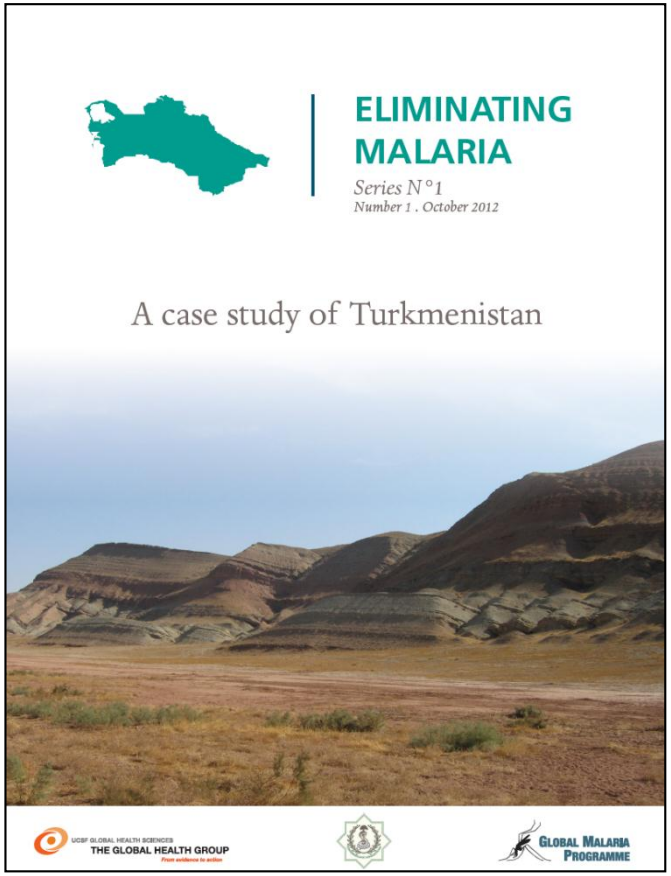

Adobe Flash Player 10
File View Control Help
Test
artemether-lumefantrine
artesunate-sulfadoxine+pyrimethamine
artesunate-amodiaquine
artesunate-mefloquine
artesunate-pyronaridine
(%) TES patients with treatment failure (%)
7
5.25
3.5
1.75
0
2005
2006
2007
2008
2009
2010
2011
Kosti
Sennar
Jalalabad
EMRO - WHO Eastern Mediterra
Kosti
Kurram
New Halfa
Sennar
Sharas
Sistan and Baluchestan Province
> 10
5 - 10
< 5
No data
%
2005
2010
2011
World Health Organization

Management of Severe Malaria

- Third edition of the Practical Handbook for the *Management of Severe Malaria* published in November 2012
  - Incorporates the current updates and knowledge in the practical management of severe malaria
  - Support (financial and human) received from RBM Case Management Working Group and MMV



Elimination case studies



- 10 case studies being produced jointly with Global Health Group
- Four launched in October 2012 : Cape Verde, Sri Lanka, Turkmenistan, Mauritius
- Six to be launched this year:Turkey, Philippines, Malaysia, La Reunion, Tunisia, Bhutan
- 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

2013 World Health Assembly process

- In January 2013, WHO Executive Board considered progress report on resolution WHA 64.17 on malaria
- US delegation, supported by other delegations, called for report to be elevated to a stand-alone technical item at 66th WHA and an update on the response to emerging artemisinin resistance
- WHO has prepared 2400-word report on malaria reviewing recent progress and key challenges; listing latest guidance; and discussing role of MPAC and need for the global technical strategy 2016-2025
- Currently considering ways to build on political momentum at WHA on malaria. Launch of Situation Room is one option
- During WHA, cluster will organize technical briefing on Global Fund new funding model (all three diseases)

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

The New Funding Model

Key features and implementation

V8 – 6 March 2013

1 Key features

The new funding model changes the way applicants apply for funding, get approval of their proposals and then manage their grants

Predictable funding	• Applicants are given an indicative funding range over a 3-year period • The Secretariat will hold indicative amounts for applicants until they apply
Timing of requests	• Applicants apply for funding when they want • Applicants can submit different disease or HCSS requests at different times • Applicants can use in-country planning cycles
Length of grants	• Three years
Early feedback	• Applicants submit a funding request through a “Concept Note” • Early feedback from the Secretariat and the TRP = higher success rate
Incentive funding	• Competitive funding in addition to indicative range • Rewards high impact, well-performing programs • Encourages full expression of demand
Grant-making	• Upfront risk and capacity assessments • Differentiated processes to ensure disbursement-ready grants • Funding requests negotiated <u>before</u> Board approval

1 How does the new model differ from the previous model?

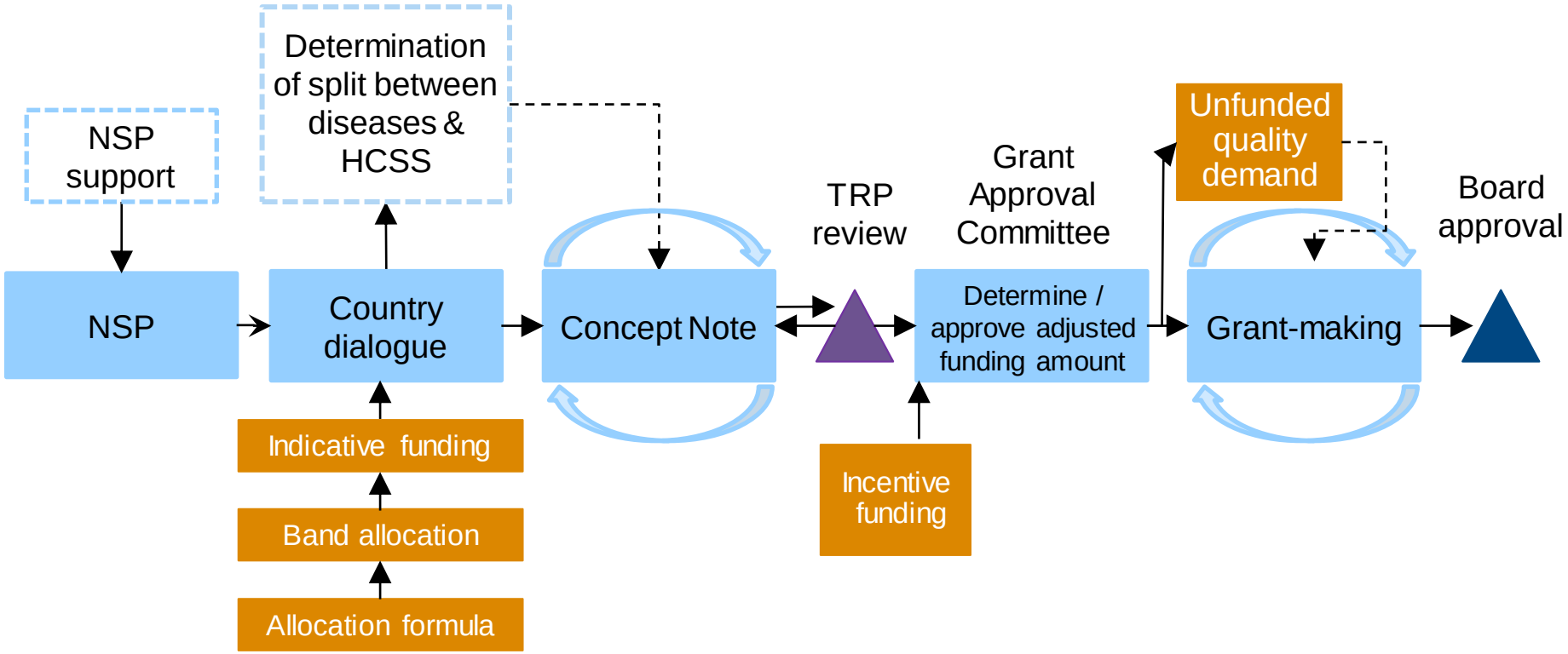
From previous model

- Passive role by the Secretariat in influencing investments
- Timelines largely defined by the Global Fund
- Hands-off Secretariat role prior to Board approval
- Low predictability: timing of Rounds, success rates and available funds
- Cumbersome undifferentiated process to grant signing with different delays

To new funding model

- More **active portfolio management** to optimize impact
- Timelines largely defined by each country
- Ongoing engagement by Secretariat
- **High predictability:** timing, success rates, indicative funding range
- **Disbursement-ready grants** with differentiated approach

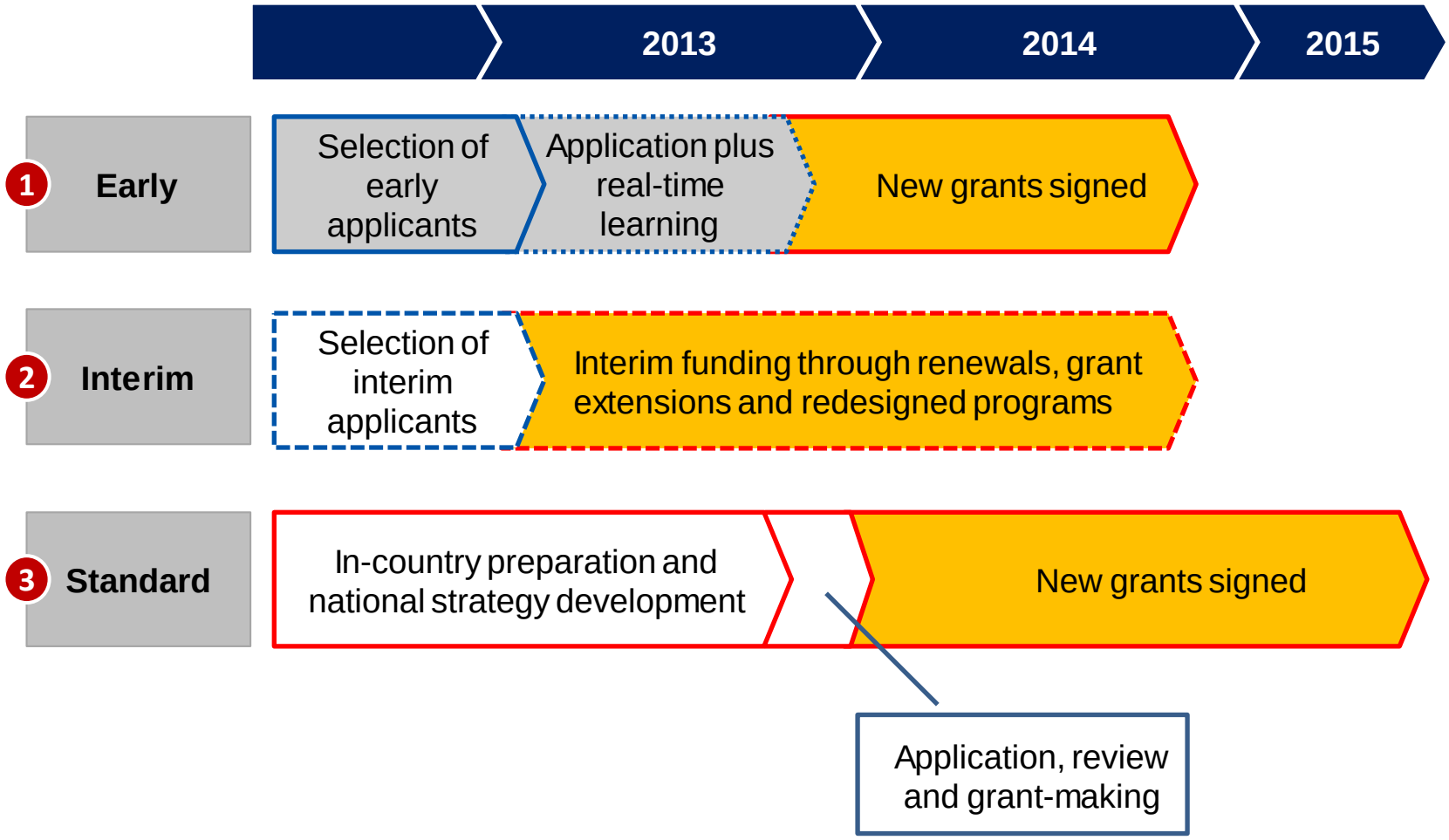
1 Overview of the new funding model



2 In new funding model, disease programs will fall into one of three categories

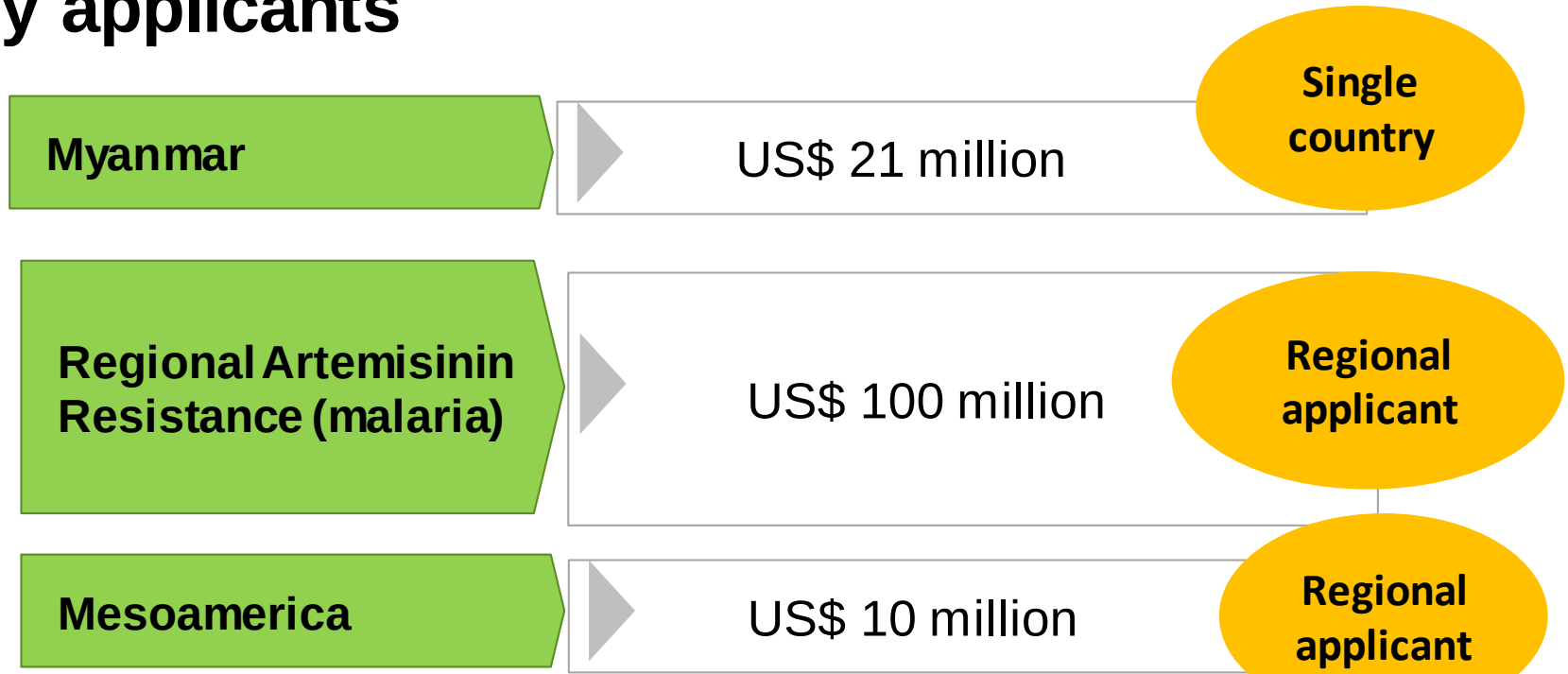
	How they receive funding	What they do
1 **Early applicants**	**New grant:** eligible for indicative and incentive funding	**All steps of the new funding model process** – country dialogue, submitting a concept note, TRP review, rant making
2 **Interim applicants**	**Renewals and extensions of existing grants, and redesigns to access funding in 2013**	Country dialogue
3 **Standard applicants**	**Prepare for applications to be submitted in late 2013 or in 2014**	Country dialogue

GF New funding model: current status &timelines



Which are the countries involved? – Malaria

Early applicants



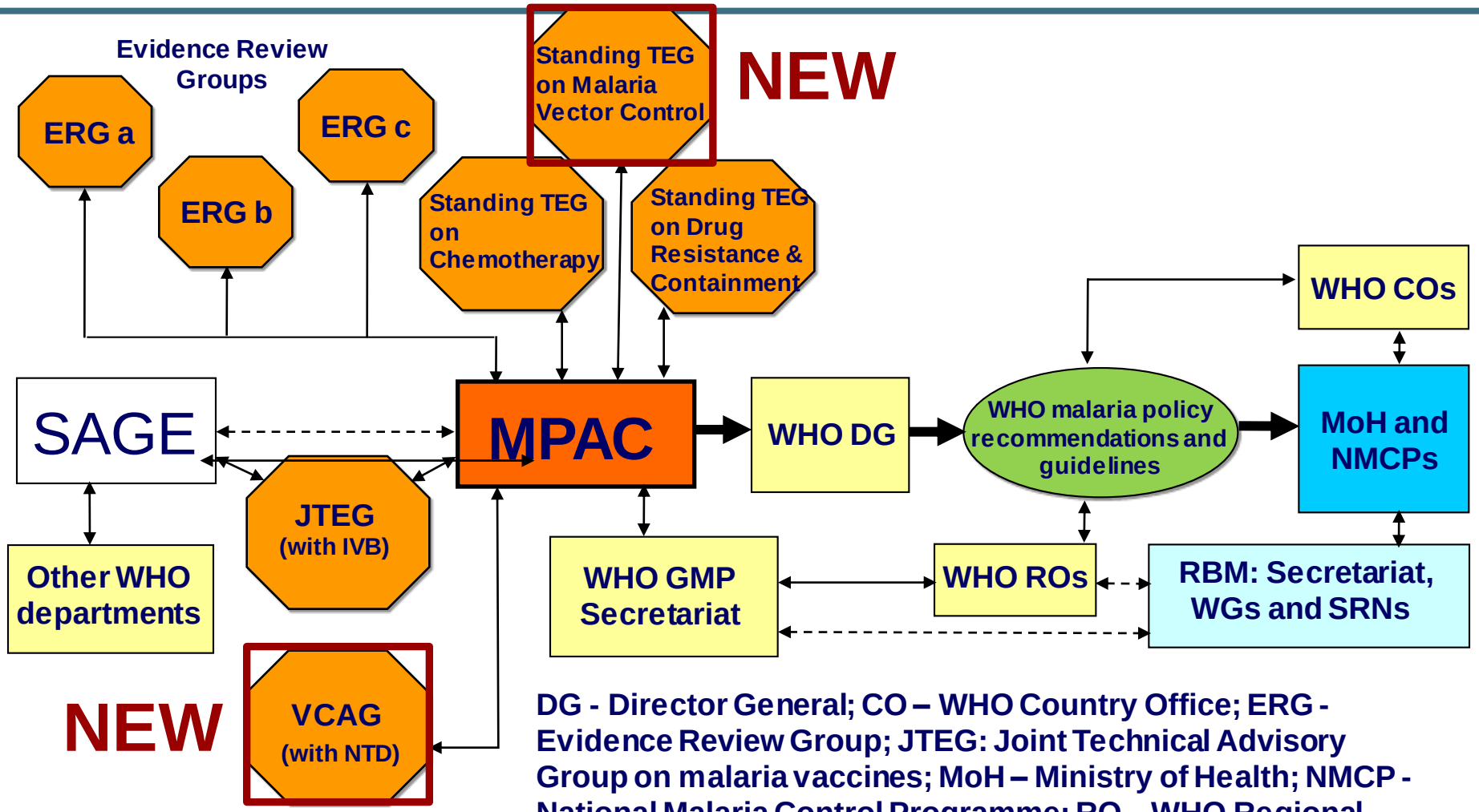
Interim applicants

3 Countries at risk of interruption of essential services or activities

Essential services or activities	For the purposes of the transition to the NFM, is defined using the same approach the Secretariat developed with the Transitional Funding Mechanism (TFM) in 2011 and 2012
Timelines	For the period of 2013 to the end of Q3 2014
LLIN replacement	For the transition to the NFM, the Global Fund will cover LLIN replacement costs if the last distribution was Global Fund financed, within the limits of funding available and other service interruptions for malaria

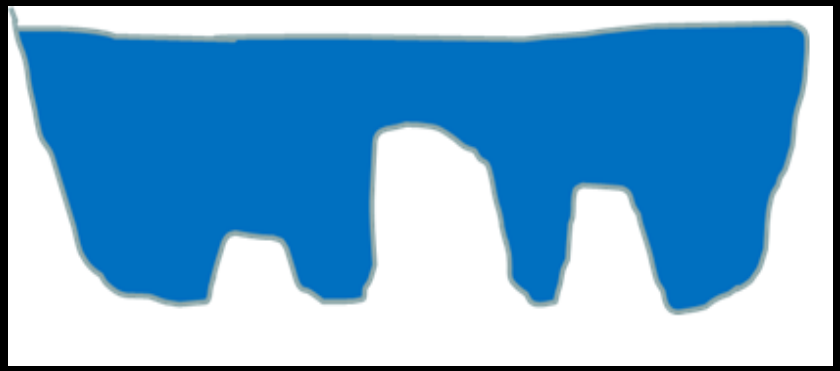
"Funding that prevents service-disruption by providing up to two years of funding to continue, at the same scope and scale, essential prevention, treatment and/or care programs currently financed by the Global Fund that face an imminent disruption if the CCM can demonstrate it cannot reprogram existing grants or identify alternative sources of funding (domestic or from other donors)."

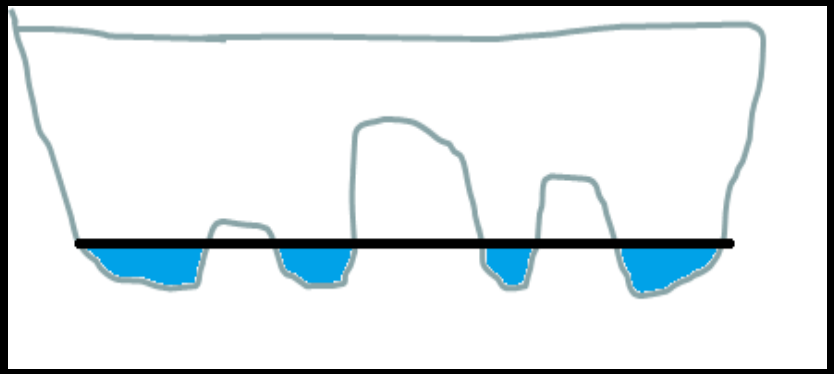
MPAC: organogram – March 2013



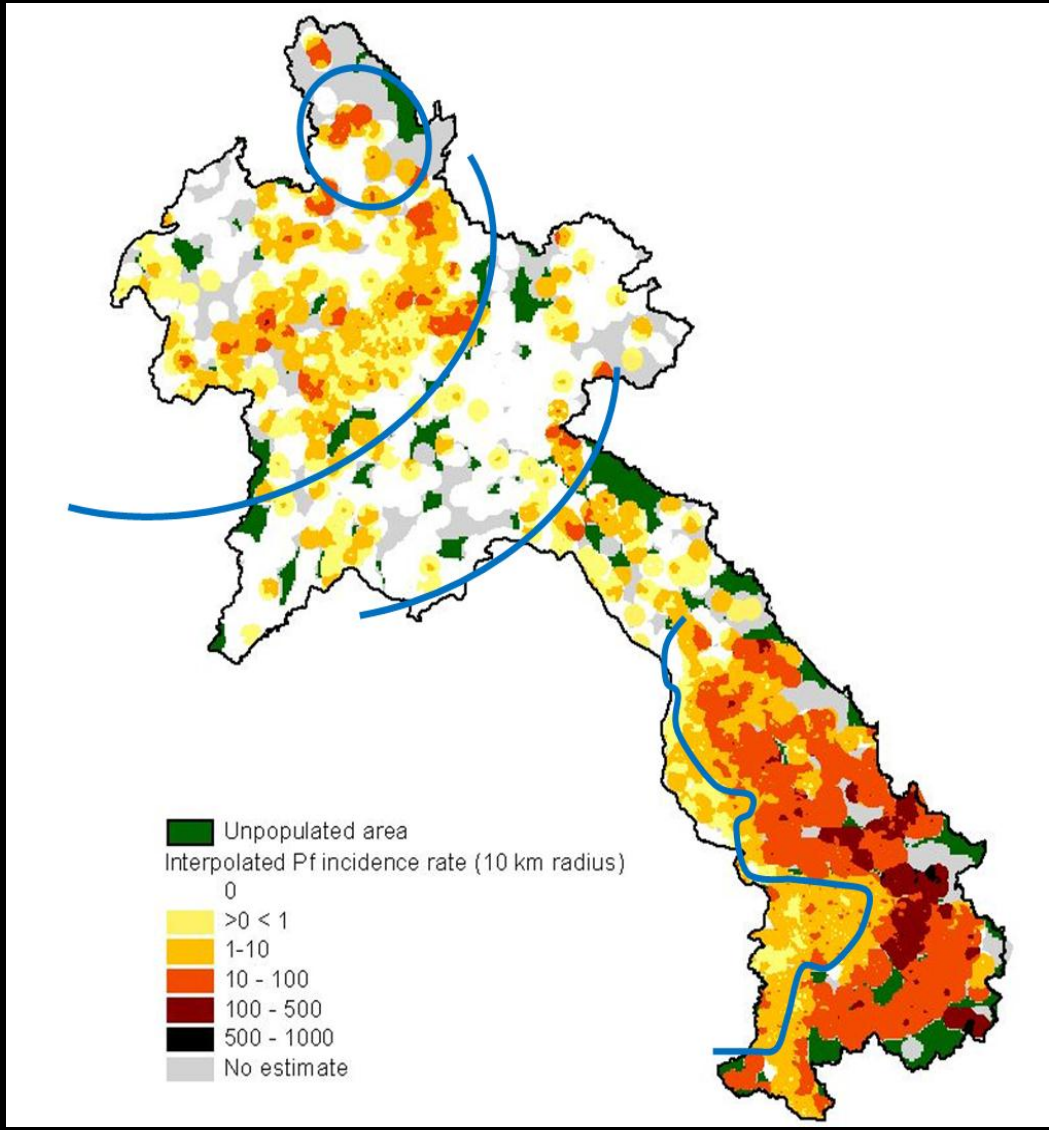
DG - Director General; CO – WHO Country Office; ERG - Evidence Review Group; JTEG: Joint Technical Advisory Group on malaria vaccines; MoH – Ministry of Health; NMCP - National Malaria Control Programme; RO – WHO Regional Office; SAGE – Strategic Advisory Group of Experts (on immunization); SRN – Sub-Regional Network; TEG – Technical Expert Group; VCAG – Vector Control Advisory Group on new tools; WG – Working Group

Reducing malaria transmission: like draining a pond





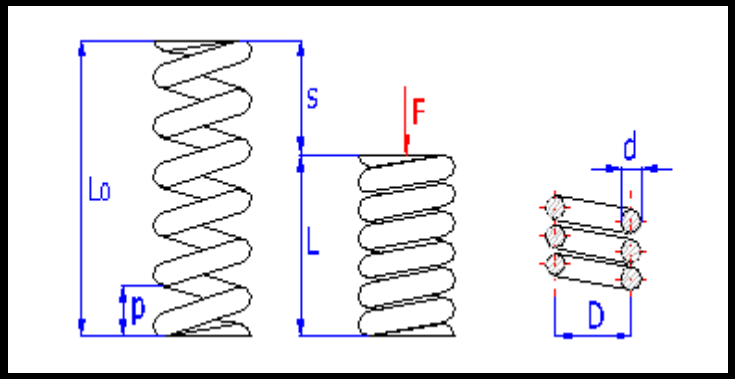
Malaria Stratification: Lao PDR



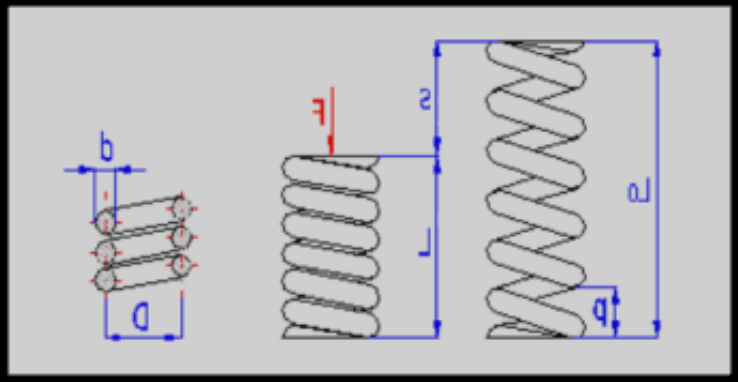
Courtesy: D. Gopinath

Why durable development matters for the future of malaria control & elimination

Investment ► Control



Dis-investment ► Resurgence



The greatest threat to continued success in malaria control and elimination is financial rather than biological

Status of the efficacy of artemisinin-based combination therapy (ACT) in Guyana and Suriname

Summary

Preliminary results from therapeutic efficacy studies in Suriname and Guyana are raising concerns that artemisinin resistance may be emerging in South America. The suspected resistance has been found in areas with a high number of migrants. Although many countries in South America have managed to dramatically reduce the number of malaria cases, the findings highlight the importance of all endemic countries conducting routine monitoring of therapeutic efficacy of antimalarial drugs. During a meeting held in Washington on 21 February 2013, representatives from Suriname and Guyana and malaria control partners agreed that confirmatory studies should be conducted in the two countries as soon as possible. Additional activities needed to contain artemisinin resistance in the region are currently under discussion.

Antimalarial efficacy surveillance in South America

Since 2001, USAID, in collaboration with the Pan-American Health Organization (PAHO), the World Health Organization (WHO), the US Centers for Disease Control & Prevention (CDC) and other partners, have supported the development and work of the Amazon Network for Surveillance of Antimalarial Drug Resistance (RAVREDA)[1], through the Amazon Malaria Initiative (AMI). Efficacy studies undertaken with support from AMI/RAVREDA in the Amazon Basin from 2001 confirmed *Plasmodium falciparum* resistance to the standard treatments (chloroquine and sulfadoxine-pyrimethamine). These results were used in guiding changes in treatment policy. By 2008, all countries in the Amazon basin were using the WHO-recommended artemisinin-based combination therapy (ACT).

In the Americas, the malaria burden has decreased by over 50% in the past decade. *P. falciparum* accounts for approximately 25% of all cases in the region. The relatively few number of cases means that undertaking therapeutic efficacy studies of antimalarial drugs, especially for *P. falciparum,* has become logistically difficult and/or unfeasible in some settings.

Molecular markers of resistance to artemisinin have not yet been identified. Instead, the measurement of parasite clearance on day 3 after treatment with an ACT is the current method used to initially detect reduced sensitivity to the artemisinin component.

Resistance to artemisinin was first reported from the Cambodia-Thailand border in 2008, catalyzing the need for a Global Plan for Artemisinin Resistance Containment (GPARC), whose development was

[1] The Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA) consists of: Brazil, Colombia, Ecuador, Guyana, Plurinational State of Bolivia, Peru, Suriname, and the Bolivarian Republic of Venezuela.

coordinated by the WHO Global Malaria Programme, in consultation with members of the constituencies of the Roll Back Malaria Partnership, and published in 2011. The GPARC calls for all endemic countries to monitor antimalarial efficacy at least once every 24 months in 4 to 6 sentinel sites. These studies include measurement of the proportion of patients positive on day 3 after treatment with an ACT.

At an AMI/RAVREDA meeting in Bogota, Colombia in September 2012, all countries using ACTs were again urged to establish sentinel sites to routinely monitor ACT efficacy including monitoring of day 3 parasitemia among treated patients. Experience from Thailand and Cambodia suggested that when more than 10% of patients have detectable parasites on day 3, confirmatory studies with artesunate monotherapy should be conducted.

A limited number of countries in South America have undertaken periodic studies to monitor the efficacy of ACTs since their introduction as a first-line treatment for *P. falciparum* malaria. Results have shown that ACTs continue to be efficacious in the Amazon basin. The studies include measurements of day 3 parasite densities after treatment with an ACT. The preliminary results from Suriname and Guyana described below reinforce the need for conducting therapeutic efficacy studies in all countries in the region. The findings reflect the importance of AMI/RAVREDA's support to efforts at monitoring and combating malaria in the Americas, and must lead to further investigations.

Country data

Suriname

In 2004, Suriname changed its first line treatment for *P. falciparum* malaria to an artemisinin-based combination therapy (ACT), artemether-lumefantrine. This, and the distribution of long-lasting insecticidal nets, indoor residual spraying, active case detection and an improved surveillance system, resulted in a more than 90 percent decrease in malaria cases. Currently, malaria cases are mainly seen among gold miners in the interior of the country.

An efficacy study for artemether-lumefantrine was conducted between July 2005 and September 2006. The incidence of day 3 parasitaemia was 2.2%, with 95.3% of cases with a negative slide on day 28 (data not PCR corrected). A second study was undertaken to assess artemether-lumefantrine efficacy in patients with *P. falciparum* malaria, in the capital city of Paramaribo in April – November 2011[2]. The treatment was directly observed; patients were followed daily until parasite clearance plus one day and then on day 7, 14, 21 and 28. Of the 67 patients enrolled, 9 were withdrawn because of protocol violations. Among the remaining 58 patients, 5 were lost to follow up before parasite clearance. Only 11 patients were followed for the full 28-day period, none of whom had recurrent parasitaemia. Among the

[2] Jitan K.J et al., Emerging Coartem resistance assessed by day 3 parasitemia in Suriname. *Am J Trop Med Hyg.* 2012 Nov. 87 (Suppl. 5): 244.

53 patients that were followed at least until parasite clearance, 15 (28.8%) still had parasites on day 3. Of the 11 patients followed until day 28, only 1 had a positive slide on day 3, which became negative on day 4. All 11 patients presented with adequate clinical and parasitological response (ACPR).

All day-3 slides were reviewed by an independent microscopist outside of Suriname, who found that 16.2% rather than 28.8% of the day-3 slides were positive. Due to the many discrepancies between the two readings, a more conservative approach is to report the proportion of slides read as positive by both microscopists, which is 10.8%.

The independent slide review furthermore led to the reclassification of one patient as ACPR. The patient had previously been classified as early treatment failure (ETF) based on a higher parasitaemia on day 2 than on day 0. The independent microscopist detected 6300 parasites/μl on day 0, instead of the 350/μl reported by the first microscopist.

Guyana

Guyana adopted artemether-lumefantrine as a first-line treatment for uncomplicated falciparum malaria in 2006. Similar to Suriname, malaria is mostly found in the interior regions. Over 90% of the malaria cases diagnosed in Guyana originate from regions where migrant populations (miners, loggers) and indigenous groups are the most affected.

Preliminary results from a study conducted in Georgetown, Guyana, from May 2011 to August 2012, also suggest a high day-3 positivity rate. Artemether-lumefantrine was given as directly observed treatment and patients were followed daily until day 3 and then on day 7, 14, 21 and 28. A total of 92 patients were included. Data before quality control showed 63/89 (70.1%) of patients were still positive at day 3. Of the 68 patients followed-up until day 28, 7 (10.3%) were still parasitemic, and were classified as treatment failure (note: these data have not been PCR corrected). Day-3 slides were double-checked at CDC Atlanta, which reported that 7/89 (7.9%) patients were confirmed to be positive at day 3. However, it should be noted that very low parasitaemia was detected. Most of these parasites were noted to be disintegrating, and therefore not likely to have been living at the time of sampling. Only 3 patients remained classified as treatment failure after microscopy quality control. One patient was classified as recrudescence after PCR correction whereas for the other patients, no amplification of DNA was possible from the filter papers collected during the trials. The treatment failure with artemether-lumefantrine was therefore 1.6%.

Neighboring countries

In Brazil, two therapeutic efficacy studies and three simplified studies, i.e. the follow-up of patients over 3 days without supervised treatment and with parasite count at day 0 and day 3 only, were conducted in 2010 and 2011. Only one case was reported to be positive at day 3, a patient in Manaus, who came from the mining area bordering Suriname.

French Guyana is currently compiling the data and is expected to share with PAHO and WHO soon.

Review of the literature

The Global Malaria Programme database, containing published and unpublished data on antimalarial drug efficacy from 2000 to 2012 was reviewed, and moderate day 3 positivity rates were reported in two studies:

Bolivia

In 2001, the day-3 positivity rate after treatment with artesunate-mefloquine was as high as 8.5%. No treatment failures were reported[3]. No other studies have been conducted since 2001.

Peru

In 2000, the day-3 positivity rate after treatment with artesunate-sulfadoxine-pyrimethamine was 2.2%[4]. All the other published studies with ACTs since 2001 did not report any day 3 positive cases.

Informal consultation on the emergence of artemisinin resistance in South America, held in Washington, 21 February 2013.

A meeting was held to review the most recent data from Suriname and Guyana as described above. Representatives attended from the Ministries of Health of Guyana and Suriname, as well as from CDC, USAID, WHO PAHO and WHO Headquarters, and the chair of DRC TEG. There was a consensus that artemisinin resistance is now suspected in both Guyana and Suriname. Given the most recent quality control of microscopy, which confirmed reduced parasite clearance on day 3, participants agreed that activities to contain artemsinin resistance, as outlined in the GPARC, should now be initiated.

It was proposed that confirmatory studies be conducted in Suriname and Guyana. It was suggested that in Suriname, the study be conducted with artesunate for three days followed by mefloquine for two days. In Guyana, it was suggested to study 1) artesunate for seven days, or 2) artesunate for three days followed by an ACT. Funding for the studies in Guyana and Suriname may be available from WHO/GMP, with an estimated budget of $100,000 USD for each country. Medicines will be provided by WHO/GMP. Clinical monitoring of all study procedures and quality control of microscopy will be available to ensure studies of extremely high quality. Blood samples taken during the studies should be made available to the Sanger Institute at Oxford University for molecular analysis. Draft protocols and a budget outline will be developed and shared by with participants of the meeting.

[3] Avila JC et al. Efficacy of mefloquine and mefloquine-artesunate for the treatment of uncomplicated *Plasmodium falciparum* malaria in the Amazon region of Bolivia. *Trop Med Int Health.* 2004 Feb;9(2):217-21.

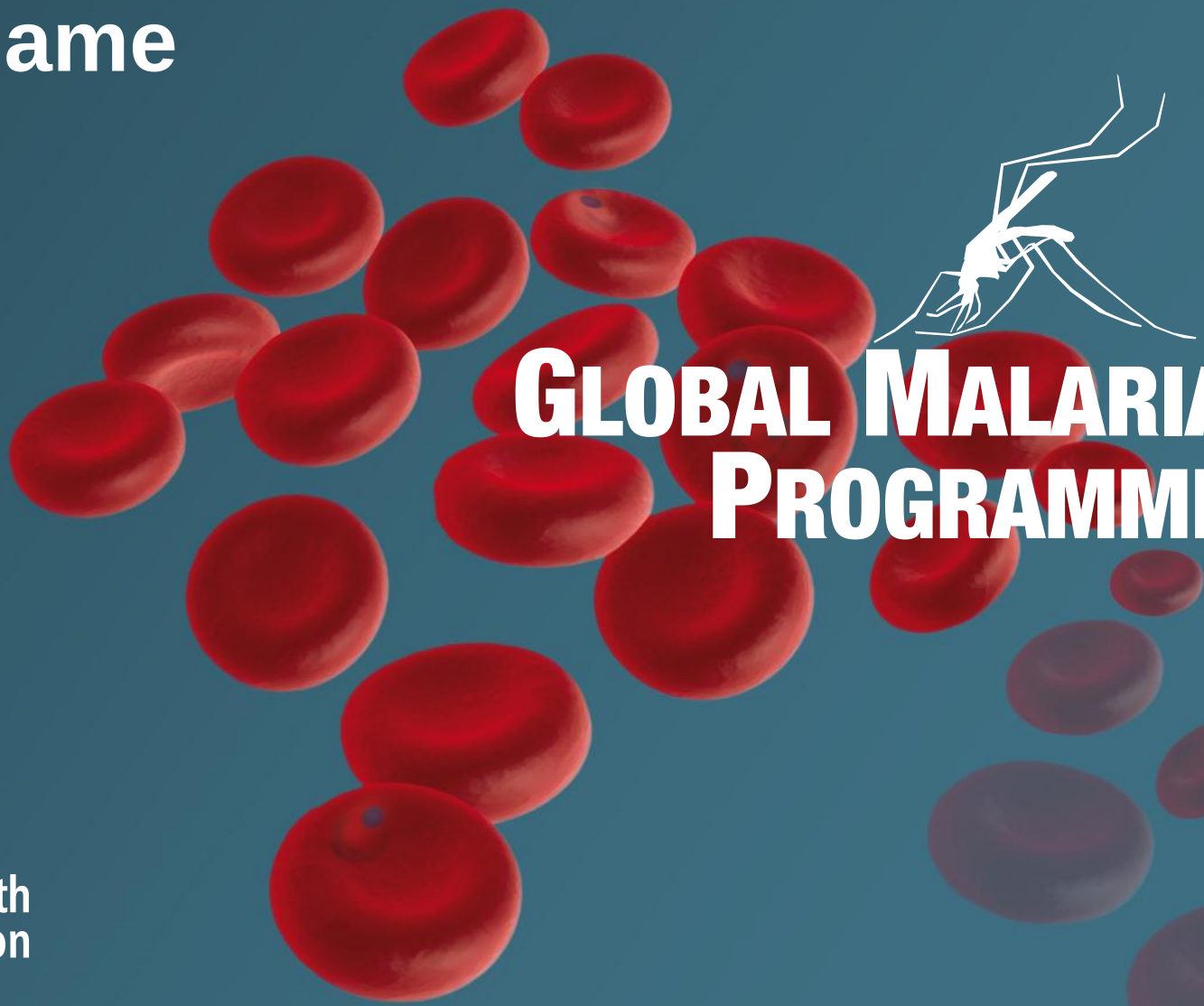
[4] Marquino W et al. Efficacy and tolerability of artesunate plus sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine alone for the treatment of uncomplicated Plasmodium falciparum malaria in Peru. *Am J Trop Med Hyg*. 2005 May;72(5):568-72.

A communications plan will be developed to ensure clear and consistent messages on the current situation. It was agreed that communication of messages would be managed by PAHO and AMI/RAVREDA in close consultation with WHO. A formal announcement of the findings will soon be issued by the PAHO office. Various stakeholders, including neighboring countries, donors and technical partners, should be aware of the data and its implications.

During the next AMI/RAVREDA meeting (8-11 April 2013), countries will discuss the findings and determine the most appropriate plans of action. Guyana is currently applying for Phase 2 of the Global Fund Single Stream Funding and will modify the objectives of the grant to align with GPARC recommendations. Suriname, which reports around 500 cases per year, will develop an elimination plan. However, these actions will only be effective with the commitment of the neighboring countries. In particular, there needs to be active engagement with French Guiana, who is currently not a member of AMI/RAVREDA. Therefore a “Guyana shield meeting” is planned in Suriname during the second half of 2013 which will provide an opportunity for French Guiana to be involved in the development of the action plan. Priorities for the other countries in the region will be to strengthen drug efficacy monitoring and improve national capacity in microscopy. All neighboring malaria endemic countries should conduct therapeutic efficacy studies of their first and second-line treatments.

Artemisinin-based combination therapy (ACT) efficacy in Guyana and Suriname

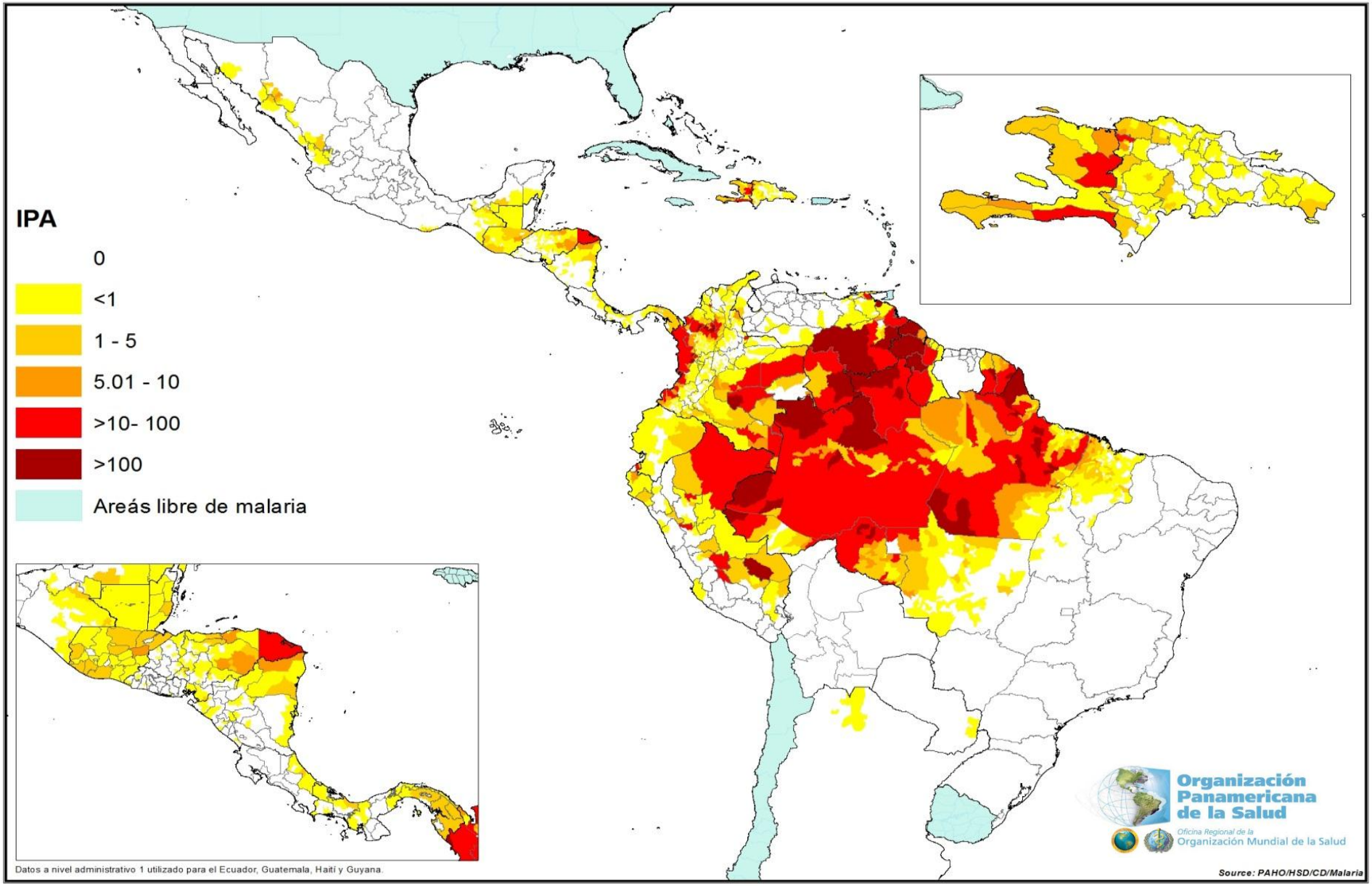
K. Carter
A. Dondorp
P. Ringwald



GLOBAL MALARIA PROGRAMME

World Health Organization

Malaria Distribution in the Americas, 2011



Technical & financial collaboration

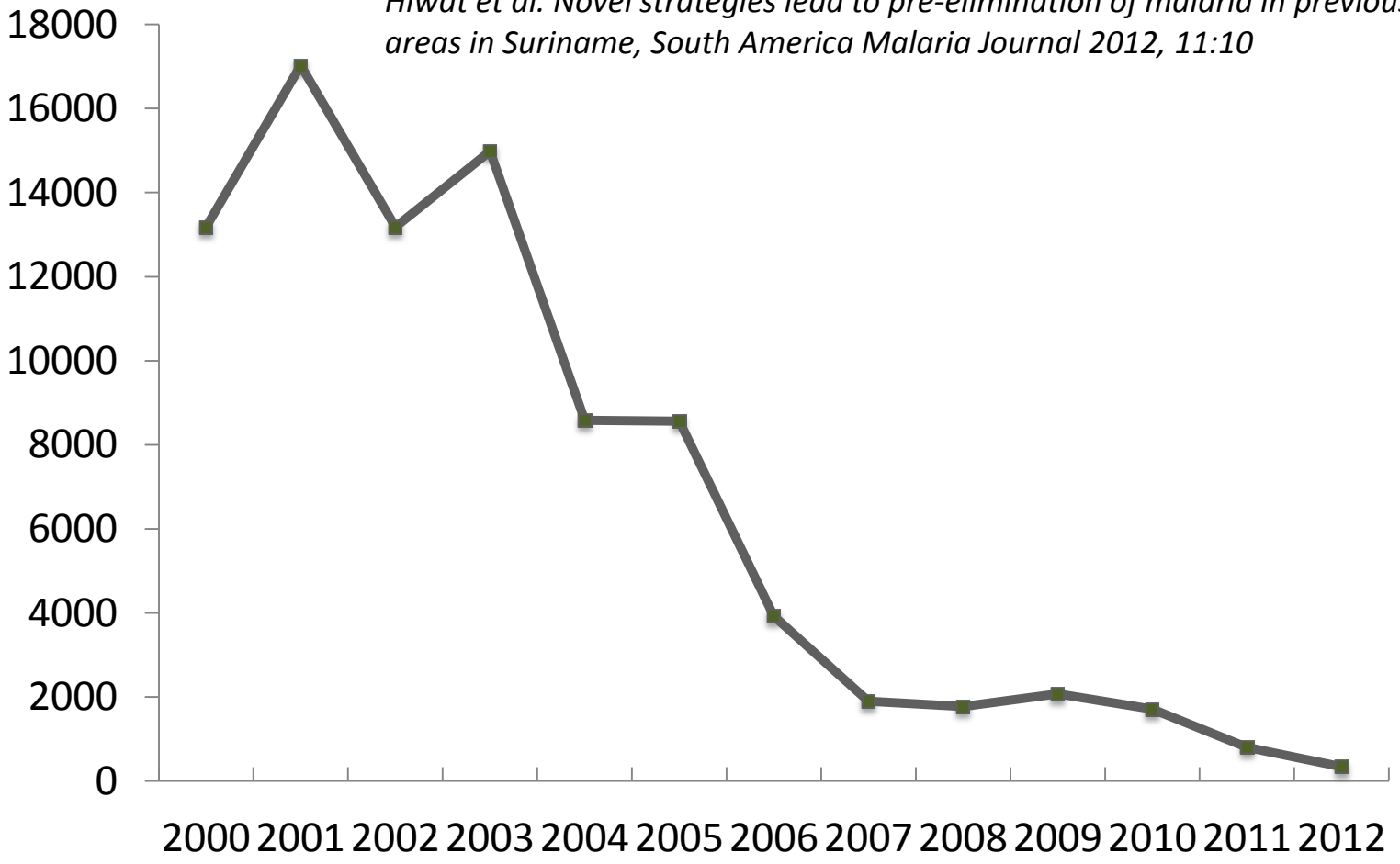
- Amazon Malaria Initiative (AMI) and the Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA), 2001
- Global Fund to combat HIV, Tuberculosis and Malaria

AMI/RAVREDA ines of Intervention:

- **Improve access to good quality diagnosis for malaria patients**
- **Monitor the efficacy of and resistance to anti-malarials**
- **Improve quality assurance and control of pharmaceuticals and other supplies for malaria prevention and control**
- **Improve epidemiological surveillance**
- **Improve vector surveillance and integrated vector management**
- **Improve, sustained networking at the regional level and system strengthening at country level**
- **Significant contribution in control efforts but persistent gaps in terms of malaria elimination and prevention of reintroduction**

Malaria cases Suriname 2000-2012

Suriname Bureau of Public Health nov 2012
Hiwat et al. Novel strategies lead to pre-elimination of malaria in previously high-risk areas in Suriname, South America Malaria Journal 2012, 11:10



Surveillance of artemether-lumefantrine efficacy in Suriname in 2011

- Number of cases in resident population too low for regular surveillance of efficacy
- Gold miners not available for frequent sampling
- Patients mainly recruited from the gold miners malaria facility in Paramaribo (Tourtonne-lab)
- Follow up for as long as patients were available (up to day 28)
- Comparison of day 3 results with surveillance data from 2005 - 2006

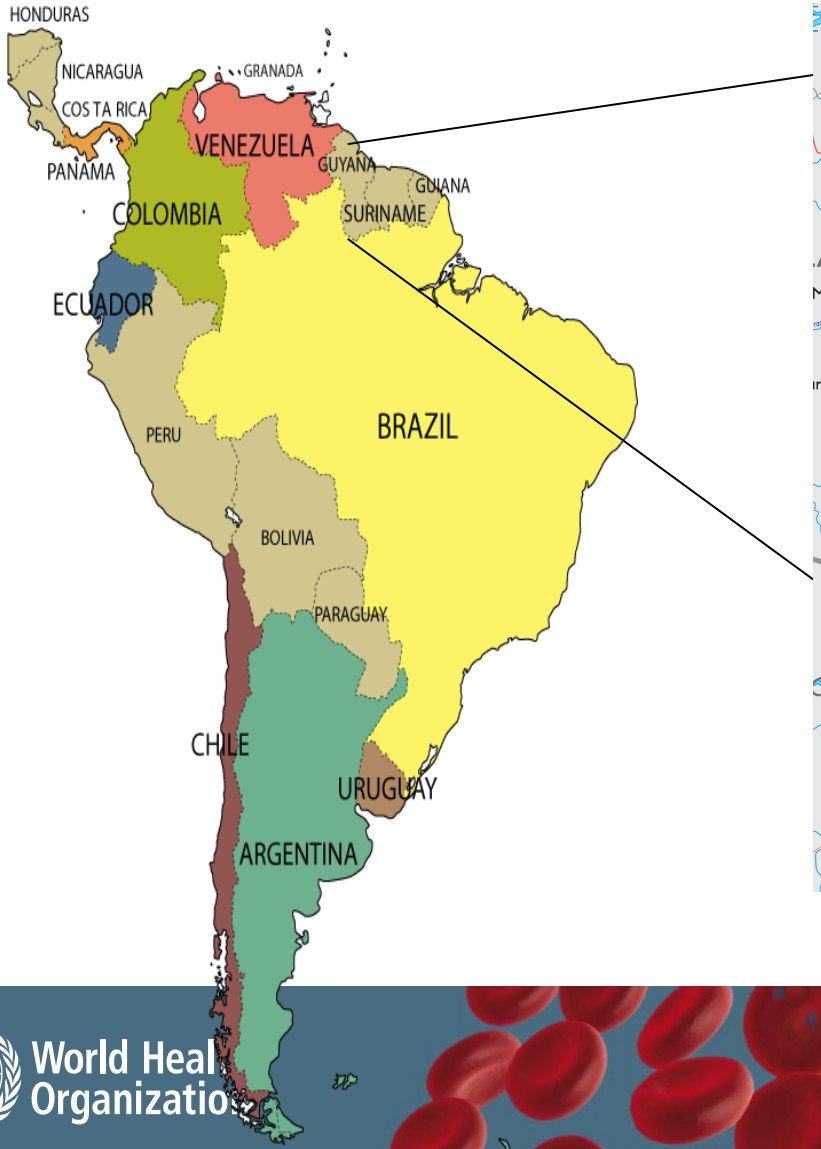
Surveillance of artemether-lumefantrine efficacy in Suriname in 2011

- **Study conducted from April - October 2011**
- **74 patients enrolled (M/F ratio 56/9; no children)**
- **Evaluable patients**
  - Until day 3: 52 cases
  - Until day 28: 11 cases
- **Results**
  - ACPR: 11/11 (100%)
  - Day 3 parasitemia: 15/52(28.8%) (in 2005 - 2006: 2%)

Assessment of quality of slide reading

- **Problems**
  - Follow up slides taken by insufficiently trained field workers
  - Slides were not prepared for long time storage (quality assessment was not foreseen)
  - 27/48 day 3 slides considered readable
  - Day 3 parasitemia: 16.2%
- **Results**
  - 3 slides read positive that were negative by initial reading
  - 3 slides negative that were positive by initial reading.
  - Day 3 parasitaemia somewhere between **10.8 and 28.8%**
- Remark: parasitaemia often at 1-2 parasites/500 WBC

Guyana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Santa Elena de Uairén
Normandia
Annai
Amotopo
Conceição do Maú
UPPER TAKUTU
UPPER ESSEQUIBO
Uraricoera
Lethem
BERBICE
CORENTINE
Boa Vista
Caracarai
Konashen

Malaria situation in Guyana

- Malaria has spread geographically to various regions, mainly focused in the hinterland Regions 1, 7 and 8
- In Guyana more than 200,000 people live in areas considered at high and medium risk for malaria
- In recent years an increase in the proportion of *P. falciparum* among the two predominant species was observed
- *P. falciparum* and mixed infections increased from 39% in 2007 to 69% in 2011

Monitoring the therapeutic efficacy of antimalarial drugs in Guyana

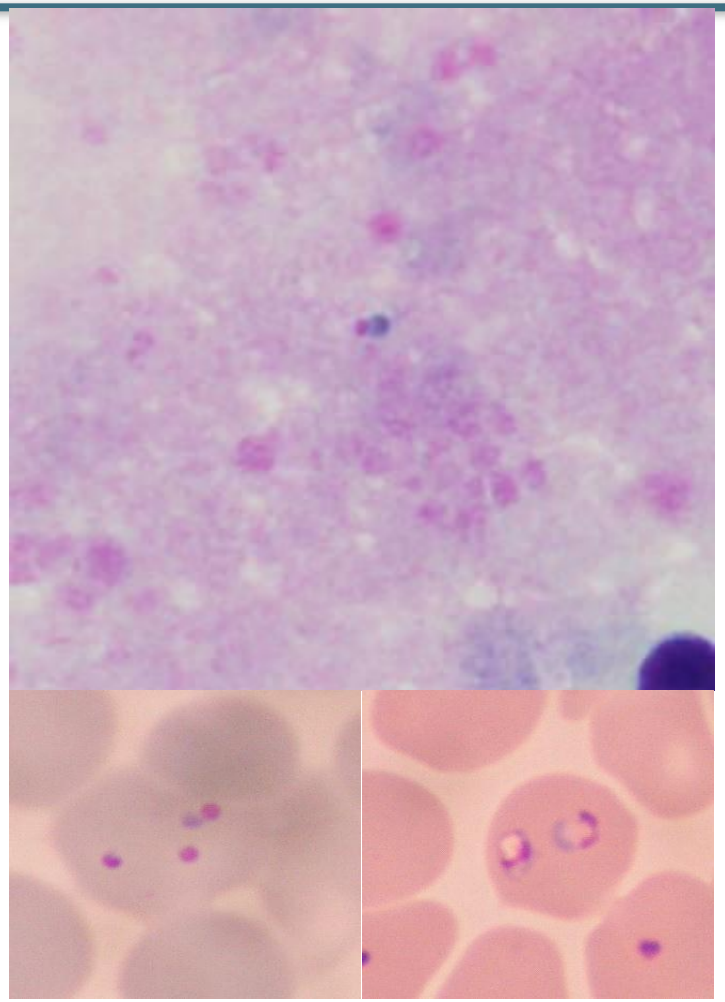
Artemether - Lumefantrine	(P.falciparum) 2004 - 2005
Artesunate - Mefloquine	(P.falciparum) 2004 -2005
Mefloquine	(P.falciparum) 2004 - 2005
Artemether - Lumefantrine	(P.falciparum) 2007- 2008
Artemether - Lumefantrine + Primaquine	(P.vivax) 2009-2010
Artemether-Lumefantrine	(P.falciparum) 2011- 2012

Surveillance of artemether-lumefantrine efficacy in Guyana 2011-2012

- **Malaria Clinic & Tropical Diseases Laboratory, Georgetown Public Hospital Corporation**
- **Study conducted from May 2011 - July 2012**
- **92 patients enrolled; 68 followed up for 28 days**
  - 87 % were adults
  - 64 % miners
  - 91% male
- **Results**
  - Treatment failures: 7/68 (10.3%) (day 7 - day 28)
  - Day 3 parasitemia: 63/89 (70.8%)

Slide reading by CDC

- **Day 3 review**
  - 7/82 (8.5%)
  - 1-2 parasites/1000 WBC
- **Day 28 review**
  - 3 slides read positive
  - 1 recrudescence (PCR); 2 PCR on-going



Malaria situation in Guyana

- Informal consultation on the emergence of artemisinin resistance in South America, held in Washington, 21 February 2013
  - Ministries of Health of Guyana and Suriname, as well as from CDC, USAID, WHO PAHO and WHO Headquarters, and the chair of DRC TEG
- There was a consensus that artemisinin resistance is now suspected in both Guyana and Suriname
- It was proposed that confirmatory studies be conducted in Suriname and Guyana
  - In Suriname artesunate for three days followed by mefloquine single dose
  - in Guyana, artesunate for seven days
- Containment activities
  - AMI/RAVREDA meeting (8-11 April)
  - Guyana shield meeting (10-11 October)
  - Guyana applying for phase 2 of Global Fund Single Stream Funding
- Communication

MPAC Meeting, 13-15 March 2013

Session 2

PAHO/WHO Statement

WHO Informal Consultation on fever management in peripheral health care settings: a global review of evidence and practice

Geneva, 22-24 January 2013

Briefing paper for the MPAC

by V. D'Acremont and A. Bosman, Global Malaria Programme, WHO

1. Background

With the increasing deployment of universal parasitological confirmation (RDTs) of suspected malaria prior to treatment, and the decreasing trend of malaria transmission in many endemic areas, an increasing proportion of febrile patients are being diagnosed as not having malaria.

Despite this, following many years' practice of treating fever as assumed malaria, health workers may ignore negative test results and still treat the patient with an antimalarial. This problem is made more difficult to resolve given the absence of guidance and medicines for the management of non-malaria febrile illnesses. This undermines the clinical benefits of parasitological confirmation of diagnosis, and aggravates the wastage of antimalarial drugs and drug pressure on parasites. In places where clinicians have been convinced not to prescribe antimalarials in RDT negative patients, limited guidance has resulted in over-prescription of antibiotics, another poor practice which will promote the emergence of antibiotic resistance, replacing one problem by another.

Over the recent years, clear algorithms for the management of fevers at community level have been developed for children under five, and are being promoted as "integrated community case management" (iCCM), with good implementation support tools. Other tools are available for peripheral health facilities for children under five years of age (Integrated Management of Childhood Illness - IMCI) and adolescents and adults (Integrated Management of Adolescent and Adult Illness - IMAI). To review the available evidence and current practices in the management of fevers in peripheral health care settings, the WHO Global Malaria Programme and the Special Programme for Research and Training in Tropical Diseases convened a WHO Informal Consultation in January 2013.

2. Purpose of the WHO Informal Consultation

The purpose of the meeting was to a) review existing evidence and guidance on the management of malaria and non-malaria fevers at primary care and community levels; b) provide practical recommendations and operational tools based on research findings and successful country experiences for the implementation of integrated management of fevers at peripheral health facility and community level; and c) to identify and discuss major research gaps.

The aims of improving management of fevers at peripheral level are:

a) to increase appropriate treatment and referral in order to
   - reduce severe diseases and deaths
   - reduce morbidity (length of febrile episode…)

b) to reduce unnecessary prescription of antibiotics and antimalarials in order to
   - reduce "drug pressure" and development of drug resistance
   - decrease the risk of drug adverse events
   - save money

The main conclusion and recommendations of the WHO Informal Consultation are reported in the sections below.

3. Review on etiologies and management of febrile illness

Emerging evidence on etiologies of fevers

Common and divergent research findings emerging from recent studies on etiologies of fevers:

Children <5 years:

- In four studies conducted in Dar es Salaam, Ifakara, Zanzibar and Karachi, 12%, 9%, 1% and 0.4% of fevers were due to malaria, 49%, 76%, 84% and 47% of fevers to Acute Respiratory Infections (ARI), and 9%, 12%, 14% and 23% to gastroenteritis (diarrhea) respectively. The remaining children had unspecific fevers without any clinical sign localised infection, except for 1% children with skin infection and very few with meningitis.
- Most (>90%) ARI were upper respiratory tract infections due to viruses (mainly influenza)
- Causes of unspecific fevers:
  - typhoid low in Tanzania (2-5%), high in Pakistan (17%)
  - urinary tract infection always low (1-6%)
  - occult bacteremia very low (2%)

Children ≥5 years and adults:

- Fevers are mainly associated with HIV: 40% of admitted febrile patients in Northern Tanzania were HIV positive while the prevalence in the community is only 3-4%
- 7%, 32% and 4% had malaria in Northern Tanzania, Cambodia and Laos respectively
- In adult outpatients in Cambodia, 80% of malaria-negative patients had upper respiratory infection (URI) and 0.6% lower respiratory tract infections.
- In studies conducted in Northern Tanzania, Cambodia and Laos, among non-malaria causes of fevers (patients with a diagnosis of ARI or other clinically documented local infections were however not excluded), *Leptospira* was found in 10%, 13% and 12% of the patients, dengue in 0%, 7% and 25% and *Rickettsia*/typhus in 10%, 4% and 26%, respectively. In Tanzania, 8% of these patients had Q fever, 5% brucellosis and 6% Chikungunya (these 3 diseases were not searched for in the Asian studies).

Recommendations for future studies on etiologies of fever

Studies conducted so far are quite heterogeneous in terms of study design, and this makes findings difficult to compare. To increase the comparability among studies in future studies:

Inclusion criteria of patients:

- Focus should be mainly on unspecific fevers (without any sign of localized infection and not associated with malaria, ARI or gastroenteritis), except where multiple diagnoses are frequent, i.e. in children in underserved areas;
- Inclusion criteria should be clearly defined, reproducible and, if possible, aligned with previous studies. A common definition for unspecific fever should be used (see above);
- Studies should also be targeting children 5-15 years and infants <2 months.

Study design:

- 'Prevalence' studies in a sample of consecutive febrile patients attending health facilities as well as incidence studies with active and passive case detection are desirable;
- Studies should be undertaken at different levels of health care (from community to hospital) and in different epidemiological settings, seasons and age groups;
- A simplified design (e.g investigating selected rather than all possible microbiological etiologies) should be used to avoid repeating extensive (and expensive) etiological studies;
- Common case definitions between studies should be used;
- Always link clinical data to laboratory results to avoid over-interpretation of positive results. Indeed the post-test probability of positive Rickettsia serology is much lower in a patient with ARI or diarrhea than in a patient with unspecific fever. Another way is to exclude patients with other causes of fever (e.g. signs of localized infection) for this type of lab test.
- When possible, compare laboratory results of febrile patients with those found of matched control groups among asymptomatic people, especially when using molecular tools, also to avoid over-interpretation of positive results.

4. Available WHO guidelines and tools for the management of fevers

Available tools

Several algorithms developed by WHO are now available targeting different levels of the health system and different age groups:

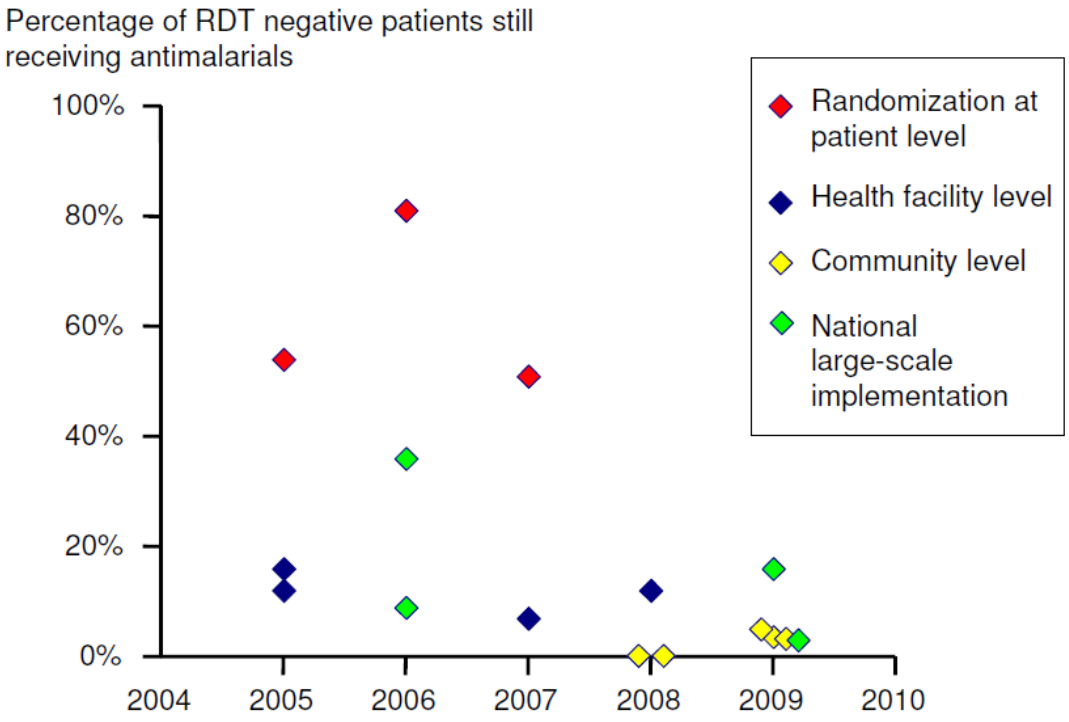
	Hospital	***Health facility***	***Community***
Children	Pocket book[1]	IMCI[2]	iCCM[3]
Adults	District manual[4]	IMAI[5]	N/A

No guidelines are available for the management of adults at community level. Guidelines for 'adults' are also targeting children above 10 years. No algorithm exists for children 5 to 10 years old.

iCCM, IMCI & IMAI should be promoted more actively. An informal review of available studies suggests that adherence to iCCM by community health workers is generally good while adherence to IMCI by clinicians at health facilities is often problematic (see Figure 1).

Deployment of ACTs and RDTs for malaria case management should promote the implementation of IMCI/iCCM enforcement. The current WHO recommendations for malaria diagnosis and treatment are well integrated in most WHO guidelines for integrated management of illnesses, except for IMAI for primary health facilities. Home Based Management of Malaria, based on presumptive treatment of malaria in children under five, should not be implemented anymore and WHO documents (published in 2002-2005) should be put in archives.

Figure 1: Level of adherence of health workers to malaria RDT result by type of study
Source: reviewed by D'Acremont



[1] *Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources*. Geneva, World Health Organization, 2005.
[2] *Integrated Management of Childhood Illness for high HIV settings: chart booklet. Geneva, World Health Organization/UNICEF, 2008.*
[3] *Integrated Management of Childhood Illness: Caring for Newborns and Children in the Community. Manual for the Community Health Worker.* Geneva, World Health Organization, Unicef 2011.
[4] *IMAI District Clinician Manual: Hospital Care for Adolescents and Adult. Guidelines for the Management of Common Illnesses with Limited Resources.* Volumes 1 and 2. Geneva, World Health Organization, 2011.
[5] *Integrated Management of Adolescent and adult Illness: interim guidelines for first-level facility health workers at health centre and district outpatient clinic: acute care*. Geneva, World Health Organization, 2009. In press.

Need for development and update

- Guidelines for management of adults at community level are needed.
- Guidelines for children 5 to 10 years should be developed.
- Continuous update based on evidence is needed, in particular (for malaria):
  - Criteria for high and low malaria risk area;
  - Malaria testing of anemic children in high malaria risk areas;
  - Malaria testing before referral/pre-referral treatment;
  - Time interval for considering a new malaria infection (presently >14 days).
- New strategies are needed to improve adherence to IMCI by clinicians working at HF level.

Criteria for integrating new diagnostic tests

- Priority should be for treatable illnesses with high disease burden (mortality, but also morbidity), detectable through reliable tests.
- In general the more specific the tests, the more expensive:
  clinical → epidemiological → severity test → pathogen-specific test
- Electronic tools should be evaluated to measure essential clinical parameters (respiratory rate, O_2 saturation, etc.).
- Some pathogen-specific point-of-care tests (POCTs) are already available: some have excellent diagnostic performance (e.g. dengue), others not (e.g. typhoid fever, with RDTs having 75% sensitivity and 65% specificity in most studies).
- New POCTs are in development:
  → that specifically detect one pathogen
  → that 'generically' identify: - patients at risk for progression to severe disease
  - patients in need for antibiotics
- There is a need to define, for each diagnostic test, clear criteria to target the use of diagnostics to specific patients.

Issues with integrated management of febrile illness that need attention

- How specific should algorithms be in relation to place and time? Should they be different in different parts of the country? Should they be different according to season?
- Algorithm should be adapted by level of health care system, and must remain simple for use at the community level
- Because health workers often leave the working place after receiving in-service training, efforts should be put in revising the pre-service training curriculum. The latter should be more evidence-based and include training on WHO algorithms.
- An algorithm to diagnose and manage typhoid fever in high endemic areas is urgently needed
- The cost/benefits of a new diagnostic test should be carefully evaluated before including it in the existing algorithm (e.g. dengue)
- The existing IMCI booklet is already demanding for health workers: maybe sections on care for acute illness could be separated from the topics, such as nutrition, vaccinations?
- How can health workers cope with the very complex differential diagnosis (that includes 20 diseases) proposed in the fever box of the IMAI district manual?

Issues with treatment that need attention

- High level of bacterial resistance to first line treatments has been observed
  → How to quickly adapt guidelines to changes in antibiotic resistance?
  → How to replace co-trimoxazole by amoxicillin (dispersible for children) for ARI?

- Consideration in terms of 'class of antibiotics' is important (not only yes/no): e.g penicillins are generally appropriate for respiratory infections, quinolones for intestinal and urinary infections, doxycycline for some causes of unspecific fevers…
- Rectal artesunate is recommended for suspected cases of severe malaria identified at the community level. However, no efficacious pre-referral antibiotic for severe febrile illness can be given as long as injectables remain not recommended for use at this level and no rectal antibiotic is available.
- WHO does not recommend differentiating the list of essential medicines between the heath facility and the community level – this is considered the responsibility of countries.

5. Agencies and NGOs experience with iCCM

Emerging evidence on iCCM implementation

- Mortality has decreased with the deployment of antimalarials in the context of Home based Management of Malaria. Studies of impact on mortality of the introduction of antibiotics in the context of iCCM are ongoing.
- Compliance to algorithms was high for laboratory based tests, such as malaria RDT, but lower for clinically based tests, such as respiratory rate measurement
- CHWs were not good at picking up danger signs[6], especially in newborns. Although frequency of danger signs is expected to be lower at community than at health facility level (due to milder presentation of disease in general), the poor performance observed was concerning.
- Patients were often not referred by CHWs to the nearest health facilities although this practive is recommended. The reasons are not very clear: one hypothesis is that they anticipate difficult compliance with referral by patients and prefer to try to manage these children on site.
- Implementation of iCCM and utilization rates of CHWs are increasing. However, the numbers of episodes for each type of disease managed by CHWs were still largely below the expected numbers based on incidence data for the same diseases, especially for diarrhea.
- Several methods for assessment of quality of care have been compared. Direct observation of the CHW versus evaluation of registries versus interviews of health workers on specific "case studies" were as good when compared to direct observation with reassessment by an expert, except for assessing ability to pick up danger signs and to diagnose pneumonia.
- Distance-based measures overestimated access to case management for childhood illness 2 to 3-fold. It is indeed critical to consider not only geographical access to the place but also access to the service, i.e physical availability of staff and of medicines.
- Salaries and other financial incentives showed to be helpful in improving retention of CHWs.
- Regarding costs, it was significantly cheaper to manage severe pneumonia at community level rather than referring patients to the next health facility.

Lessons learned from iCCM implementation

Experiences and lessons learned should be taken into account when planning scale-up of integrated Community Case Management

[6] In iCCM, the 'General danger signs' (signs of severe illness requiring immediate referral) have been mixed together with the 'Other danger signs to refer' (signs of persistent illness or severe malnutrition that cannot be managed at community level and need thus to be referred but not immediately), which has brought confusion around the definition of 'Danger signs'. Studies on iCCM have up to now not distinguished between these two categories of danger signs.
Definitions: **'General danger signs'**: Not able to drink or feed anything, Unusually sleepy or unconscious, Convulsions, Chest indrawing (will be removed in the next update), Vomits everything**. 'Other danger signs to refer'**: Fever for the last 7 days or more, Cough for 21 days or more, Diarrhoea for 14 days or more, Blood in stool, Red on MUAC (mid-upper arm circumference) strap, Swelling of both feet.

- Supervision of CHWs is well performed by a senior peer CHW, rather than by clinicians based at HF, who have often not received specific training on iCCM or IMCI, and do not have experience in using clinical algorithms.
- Country-specific solutions should guide, from the start, strategies for the retention of CHWs.
- To tackle problems of repeated drug shortages, most iCCM programmes have introduced a parallel drug distribution system: during the iCCM scale-up phase the efficiencies and sustainability of such systems need to be assessed.
- To improve treatment seeking behaviour, appropriate communication activities are needed so that communities know the type of care they can expect.
- M&E for iCCM tend to be weak. It is therefore necessary to use innovative technologies, including using telephone communications.
- Extension of CHW tasks: Newborn and healthy child care should probably be integrated to iCCM. Care for children 5-15 years and for adults has not been included in WHO guidelines for integrated management at community level, but there is increasing demand for these by many countries who are addressing care of all age-groups at community level.

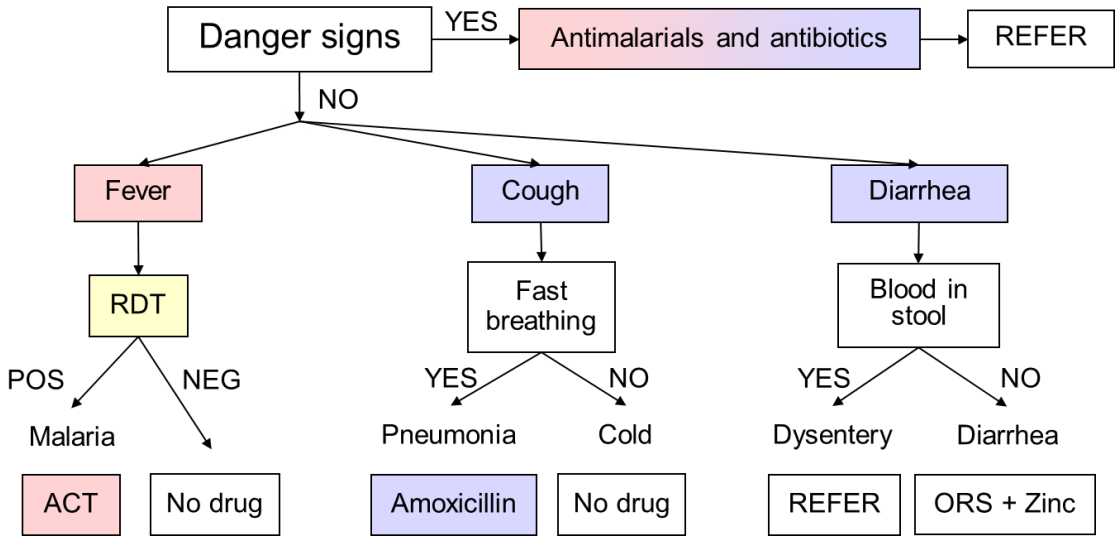
6. Country experiences with community case management of fevers in the public sector

The iCCM algorithm has been adapted to various degrees in different countries. Some adaptation is obviously needed but the core of the generic iCCM algorithm (see Figure 1) should not be modified when used in countries implementation programs. Indeed the core elements of the algorithm are evidence based and should not be changed from place to place.

The core elements of the WHO algorithm that should not be modified are the following:

- Management of fever should always include not only diagnostic testing and treatment for confirmed malaria, but also assessment and management of ARI and diarrhea
- Malaria-negative children presenting without general danger signs should not be systematically referred: these children need assessment for other conditions.
- Children with severe febrile illness should always be given pre-referral antibiotics prior to referral (especially if the malaria test has still been performed and is negative)
- Fever should not be treated presumptively with antimalarials. A diagnostic test should always be performed (except in patients with danger signs in need for immediate referral)
- Children who have a negative diagnostic test and who do not have evidence of severe illness should not be systematically treated with antibiotics. They need assessment for other conditions and antibiotics only if indicated.
- There is no need to assess fast breathing in the absence of cough or difficult breathing. This would lead to overtreatment with antibiotics

Figure 2: Core of the iCCM algorithm that should not be modified in country adaptations



The major problems that arose during iCCM implementation were due to the low quality of care at health facilities to which CHWs are supposed to refer patients. The consequences of the limited efforts in HF strengthening in parallel to iCCM implementation were the following:

- Supervision: clinicians of HFs were not able to provide supportive supervision to CHWs
- Supply chain: RDTs and medicines were often available at community but not HF level
- Quality of care: services at community level outperformed quality of care at HFs
- Access to care: 'opening hours' of CHWs were broader than that of HFs
- M&E: reliable data from community was available but not used at primary care level

All these problems led sometimes to back referral of patients from health facilities to CHWs.

7. Country experiences with community case management of fevers in the <u>private</u> sector

Use of malaria RDT, ACT and correct management of non-malaria febrile illnesses should be promoted not only in the public but also in the private sector, for the following reasons:

- The private sector is an important source of care in many (but not all) settings.
- Pneumonia kills an even greater number of children than malaria.
- In high endemic areas, a patient can often have both malaria and other diseases, because the clinical presentations do overlap or because they suffer from more than one disease at the same time (e.g. malaria and pneumonia).
- In low endemic areas, most patients have a negative RDT result. If management of other cause of fevers is not provided, this means that almost all patients will not receive appropriate care and will need to be referred to the nearest health facility.
- However, case management is a service, not a commodity, which means that it is more difficult to implement than the deployment of new medicines.

Therefore, when subsidized malaria RDTs are made available for the private sector, diagnosis and treatment for common non-malaria causes of fever should also be provided.

<u>What needs to be done to provide diagnosis & treatment for non-malaria fevers in private sector</u>

- Clear analysis and segmentation of the private sector should be done (e.g. drug peddlers, retail shops, non-registered and registered drug shops, private clinics (by level), not-for-profits…).

- The approaches need to be adapted to the target segment of the private sector (e.g. also providing appropriate incentives)
- The appropriate mechanisms for supervision and efficient surveillance methods should be piloted on a small scale and progressively extended based on the lessons learnt.
- The effective mechanisms for quality assurance of diagnostics, medicines and quality of care, which are operational for the public sector, should be progressively extended to the private sector.
- The need for consumers to be well informed and empowered through appropriate interventions (e.g. 'branding' of the accredited shops).
- The microeconomics of private sector outlets, and factors affecting consumer demand, need to be better understood.

Most of these interventions are similar to what is required for the public sector, and it may be useful to think about the challenges holistically across both public and private sectors

8. Moving forward: research priorities

Emerging evidence on effective strategies for diagnosis and treatment of febrile illness

- Withholding antimalarials in patients with a negative RDT is safe even in high endemic areas (several studies; a formal systematic review is ongoing)
- IMCI leads to overtreatment with antibiotics (poor specificity of respiratory rate measurement to diagnose pneumonia)
- One study in Pakistan, has indicated that the clinical outcome of children with pneumonia (IMCI definition) was not different when receiving amoxicillin or placebo (Hazir *et al*)[7]
- Several studies have shown that management of severe (but not very severe) pneumonia (WHO definition)[8] is safe at community level. Update of IMCI on this point is in progress.
- Several studies have shown that management of children under five according to iCCM is safe at community level

Recommendations for research on effective strategies to improve diagnosis and treatment of febrile illness

- Study design: clinical outcomes (cure versus treatment failure) rather than laboratory diagnosis should be the primary endpoints of the study. A common definition of 'treatment failure' should be defined for each disease, as attempted for ARI.
- Studies on the safety of withholding antibiotics for "non-severe" pneumonia in children should be repeated in Asia and undertaken in Africa.
- Research should aim to define optimal care of non-specific fevers in children and adults.
- Studies are needed on cure rates of specific classes of antibiotics in patients with non-specific fevers (e.g. doxycycline for patients suffering potentially from leptospirosis or rickettsiosis/typhus).
- Risk factors (clinical and laboratory) for disease progression to severe illness need to be assessed.
- Research should clarify the need for 'disease severity' vs 'pathogen-specific' laboratory tests.
- Studies should assess the benefit of using new respiratory rate counters and pulse oximetry.
- Research should build on existing algorithms for management of febrile patients and target additional curable illnesses of public health importance.
- Research should evaluate usefulness of new tools, e.g. electronic guides, to improve compliance and data collection.
- Modeling research is needed to define appropriate cost-effectiveness thresholds for the target product profiles of new diagnostic tools.

[7] Hazir T, Nisar YB, Abbasi S, et al. Comparison of oral amoxicillin with placebo for the treatment of world health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in pakistan. Clin Infect Dis 2011;52(3):293–300.

[8] Definitions: **Pneumonia:** Children with no lower chest indrawing who have fast breathing; **Severe pneumonia:** Children with lower chest indrawing; **Very severe pneumonia:** Children unable to drink, with convulsions, abnormally tired or difficult to wake, or with persistent vomiting.

9. Summary of recommendations to programs and countries

These recommendations are based on the emerging evidence presented during the meeting and summarized in the grey boxes above, as well as on lessons learned from pilot programs and scaling-up efforts discussed during the meeting.

1. Studies on etiologies of fevers should be undertaken at different levels of health care and in different epidemiological settings, seasons and age groups (based on Section 3).

2. Malaria diagnostic testing and treatment should be deployed as part of promoting programmes for the integrated management of fevers, based on WHO algorithms available for different age groups and levels of care (based on Section 4).

3. Evidence from studies and lessons learned from implementation should be taken into account when planning scale-up of integrated Community Case Management (iCCM) (based on Section 5).

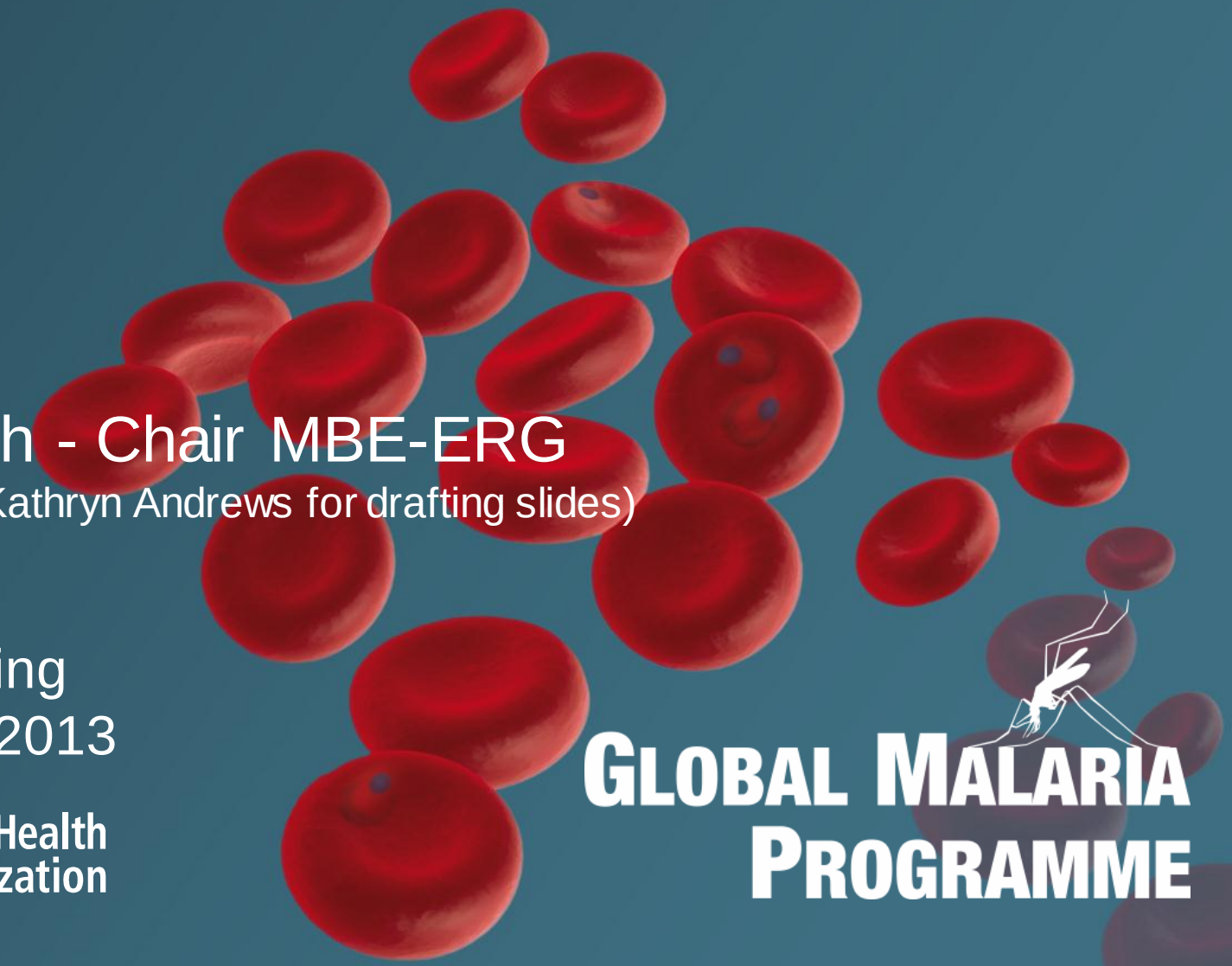
4. The core elements of the generic WHO iCCM algorithm should not be modified when the algorithm is going through local adaptation for the use in countries implementation programs (based on Section 6, first part).

5. iCCM programs should be implemented together with strengthening quality of care at health facilities level, based on IMCI and IMAI for primary care and hospital levels (based on Section 6, second part).

6. When subsidized malaria medicines and RDTs are made available for the private sector, diagnosis and treatment for common non-malaria causes of fever should also be provided, based on WHO algorithms for iCCM (based on Section 7).

7. Research looking at new strategies for effective diagnostic and treatment of febrile illness should be encouraged, using clinical outcomes as primary study endpoints rather than laboratory results, in order to modify or expand the current WHO algorithms (based on Section 8).

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



Peter Smith - Chair MBE-ERG
(with thanks to Kathryn Andrews for drafting slides)

MPAC meeting
13th March, 2013

World Health Organization

GLOBAL MALARIA PROGRAMME

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 to prioritize countries for resource allocation
    b) Understand trends over time to assess 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 2012):

Review the issues and determine key questions

Meeting 2: (January 22-24, 2013, Geneva):

Individuals (Thom Eisele, Peter Gething, Li Liu, Christopher Murray and Tom Smith) representing major groups involved in malaria burden estimation presented their approaches to the ERG and answered questions on their methods

Meeting 3: (Second quarter 2013)

Review evidence gathered and formulate recommendations to MPAC that address questions posed *(after follow-up ERG teleconference, this may no longer be necessary)*

Morbidity estimation methods

Malaria Atlas Project (MAP)

- Cartographic approach uses geo-referenced *Pf*PR surveys (~22,000 up to 2010) and environmental covariates, adjusts for age groups and years, but not seasonality (substantial increase in *Pf*PR surveys in recent years).
- Prevalence is converted to incidence using population estimates and relationship between *Pf*PR and case incidence from ~140 longitudinal studies with active case detection (ACD) – considerable variability in the relationship in different surveys.
- Results are considered most reliable in Africa and least reliable in India, China, and Myanmar (fewer prevalence data)
- Future work: research to generate infection prevalence and case incidence time series for 34 high-endemicity countries in Africa, using additional covariates - i.e. will produce estimates of cases by year.

Morbidity estimation methods

WHO

- Surveillance/HMIS approach: used for countries outside the WHO African Region and low transmission countries in Africa
  - Number of reported malaria cases adjusted for completeness of reporting, likelihood that cases are parasite-positive, and extent of health service use
  - Model assumptions should be tested using MIS data
- Risk approach: used for high-transmission countries within the WHO African Region
  - Uses MARA map for estimates of malaria risk (high,low or no), and adjusts post-hoc for ITN coverage using efficacy value from Cochrane review (ITN↑1%➔Inc.↓0.5%)
  - Advantage = simplicity: Disadvantage = crude.
  - MARA should be updated with MAP, and ITN efficacy may be unrealistic

Ways forward for malaria morbidity estimation

Recommendations for WHO

1. For 2013: WHO should continue to estimate cases as currently, but should vary/test assumptions regarding value of ITN effectiveness and test positivity among febrile children seeking care vs. those not seeking care.

2. In 2014 and beyond:

   - Sub-Saharan Africa: WHO should derive case estimates based on time-series of *Pf*PR assembled by MAP and a refined model of relationship between prevalence and incidence (including survey data, seasonality information, new covariates)

   - Outside Africa and in countries with robust surveillance data: estimates should be based on reported cases; as surveillance systems become stronger, more countries will be able to use HMIS method

3. Uncertainty around estimates should always be presented with mean values, and country consultations should remain integral to estimate generation in order to understand data quality and anomalies, and to validate results

4. Generation of a more user-friendly cartographic methodology should be explored

Ways forward for malaria morbidity estimation

Recommendations to improve the science

1. Explore methods of collecting additional prevalence data should be collected (through RDTs at antenatal visits (method used to monitor HIV prevalence), EPI visits, or in school deworming campaigns), which would improve MAP estimates
2. More data on relationship between incidence and prevalence must be gathered
    - Concerns about possibility of bias in longitudinal surveys with ACD
    - ERG members have agreed to compile a list of data that could supplement the MAP database

Mortality estimation methods

Institute for Health Metrics and Evaluation (IHME)

- Cause of Death Ensemble Model (CODEm - weighted average of different models) used to estimate mortality from nearly 300 causes of death, including malaria; model is data-driven, and chooses an ensemble of models based on out-of-sample predictive validity.
- Uses VAs and environmental data. Details of methods used is a little opaque at present and not all data in public domain.
- High estimates for adult deaths driven empirically by Verbal Autopsy (VA) data in older age groups and by redistribution of deaths from unspecified causes to malaria
- Additional research is required to resolve disagreement between modeled adult mortality results and clinical experience – especially assessing validity of VA data.
- Likely that IHME estimates (for all causes of death, including malaria) will be updated annually.

Mortality estimation methods

CHERG: age under 5y deaths

- Multi-cause model of 8 child causes of death, including malaria
- Uses VA to partition all cause death rate between causes (only 20 VA data points in Africa).
- Exclusion criteria may have eliminated some high-quality VA studies from the analysis
- Post-hoc adjustment for effect of ITNs may improperly influence estimates

WHO: age 5y+ deaths

- CHERG's under-5 deaths in Africa used to estimate deaths age 5+ via relationship between age-specific malaria death rate and intensity of malaria transmission (from 1 study!)
- Outside of Africa, CFR of 0.3% is applied to total number of estimated cases of *P. falciparum*

Ways forward for malaria mortality estimation

Recommendations for WHO

1. For 2013: WHO should continue to estimate malaria deaths as currently, but should also estimate *P. vivax* deaths separately
2. In 2014 and beyond: the recommended approach has not yet been decided. There appear to be substantial weaknesses in all the current methods
3. Uncertainty around estimates should always be presented with mean values, and country consultations should remain integral to estimate generation in order to understand data quality and anomalies, and to validate results

Ways forward for malaria mortality estimation

Recommendations to improve the science

1. Existing data should be assembled to examine evidence base for IHME's high adult death estimates (e.g. INDEPTH)
2. Novel research should be conducted to examine age patterns in malaria deaths and relationship between *Pf*PR and mortality (case-control studies comparing parasite prevalence in those dying of any cause and controls; prospective cohort studies of all-cause mortality in relation to malaria exposure)
3. To explore reasons for differing results, CHERG should rerun its model using less restrictive VA inclusion criteria, and IHME should rerun its model without redistribution of unassigned VA deaths
4. Consider possible need for an MPAC standing committee to evaluate new estimation methods for both morbidity and mortality, as methods evolve.

WHO Evidence Review Group:
Malaria Burden Estimation

Report on the Second Meeting
WHO Headquarters, Geneva, 22-24 January 2013

Contents **Page**

Introduction

A meeting of the Malaria Burden Estimation (MBE) Evidence Review Group (ERG) was convened by the Global Malaria Programme (GMP) of the World Health Organization (WHO) to:

- review current methods in malaria morbidity and mortality estimation with the participation of the experts involved in the development of currently used methods,
- try to achieve consensus on the methods that should be used by WHO and in the World Malaria Report (WMR), and
- identify research bottlenecks that prevent reconciliation of different methodologies/results and how these may be addressed.

Thom Eisele, Peter Gething, Li Liu, Christopher Murray and Tom Smith were invited to this ERG meeting to represent groups that have contributed substantially to malaria burden estimation in recent years. This report summarizes:

- presentations given by meeting participants,
- major discussion points arising,
- recommendations on how WHO should proceed with malaria morbidity and mortality estimation, and
- recommendations on future studies.

Estimating case incidence: Malaria Atlas Project. *Peter Gething*

The "cartographic risk-based approach," which has been in existence for more than 10 years, enables malaria burden estimation in the absence of routine case reporting. The developers have assembled a large database of malaria prevalence surveys and have used these to construct a global map of prevalence rates. To convert prevalence information into incidence information, incidence data from longitudinal studies involving active case detection (ACD) are used in conjunction with a map of parasite prevalence to estimate location specific incidence rates. When multiplied by population, the method yields estimates of numbers of cases. An advantage of the cartographic method is that incidence rates can be estimated at a local scale rather than just as a national estimate.

An early map of malaria risk was produced by Lysenko in the 1960s, where limited *Pf*PR data and expert opinion on climatic boundaries were used to estimate endemicity in 5 strata at the assumed endemicity peak in 1900. More recently, the Mapping Malaria Risk in Africa (MARA) project produced a map for sub-Saharan Africa that categorized areas according to climatic suitability for malaria transmission.

Identifying extent of malaria transmission. Annual parasite incidence (API) data were disaggregated to the lowest possible administrative unit; for some countries, this was very small (Brazil had admin5 data, which corresponds to approximately 150 people), but for others this was extremely large (India had admin2 data for which the median population size exceed 1 million).

Estimating malaria transmission intensity. The primary input data for MAP estimates are parasite rate surveys. The 7,953 parasite prevalence survey locations used in the 2007 MAP estimates measured *Pf*PR by microscopy and RDT (not molecular diagnostics, which generally yield higher levels of parasitemia). The data were derived from published literature, MIS surveys with cluster-level GPS coordinates, and grey literature from researchers working in the field. Embedded in the modeling framework is an age-correction model that takes advantage of the >100 studies with prevalence reported by very fine age groups in order to standardize prevalence estimates to a 2-10 year age range. In addition to age, the model also takes into account how many years ago the survey occurred and whether it took place in an urban or rural location. Seasonality is not considered in the model (although seasonality is recorded in the data, and DHS occur in dry seasons while MIS occur in rainy seasons). The prevalence data reveal large numbers of 0 *Pf*PR values, indicating that prevalence surveys are not only conducted in areas where malaria transmission is highest. The methods are depicted in a schematic in Figure 1.

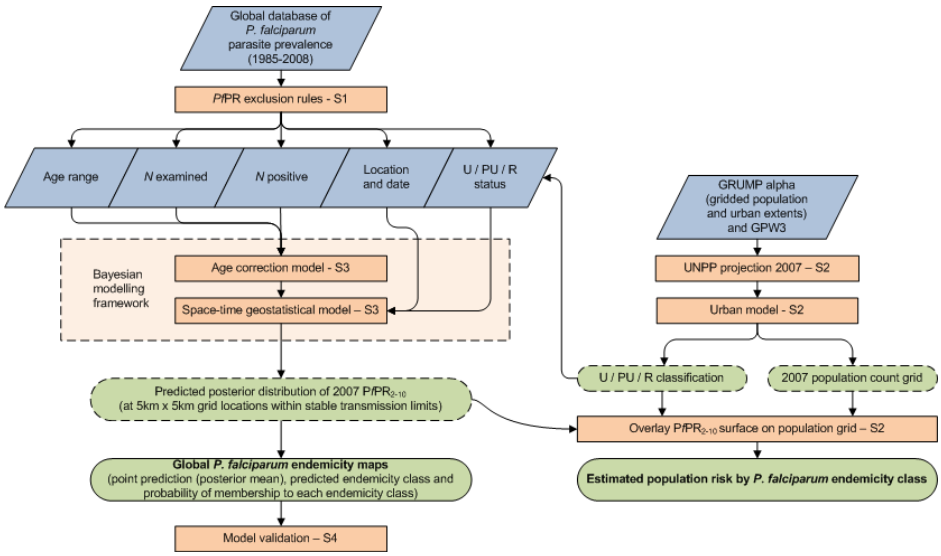


Figure 1: schematic of geospatial model of stable risk. *Source: Peter Gething*

Estimating malaria case incidence rates from parasite prevalence rates. The data used to model case incidence from *Pf*PR are from a systematic literature search, with the inclusion criteria that the data be no older than from 1985, come from community-based longitudinal studies of prospective ACD of fever (where ACD occurred at intervals of at least every 14 days), covered all age groups (which, surprisingly, did not eliminate many studies), and covered a complete 12-month period. These inclusion criteria would eliminate cross-sectional studies, surveys with restricted age groups, and rolling MIS surveys, but would include the control arms of case-control studies. Although longitudinal studies ensure the reliability of the incidence estimates, the studied populations often receive high-quality treatment and become less and less representative over time during follow-up (producing a downward bias). The case incidence data were matched to co-reported or mapped mean *Pf*PR, yielding 141 ACD-*Pf*PR_{2-10} pairs that were used in the incidence-prevalence model.

The relationship between age-specific incidence and age-adjusted *Pf*PR is a noisy one. The non-parametric Bayesian regression used did not require prior parameterization of the relationship; rather, a family of curves (linearly increasing or decelerating) was specified (with some forms disallowed). In the next iteration of the MAP project, the incidence-prevalence relationship will be stratified by age (it is expected that the relationship between incidence and *Pf*PR would be different in under-5s and in adults, given adult immunity, and would vary with overall endemicity), and will include covariates in the model, such as ITN coverage (this will be challenging as covariates are infrequently available).

Estimating case numbers. Case numbers are estimated by multiplying estimates of case incidence by the population estimated for each pixel. The availability of more detailed population maps is facilitating improvements in cartographic methods: Andy Tatem's AfriPop (to be followed by AsiaPop and AmeriPop, and stratification by age and sex) is providing improved population distribution data to replace GRUMP and LandScan.

Estimating uncertainty. Uncertainty is propagated at every step in the modeling process. Although the mapped results appear very smooth, the model generates a complete posterior distribution of *Pf*PR for each pixel, and the variance of the distributions can be large. The posterior distribution of the incidence-prevalence model is applied to each *Pf*PR pixel's distribution to get a distribution of incidence rates. Each incidence pixel's distribution is applied to the pixel's distribution of population in order to get a distribution for each pixel of cases per year. The computing power required to run the joint simulation to calculate this uncertainty costs $15,000. The temptation on behalf of policy makers is often to ignore uncertainty and simply consider the mean values; it is a challenge for researchers to present uncertainty in a way that can be used in decision-making. The smoothness of the resulting map may be misleading in elimination schemes because it can give false hope of elimination when the underlying distribution is much more uncertain than the mean values indicate.

The resulting estimates are most reliable in Africa, and least reliable in India, China, and Myanmar (India in particular has vastly insufficient data and prevalence surveys are mainly conducted in high risk population groups or during epidemics). Thus, the strength of the method varies from one setting to another, and it is particularly weak where data are only available at high administrative levels, which may lead to overestimation of populations at risk. The strengths of the method are that it is not reliant on routine reporting systems, is consistent across all countries, and can quantify uncertainty, including that in the assumptions and input data. Although the ideal metric is cases, parasite rates are a direct measure of transmission and can provide an empirical baseline that incorporates the effects of interventions (assuming that *Pf*PR surveys are up-to-date). The spatial (i.e. systematic choice of survey locations) and temporal (i.e. variable age of data and seasonality) fidelity of the data, and the potential for a wide range of confounders remain key challenges.

The 2010 MAP estimates use 22,212 survey points (over 2.5 times as many observations as the 2007 version), employ a refined methodology using 20 environmental covariates and regional modeling, and extend the studied relationship to *Pf*EIR. The 2010 version is meant to replace, not be compared to, the 2007 version, and it is far more detailed/refined. As prevalence decreases, it will become increasingly important to discriminate between 10% and 20% prevalence, which the new model is better situated to do. Similar work has been done for *P. vivax*, which is most useful in Latin America. It incorporates the prevalence of Duffy negativity, but estimating relapses remains a challenge.

Future work includes BMGF-funded research to generate infection prevalence and case incidence time series from 2000 to present for 34 high-endemicity countries in Africa. With increasing use of mobile phones, geo-referenced facility data could be collected. Currently, validating the incidence-prevalence model is difficult (doing predictive validity tests on holdouts is impossible given the small sample size of 141 studies), but conducting studies at the community level to collect data on *Pf*PR and case incidence could help validate the results. Although there may be some appeal to generating country-specific maps using country-specific incidence-prevalence data, the downside is that

results across the globe will no longer be comparable because estimates for different countries will come from different years.

In high-endemicity, weak-HMIS areas, the cartographic approach may be the strongest option. In low-endemicity, strong-HMIS areas, the surveillance-based approach may be preferable. In intermediate settings, a hybrid of the two methods may be optimal. The next challenge will be to develop an application, potentially web-based, for this approach so that countries can generate their own estimates and adjust input data. Further discussion is required to assess whether this work is better done at the University of Oxford, or whether there is demand for developing a simplified application for use at country-level.

Case estimates from WHO. *Richard Cibulskis*

WHO uses two methods to estimate malaria cases: 1) the "surveillance/HMIS approach" (using data on reported cases) and 2) the "risk approach."

1) Surveillance/HMIS approach. This approach is used for countries outside the WHO African Region and low transmission countries in Africa.[1] Estimates of the number of cases are made by adjusting the number of reported malaria cases for completeness of reporting, the likelihood that cases are parasite-positive, and the extent of health service use. Suspected cases reported through the NMCP reporting system are split into presumed (unconfirmed) and tested; tested cases are further split into confirmed negative and confirmed positive cases. The test positivity rate from the confirmed cases is used to estimate the number of confirmed cases within the cases that do not receive a diagnostic test (presumed cases).

Since the NMCP data only provide information on cases coming through the public sector, household surveys (DHS, MIS, MICS) are used to estimate the percentage of patients with fever that receive care through the private (as opposed to public) sector. If data from more than one household survey were available for a country, estimates of health service use for intervening years were imputed by linear regression. If only one household survey was available, then health service use was assumed to remain constant over time; analysis (using multiple surveys from the same country) of percentage of fever cases seeking treatment in public sector facilities reveals that this percentage varies little over time. A limited number of studies indicate that the fraction of fever cases that are malarious and receive treatment in the private sector is the same as the fraction of fevers that are malarious in the public sector. For fever cases that do not seek treatment, the method calculates an estimate assuming that the fever cases not seeking treatment have the same likelihood of being malarious as the cases that do seek treatment, and an estimate assuming that the fever cases not seeking treatment are not serious enough to be malarious. Such a procedure results in an estimate with wide uncertainty intervals around the point estimate. The method uses spreadsheet software called @Risk to estimate

[1] Botswana, Cape Verde, Eritrea, Madagascar, Namibia, Swaziland, South Africa, and Zimbabwe

uncertainty using measured or assumed uncertainty ranges around each input to the model.

The strengths of this method include that countries can apply it themselves, and see first-hand that the reported number of cases are likely actually only a fraction of the true country-wide cases. A disadvantage of the method is that some of the inputs to the model are measured imprecisely. Reporting completeness is estimated by malaria programmes with wide ranges. The size of the health facilities from which reports are missing can have an influence on the reported number of cases and this is not taken into account. HMIS reports are sometimes more incomplete in poorer/rural areas with more malaria risk. In adjusting for treatment seeking outside of the public sector using household surveys, recall bias may occur with only more serious fevers requiring heath facility treatment being recalled (potentially underestimating the number of cases not seeking treatment). In some situations fever cases that do not seek care may have a greater likelihood of being malarious than those that seek care (if because they live in remote and highly malarious areas without access to treatment). It is possible to further examine the propensity of fever cases to be malarious using MIS data (by comparing parasite prevalence rates among children who had a fever and sought care as opposed to those who had a fever and did not seek care).

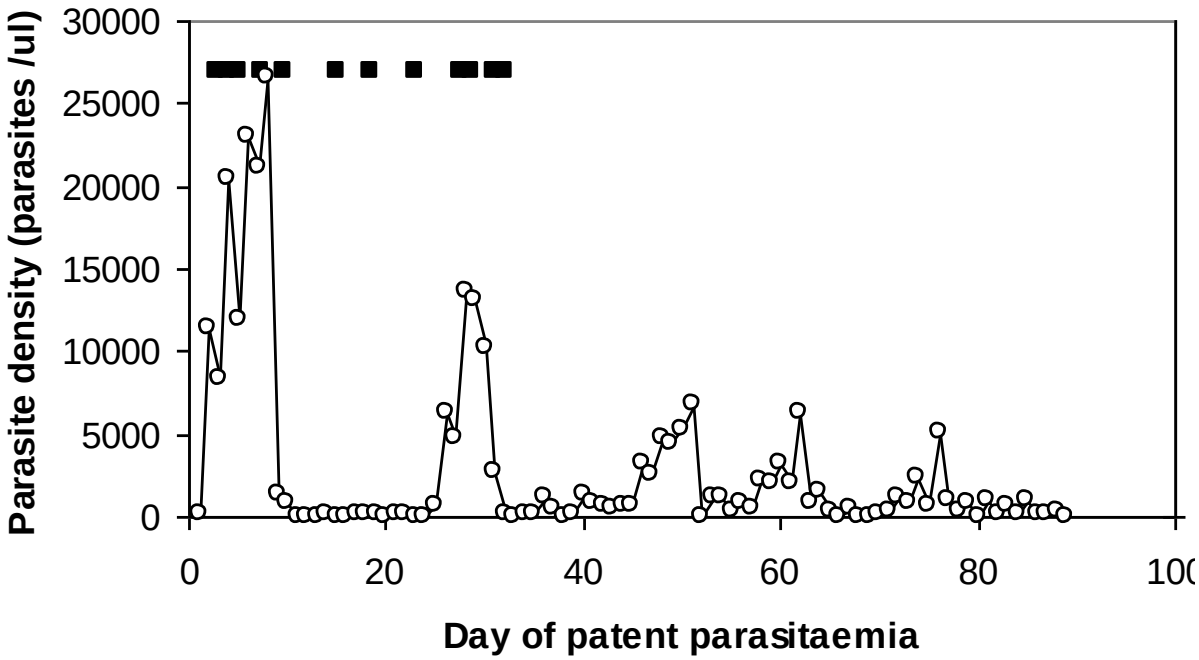
2) The risk approach. This approach is used for high-transmission countries within the WHO African Region. For some African countries the quality of surveillance data does not permit a convincing estimate to be made based on the number of reported cases. For these countries, an estimate of the number of malaria cases was derived from an estimate of the number of people living at high, low or no risk of malaria. Malaria incidence rates for these populations are inferred from longitudinal studies of malaria incidence recorded in published literature. Incidence rates are adjusted downward for populations living in urban settings and based on the expected impact of ITN programmes. ITN coverage (estimated from a model developed by IHME) is then used in a post-hoc fashion to reduce incidence based on protection by ITNs. The protective effectiveness is assumed to be equal to the efficacy, and is taken from a Cochrane Review on the efficacy of ITNs. Thus, for each 1% increase in percent of households owning at least 1 ITN, incidence is assumed to be reduced by 0.5%. No other malaria control interventions are taken into account in the current model (although incidence rates may already take into account high levels of treatment since they were derived from longitudinal studies in which treatment was provided to all malaria cases). The number of cases is estimated by multiplying the population at different levels of risk by the incidence rates for each risk category. The procedure was initially developed by the RBM Monitoring and Evaluation Reference Group in 2004.

The method currently uses estimates of risk from MARA maps and could be improved by using parasite prevalence maps generated by MAP to better define levels of risk. The advantage of this method is that it is simple enough for countries to calculate themselves, and the approach facilitates calculation of the number of malaria cases expected to occur with different levels of ITN coverage. A disadvantage is that no contemporary assessment of malaria risk or case incidence is used as an input to the model. Rather, it

projects what might occur if ITNs had the same effectiveness as measured in randomized controlled trials (a multi-country analysis of observational data conducted by IHME suggested that the effectiveness of ITNs was highly consistent with results from clinical trials).

Definition of a case

In estimating malaria morbidity the definition of "malaria case" must be clear. However, defining a case of malaria is complicated; Figure 2 shows the parasite density over time for an individual (untreated) patient. Is this one case only, one case with multiple relapses, one case with multiple episodes, or multiple cases? For longitudinal studies in which malaria in patients is detected and treated promptly, multiple fevers arising from the same infection are unlikely. If malaria is untreated then multiple episodes of malaria can arise from a single infection. For most purposes it is the number of episodes that is of interest, as each will cause disability. However, it is necessary to be clear about the length of the interval between episodes (fever symptoms) that would define one episode or two. In practice this may be taken as one or two weeks.



○: Parasite density; ■ day with fever (core temperature >=103 °F).

Figure 2: Pattern of parasitaemia and febrile illness in a malaria-therapy patient (Patient S-519). *Source: Tom Smith*

Estimating malaria deaths

CHERG malaria mortality estimates among children under age 5. *Li Liu*

In 2012, CHERG published an update of its analysis on causes of death among children, producing a time-series for 2000-2010 for all-cause mortality and for 8 specific causes of death, including malaria. A strength of the multiple-cause approach is that the method is not focused only on malaria, making the method less prone to researcher bias and favoritism toward a particular disease. Malaria mortality for low-burden African countries and countries outside of Africa was estimated using a fixed case-fatality rate (CFR) and WHO's estimates of malaria cases (as previously described). Deaths in high-burden African countries were estimated using studies which had employed the verbal autopsy, multi-cause model (VAMCM) among children aged 1-59 months.

The cause-specific mortality fraction (CSMF) data came from 113 community-based verbal autopsy (VA) studies that met the following inclusion criteria: two or more causes of death reported among children aged 1-59 months; from 1980 or later; 12 (or multiples of 12) month duration; at least 25 deaths each represented once; and <25% of deaths due to unknown causes. These criteria result in fewer than 20 data points in Africa and apparently exclude, for example, some high-quality VA studies in Ghana. It may be of value to examine which data points were excluded from the analysis. ERG members familiar with VA studies will provide a list of studies they think could be included in order to examine the effects of expanding the dataset. CHERG researchers may need to approach investigators in the field to ask for VA data in the form required to assess the inclusion criteria.

Among the 113 study data points, 68 did not have a malaria CSMF. In countries with *P. falciparum* transmission, deaths in the "other" category were re-allocated to missing causes using the probability patterns from studies with those causes reported; deaths with "unknown" causes were excluded. This procedure was done stepwise, whereby the missing CSMFs were imputed first for studies with only one cause missing, then two causes missing, etc., until all missing values were filled. Unfortunately, this imputation method does not take into account underlying risk of malaria. This may be problematic because in locations where malaria is well-controlled (and therefore no malaria deaths are reported) deaths may be inappropriately allocated to malaria from their "other" category.

A covariate selection process was undertaken in a stepwise fashion to identify significant covariates. It may be of concern that stepwise covariate selection was performed given the flaws inherent in that method, and that the covariate selection was not done using the same model specifications as used in the actual prediction model. The covariates that were chosen based on the selection process were the CHERG malaria risk index, which was assumed to be constant over time (the next iteration of CHERG malaria mortality work will use MAP's upcoming *Pf*PR time series), and percent of births attended by a skilled birth attendant (SBA). Because only 29 of the 113 studies had site-specific SBA, values were borrowed from national and subnational sources such as DHS/MICS surveys,

and all site-specific malaria risk index values were assumed to be the same as the national values.

The model used was a multinomial logistic regression (used to ensure that all the CSMF sum to 100%) of the malaria CSMF divided by the pneumonia CSMF. Given the higher reliability of the pneumonia CSMF, it was used to "anchor" the malaria CSMF:

$$ln\frac{CSMF_{malaria}}{CSMF_{pneumonia}} = f(CHERG\ malaria\ index,\ \%\ SBA)$$

Given that ITN coverage was not retained in the model based on the covariate selection process, a post-hoc ITN adjustment was performed. Using the protective effect of ITNs (55% according to Eisele et al) and IHME's ITN coverage time series, the resulting mortality estimates from the model were adjusted to account for the life-saving effect of ITN scale-up, and the "averted" malaria deaths were redistributed to the remaining 7 causes proportionally. This step may over-adjust for the effect of ITNs because the all-cause mortality envelope used by CHERG already takes into account mortality reduction due to reductions in malaria deaths. Bootstrapping was used to generate uncertainty intervals.

The results appear to be driven by the need for all diseases to fit into one mortality envelope (i.e. if measles and pneumonia decline rapidly, malaria deaths may appear to increase simply because other diseases must comprise the remainder of the envelope). Since the CHERG malaria index is constant over time, the SBA covariate and the ITN post-hoc adjustment are responsible for the trends seen. The inclusion of other covariates might result in very different results. More recent VA data may be required to yield a significant coefficient on ITN coverage (most VA data are from when ITN coverage was low).

Next steps for CHERG include incorporating the upcoming *Pf*PR time series, modeling results for different age groups within the 1-59 months range, and exploring use of a Bayesian framework for comparison purposes.

WHO malaria mortality estimates among adults. *Richard Cibulskis*

WHO uses CHERG's under-5 deaths in Africa to estimate deaths among those age 5 and over in Africa by using the relationship between age-specific malaria death rate and intensity of malaria transmission (Ross et al). The estimated malaria-specific mortality rates in children from CHERG were used to approximate the malaria transmission intensity and the corresponding malaria-specific mortality rates in older age groups. This relationship is inferred from mathematical modeling of malaria transmission and immunity with the primary data source being one study in Tanzania.

Outside of Africa, WHO applies a CFR of 0.3% (range 0.15% to 0.45%) to the total number of estimated cases of *P. falciparum*. A literature review of malaria CFR yielded

values that range between 0.1%-0.4% among all malaria cases and higher rates of 3%-33% among cases admitted to hospital. The ERG was not convinced that there was currently a strong case for changing WHO's choice of 0.3% CFR among all malaria cases. Additional consultation should be taken regarding a CFR for *P. vivax*.

IHME malaria mortality estimates. *Christopher Murray*

IHME spearheaded the recently-published Global Burden of Disease Study (GBD) 2010, which generated estimates of morbidity and mortality of nearly 300 causes in a highly comparable way. The 5 principles of cause of death (CoD) modeling used by IHME include 1) identify all available data, 2) maximize comparability and quality of each dataset, 3) develop a diverse set of plausible models, 4) assess the predictive validity of each plausible individual model or ensemble of models, and 5) choose the model or ensemble model with the best performance with regard to in- and out-of-sample predictive validity tests. For CoD modeling, the 4 families of models considered are 1) mixed effects linear models of the logit cause fraction, 2) mixed effects linear models of the log mortality rate, 3) spatial temporal models of the logit cause fraction, and 4) spatial temporal models of the log rate. IHME supports putting faith in data and limiting choices based on expert opinion, and has developed its methods accordingly. Ensemble modeling, used in the Netflix Challenge and weather forecasting, uses weighted averages of individual models. The ability to use multiple models and to test them with predictive validity helps eliminate the need for a researcher to select a preferred model.

Some of the predictive validity tests include train (70% of the data) and test (2 x15% of the data) samples, knocking out historical data or using knock-outs that mimic the pattern of missingness in the data. The root mean square error (RMSE), the predictive validity of the first difference, and the percent of data included in the uncertainty interval are used as metrics of model strength.

The covariate selection process tested all combinations of identified covariates, such as rainfall, ITN coverage, Lysenko patterns of malaria risk, MAP *Pf*PR, female education, etc. Other covariates such as interactions between drug resistance and *Pf*PR, and HIV seroprevalence (to account for misclassification of HIV deaths to malaria) were also examined, but not retained in the final modeling process. Cases of malaria were not included as a covariate. Although the covariate selection process may select models with collinear covariates, the aim of the Cause of Death Ensemble model (CODEm) is to generate predictive models with the best fit, not evaluate causal relationships.

In addition to available VR data, VA and subnational VA data from both published and unpublished studies were included. The ITN effects are driven primarily by studies in Ghana and Zambia where the VA studies report ITN coverage. A limitation of both the IHME and CHERG analyses is a dearth of CoD data during the period of ITN scale-up.

The dependency of malaria mortality estimation on VA studies introduces a wide array of uncertainty and unreliability. Most VA studies rely on physician coding (PCVA), which has an accuracy of less than 45% at the all-cause level. Based on the sample of 12 thousand deaths from the 5 GC-13 study sites (Philippines, Mexico, Andhra Pradesh, Uttar Pradesh, Tanzania) in a VA validation study, physicians correctly assigned the cause of malaria to a true malaria death 30% of the time. It may be of concern that few of these areas have high malaria endemicity; further study is required to examine physician coding in areas of higher malaria risk. Specifically, performance of VA at different levels of malaria risk could be evaluated by conducting studies in several areas whose primary difference is malaria endemicity. Looking at the VA validation study, comparing the cause fraction of death from gold standard diagnosis and that from VA assigned cause of death shows a substantial systematic bias to over-assign malaria as the cause of death when the true cause fraction is below 10%. In this way, VA studies conducted among populations with a low true cause fraction of death for malaria are more likely to report overestimates of the malaria cause fraction of death and studies conducted among populations with higher true malaria cause fractions are more likely to be accurate. The pattern holds for both children and adults. The generalizability of these results, and the underlying true diseases that are commonly coded as malaria should be areas of further study. Giglioli's study in Guyana was mentioned as an example of a natural experiment in malaria cause of death coding before and after implementation and control phases. The magnitude of the overestimation of malaria cause fraction where the true cause fraction is low was not adjusted for in the modeling (VA results were not adjusted at this level in the overall GBD study due to the effect on other disease's cause fractions). The quality of the gold standard diagnosis in the validation study was not assessed though it was assumed to be high given the reputation of the chosen sites. It was noted that the validation study site in Tanzania was not the same as a site in the same country where a quality of diagnosis study showed substantial overdiagnosis of malaria.

Deaths assigned to garbage codes (ill-defined or impossible causes of death, such as from disseminated intravascular coagulation or unspecified parasitic disease, unspecified fever, convulsions) were redistributed based on observed proportions or information from studies. This may be problematic because in areas of high malaria endemicity, doctors recording a cause of death are likely to know which deaths are due to malaria and which are not; therefore, if a death is coded as "other parasitic", it is likely truly not malaria. In published studies, up to 10% of under-5 deaths are misclassified; in all studies up to 30% can be. Currently, the uncertainty in the garbage code redistribution process is not propagated through the IHME modeling process due to computational limitations.

IHME's high estimates for adult deaths are driven empirically by verbal autopsy data in older age groups and by redistribution of deaths from unspecified causes to malaria. For example, in South Asia age 60+, a large number of unspecified deaths are reassigned as malaria resulting in a 2.5 fold increase in malaria deaths. Redistribution of deaths from unspecified causes resulted in about 20% increase in malaria deaths globally. Other studies also show a significant number of deaths in the oldest age groups, but have generally been assigned out of malaria owing to perceived implausibility.

The results show a peak of deaths in 2004. The covariates that have the most influence on the predicted trend are ITN coverage, *Pf*PR, and antimalarial drug resistance. Another key finding is the level of uncertainty in predicting malaria mortality. While for cardiovascular disease the RMSE hovers around 0.5, the RMSE can be as high as 1.45 in some age-sex-region groups for malaria, which is not a surprise given the generally non-specific nature of malarial illnesses and the overlap with other febrile conditions.

After all diseases are modeled, the program CoDCorrect sums the draws from the posterior distribution of each cause and scales them to equal the draw of the all-cause mortality distribution for each country-year-age-sex group. The net effect of this process is that causes that have larger uncertainty are scaled up more than causes that are more certain; this approach is better than a multinomial approach because it is better suited for situations of spatial and temporal correlation. After "squeezing," malaria deaths only change by 10% at the global level, but the country-level results can be quite different, primarily due to the large number but high uncertainty of malaria deaths in DRC and Nigeria.

There are now plans for the GBD study to be updated yearly; it will continue to re-predict back to 1980. The anticipation is that over the years, the numbers will fluctuate less and less and converge on well-validated estimates. IHME has also been requested to produce estimates for a wider range of causes of death and to include forecasts for the next 15-25 years. The downsides to forecasting include the reliance on large assumptions and the concern that policymakers may rely too heavily on projections whose assumptions are not evident to them.

CODEm methods produce similar results for children as the WHO methods do, but vastly different estimates of adult deaths. Tom Smith's hypothesis is that VA studies are more accurate for children than for adults. IHME could rerun its models without the redistribution of VA deaths to see how much the results change. Ideas for validation of adult death estimates include surveillance of adult febrile illness, which would involve performing an HIV test, chest X-ray, and RDT on each patient. Ideally, odds ratios of adult deaths given various levels of parasitaemia should be generated. Adult mortality case-control studies should also be conducted. Cases would be adult deaths in hospital (where the severely sick patients are all given an RDT prior to death), and controls would be age- and sex-matched individuals from the same communities (with same *Pf*PR). The Ghana DSS sites could be a resource for examining adult malaria deaths, and a proposal could be developed to appeal for Gates Foundation funding to run a case-control or cohort study to elucidate the issue of adult deaths appearing in CoD coding.

Ways forward for malaria morbidity estimation.

1. For 2013, WHO should continue to estimate case numbers as currently, but WHO should vary the value of ITN effectiveness used on the post-hoc ITN adjustment to examine the effect of doing this on estimates. Using MIS data, WHO should examine the test positivity rate from survey finger/heel sticks among children who had a fever and sought care as opposed to those who had a fever and did not seek care.

2. In 2014 and subsequent years, it is recommended that WHO case estimates are derived from surveillance data for countries outside of Africa and selected countries in Africa with adequate surveillance systems as is presently done. For countries in Africa that lack adequate surveillance data, it is recommended that WHO derive case estimates from maps of estimated current parasite prevalence and population density assembled by MAP. This requires MAP to develop methods to estimate parasite prevalence by year for 2000 to 2014. Models of the relationship between prevalence and incidence will then be used to derive case number estimates. In refining the prevalence-incidence model, survey data (not just longitudinal studies, which may be biased by treatment of incident cases) and seasonality data should be incorporated, as well as other covariates (including treatment). In the WMR 2013, WHO should clearly state its plan to change the methodology in 2014 for sub-Saharan Africa.

3. As surveillance systems are strengthened in Africa it should be possible for case estimates to be derived from surveillance systems in an increasing number of countries. WHO should develop clear criteria that determine when a country in sub-Saharan Africa is ready to transition from the risk-based approach to the surveillance-based approach. These should include comparing parallel estimates of case numbers derived from surveillance and risk-based approaches.

4. For countries which have abundant parasite prevalence and surveillance data (such as Indonesia and Zambia) it is recommended that MAP/WHO apply both the surveillance method and the risk-based method and compare the results to understand why differences arise and in what settings a surveillance approach or risk-based approach might be preferred. Further work in resolving uncertainties in estimates may also be possible in India through the National Institute of Malaria Research.

5. WHO should aim to report not only on malaria cases (defined as any episode of fever with parasites) but also aim to estimate the number of infections, malaria attributable fever cases and severe malaria cases.

6. WHO should further examine how the HIV team estimates HIV infection rates to see whether there are lessons to be learned from them.

7. While estimates produced by WHO HQ would make use of the full computing capacity offered by MAP, country consultations will continue to be crucial in order to understand data quality and anomalies, and to validate results. There will be value in

developing a stripped down version of the cartographic approach that can be implemented on a spreadsheet which countries could employ themselves.

8. MAP/WHO should identify countries in which there are a dearth of prevalence data, as well as those with limited studies examining the incidence-prevalence relationship, and work with partners to find ways of filling the gaps. Future surveys should consider collecting prevalence data from a wider range of age groups and ask questions about why people do not seek treatment for fever. ERG members have agreed to compile a list of data that could supplement the MAP database.

9. Additional prevalence data could be collected through RDTs at antenatal visits (a population that has been used extensively for estimating HIV prevalence rates), EPI visits, or when testing for helminths in school deworming campaigns. These additional data from sentinel sites on malaria parasite prevalence could be used to strengthen cartographic methods of prevalence estimation.

Ways forward for malaria mortality estimation

1. Some concern was expressed about both the (over) simplicity of WHO's estimation methods and also about IHME's estimate of the large number of adult deaths in sub-Saharan Africa, based predominantly on a limited number of verbal autopsy studies. The problem of discrepant estimates for adult deaths in sub-Saharan Africa from IHME and WHO was not resolved and is unlikely to be resolved in the short-term. For 2013 it was recommended that WHO continues to estimate malaria deaths as currently but considers including *P. vivax* mortality. WHO should clearly present the uncertainty in its estimates and the reasons for the discrepancies between its and IHME's estimates. Ways forward beyond 2013 are not yet clear. Some areas of further research were proposed, however:

2. *Assembling existing data to examine the evidence-base for the IHME estimates of malaria mortality in adults.* The IHME method relies heavily on verbal autopsy studies and research is required to determine why these studies are indicating higher proportional mortality rates from malaria than seems to accord with clinical experience and opinion. WHO and IHME should also engage with INDEPTH to investigate the reliability of the designation of malaria deaths in adults in verbal autopsy studies - Seth Owusu-Agyei should be involved in these discussions and can provide a link with INDEPTH research. In addition, the proportion of adult deaths attributed to malaria should be plotted against malaria endemicity to investigate whether or not this shows an expected pattern. Tom Smith's model should be re-examined with the age 65+ data included to see how the results compare to IHME's.

3. *Assembling high quality data on malaria deaths in those aged over 5 years.* Peter Byass, Fred Binka, Alan Schapira, Brian Greenwood (11 African RTS,S sites), John Aponte (Mozambique and Brazil sites) and Ashwani Kumar (India study of mortality in 3 different areas with different API) are potential sources of information and data

to further examine adult mortality. It may be useful to also examine the age distribution of admissions to hospital for severe malaria.

4. *Empirical research to reduce dependence on VAs for malaria.* Alternative sources of data on malaria specific mortality rates would be: (i) case-control studies comparing malaria parasite prevalence rates in those dying (of any cause) and controls (hospital and/or community controls), and (ii) prospective (cohort) studies of all-cause mortality in relation to malaria exposure as measured either by prevalence or EIR. Data relevant to (ii) exist in a number of DSS sites, in particular the MTIMBA database. Malaria prevalence surveys have been carried out in many DSS, making it possible to consider a multi-site prospective analysis of age-specific mortality in relation to prevalence This could probably be done for at least the following sites: Kilifi, Manhica, IHI (Kilombero-Ulanga, Rufiji?), CDC Kisumu, Kintampo, Navrongo, Farafenni, and Basse, The Gambia.

5. *Examining the effect of model choices on estimates:* CHERG inclusion criteria may have caused several high-quality VA studies to be excluded, and investigation is recommended as to why some studies were dropped and the impact of doing so. ERG members with knowledge of VA studies will compile a list of studies they believe should be included that may have been not included. Important differences in results may be illuminated if CHERG runs their models on the same malaria VA datasets used by IHME. It would also be of interest to rerun IHME's CODEm procedure without redistribution of unassigned deaths from VA studies. Since VA studies are the heart of malaria mortality estimation, and many of the differences between WHO's and IHME's estimates may be due to redistribution of VA deaths to malaria, the ERG is interested to see whether IHME's adult death estimates change substantially if the redistribution step is skipped.

Conclusion

While there seems to be a reasonable way forward with respect to the estimation of malaria case numbers, including retrospective adjustments of numbers in previous years, the most appropriate method for estimating malaria deaths is currently unclear. After reviewing this report and engaging in a follow-up teleconference, the ERG will decide on the necessity for, and the timing of, any additional meeting. As estimation methods and relevant data for estimating the burden of malaria are likely evolve, the ERG and MPAC should consider whether a standing committee on malaria burden estimation is required to advise WHO on a continuing basis as new studies and methods are developed.

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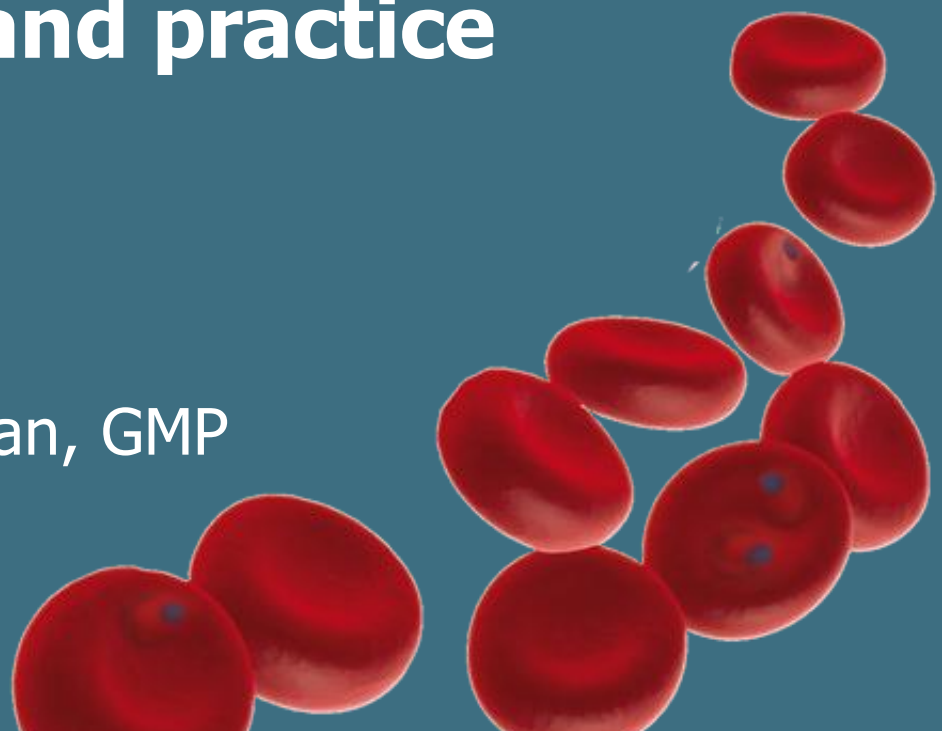
WHO Informal Consultation on fever management in peripheral health care settings: a global review of evidence and practice

V. D'Acremont and A. Bosman, GMP



World Health Organization

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WHO Informal Consultation on fever management in peripheral health care settings

Background for organising the meeting:

- Deployment of malaria testing + decreasing malaria transmission = ↑ proportion of febrile patients being diagnosed as not having malaria

- If no guidance and medicines for management of non-malaria fevers

  → clinicians tend to ignore the malaria test result

  → or they tend to overprescribe antibiotics

  Consequences: - undermines clinical benefits of parasitol. diagnosis
  - aggravates wastage of antimalarials and antibiotics
  - accelerates development of resistance to antimicrobials

- Clear algorithms for management of fevers at different levels of the health system, as well as good implementation support tools, are now available

WHO Informal Consultation on fever management in peripheral health care settings

Main aims of improving management of fevers:

To increase appropriate treatment and referral to

→ reduce severe diseases and deaths
→ reduce morbidity (length of febrile episode…)

To reduce unnecessary antibiotics and antimalarials prescription to

→ reduce drug pressures and development of resistance
→ decrease risk of drug adverse events
→ save money

Objectives of the meeting:

a) Review existing evidence and guidance on management of malaria and non-malaria fevers at primary care and community levels

b) Provide practical recommendations and operational tools for implementation of integrated management of fevers at peripheral level

c) Identify and discuss major research gaps

Section I - Review on etiologies and management of febrile illness

Recommendation 1

Studies on etiologies of fevers should be undertaken at different levels of health care and in different epidemiological settings, seasons and age groups.

Section I - Review on etiologies and management of febrile illness

Recommendation 1

Studies on etiologies of fevers

Emerging research findings

Children<5 years: - 0-12% malaria, 40-80% ARI, 10-25% diarrhea
- ARI mostly UARI and due to viruses (influenza, RSV)
- the remaining children had unspecific fever:
  - typhoid low in Africa, high in Asia
  - urinary tract infection always low
  - occult bacteremia very low

Children >5 and adults: - driven by HIV (40% in one study), 4-32% malaria
- Causes in malaria-neg. adults (with or without ARI/diarrhea):
  - OPD in Asia: Dengue, scrub typhus, JEV, leptospirosis
  - IPD in **Tanzania:** Chikungunya, leptospirosis, rickettsiosis, Q fever, brucellosis

Ref: D'Acremont, Bjorkman, Crump, Bell, Bhutta, unpublished

Section I - Review on etiologies and management of febrile illness

Recommendation 1

Studies on etiologies of fevers

Recommended study design

What?

- Focus mainly on non-specific fevers (absence of pneumonia, malaria & diarrhea)

Who?

- Inclusion criteria should be clear, reproducible and if possible as previous studies
- Do not forget children 5-15 years and infants <2 months

How?

- Use a simplified design and avoid repeating extensive etiological studies
- Use common case definitions between studies
- Always link clinical data to lab. results to avoid over-interpretation of positive results
- When possible, compare with lab. results in matched asymptomatic control groups

Section II - Available WHO guidelines and tools for the management of fevers

Recommendation 2

Malaria diagnosis and treatment should be deployed as part of promoting programmes for the integrated management of fevers, based on WHO algorithms available for different age groups and levels of care.

Section II - Available WHO guidelines and tools for the management of fevers

Recommendation 2

WHO algorithms for the integrated management of febrile illness

Available tools

	Hospital	*Health facility*	*Community (& informal private)*
Children	Blue book	IMCI	iCCM
Adults	District manual	IMAI	?

- IMCI & IMAI should be more widely disseminated
- Adherence to iCCM by community health workers is good
- The algorithm for malaria diagnosis and treatment is well integrated in most guidelines, except IMAI for HF level

→ no more malaria management without IMCI/iCCM
→ Home-based Malaria (2002-05) should be archived

Section II - Available WHO guidelines and tools for the management of fevers

Recommendation 2

WHO algorithms for the integrated management of febrile illness

Need for development and update

- Guidelines for age-groups above 5 years old managed at community level
- Guidelines for children 5 to 10 years
- Continuous update based on evidence, in particular (for malaria):
  - Criteria for high and low malaria risk area
  - Malaria testing of anemic children in high malaria risk areas
  - Malaria testing before referral/pre-referral treatment
  - Time interval for considering a new malaria infection (presently >14 days)
- New strategies to improve adherence to IMCI by clinicians working at HF level

Section II - Available WHO guidelines and tools for the management of fevers

Recommendation 2

WHO algorithms for the integrated management of febrile illness

Criteria for integrating new diagnostic tests

- Detecting illnesses with high disease burden and treatable
- More specific they are, more expensive

  clinical → epidemiological → severity test → pathogen-specific test
- Electronic tools to measure essential clinical parameters (RR, O2 Sat, temp.)
- Some pathogen-specific POCTs already available

  → some usable as they are (Dengue), others not yet (Typhoid)
- New POCTs are in development that

  → specifically detect one pathogen

  → 'generically' identify: - patients at risk for severe disease

  - patients in need for antibiotics
- Guidance to HWs' to target the use of tests to selected patients

Section II - Available WHO guidelines and tools for the management of fevers

Recommendation 2

WHO algorithms for the integrated management of febrile illness

Need for rethinking essential treatments

- High level of bacterial resistance to first line treatments:
  → How to quickly adapt guidelines to these changes?
  → How to replace co-trimoxazole by amoxicillin (dispersible) for ARI?
- Should also think in terms of 'class of antibiotics' (not only yes/no)
- No injectables for community level (pre-referral antibiotic???)
- No evidence can differentiate the list of medicines by level of health care → responsibility of countries

Section III - Agencies and NGOs experience with iCCM

Recommendation 3

Evidence from studies and lessons learned from implementation should be taken into account when planning scale-up of integrated Community Case Management (iCCM).

Section III - Agencies and NGOs experience with iCCM

Recommendation 3

Evidence from studies and lessons learned on iCCM

Evidence generated by operational research

- **Mortality:** ↓ when antimalarials introduced (ongoing studies for antibiotics)
- **Compliance to algorithm:** high for lab-tests (RDT), low for clinical-tests (RR)
- **Danger signs:** CHWs not good at picking them up, especially in newborns
- **Referral:** not done (why?)
- **Utilisation of CHWs:** is increasing but still below expected incidence of diseases
- **Measurement of quality of care:** direct observation without re-examination, registers, case scenarios, all not enough to assess danger signs & pneumonia
- **Access to care:** not only distance to CHW, but also staff and medicine availability
- **Salaries:** help retention of CHWs
- **Costs:** much cheaper to manage severe pneumonia at community level

Ref: Pagnoni et al, AJTMH, special supplement on iCCM, Dec 2012

Section III - Agencies and NGOs experience with iCCM

Recommendation 3

Evidence from studies and lessons learned on iCCM

Lessons learned from implementation

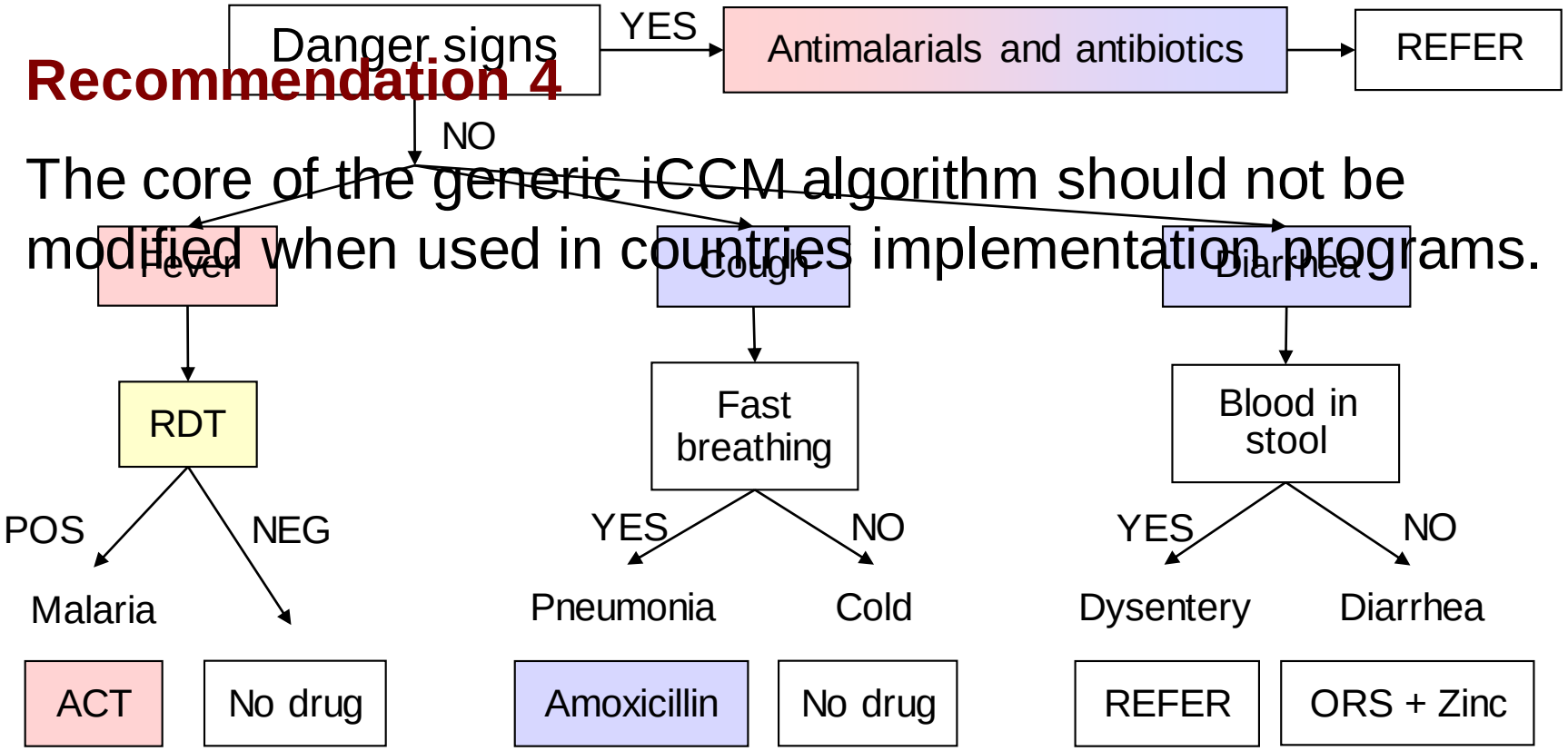
- **Supervision of CHWs:** by a senior peer rather than a clinician of HF
- **Retention of CHWs:** find country specific solutions from the start
- **Repeated drug shortages:** not sustainable having iCCM parallel systems
- **Seeking behaviour:** communities need to know what care they can expect
- **Weak M&E:** use innovative technologies (e.g. phones)
- **Extension of CHW tasks:** Newborn and child care initiatives should be integrated with iCCM (what about children 5-15 years and adults?)

Ref: Young et al, WHO/UNICEF joint statement on iCCM, 2012

Section IV – Country experiences with community case management of fevers – Public sector

Recommendation 4

The core of the generic iCCM algorithm should not be modified when used in countries implementation programs.



Section IV – Country experiences with community case management of fevers – Public sector

Recommendation 4

The core of the generic iCCM algorithm should not be modified

Need more emphasis on the following

- Management of fever always with management of at least ARI and diarrhea
- Mild malaria-neg. cases should not be systematically referred
- Severe cases should be given pre-referral antibiotics (especially if malaria test is neg)
- Fever cases should not be treated presumptively with antimalarials
- Mild malaria-neg. cases should not get antibiotics systematically
- Fast breathing should be assessed only in the presence of cough (overtreatment)
- Pneumonia cases should be treated with amoxicillin rather than cotrimoxazole

Section IV – Country experiences with community case management of fevers – Public sector

Recommendation 5

iCCM programs should be implemented together with strengthening quality of care in health facilities, based on IMCI and IMAI for primary care and hospital levels.

Section IV – Country experiences with community case management of fevers – Public sector

Recommendation 5

iCCM programs together with evidence-based care at HF level

Consequences of the absence of HF strengthening

- **Supervision:** clinicians of HF not able to supervise CHWs
- **Supply chain:** RDTs and medicines available at community but not HF level
- **Quality of care:** services at community level outperform HFs
- **Access to care:** 'opening hours' of CHWs broader than that of HFs
- **M&E:** reliable data from community not well used at primary care level

→ back referral of patients from health facilities to CHWs…

Section IV – Country experiences with community case management of fevers – Private sector

Recommendation 6

When subsidized malaria medicines and RDT are made available for the private sector, diagnosis and treatment for common non-malaria causes of fever should also be provided, based on WHO algorithms for iCCM.

Considerations supporting this recommendation

- Private sector is an important source of care in many (not all) settings
- Pneumonia kills even more than malaria…
- In high endemic areas, a patient can have both malaria and another disease
- In low endemic areas, most patients have negative RDT → would need referral

→ Case management is a service, not a commodity…

Section IV – Country experiences with community case management of fevers – Private sector

Recommendation 6

Provision of diagnosis & treatment for non-malaria fevers in private sector

What needs to be done?

- Clear segmentation of the private sector *(e.g drug peddlers, retail shops, non registered and registered drug shops, private clinics (by level), not-for-profits…)*
- Adapt the approach to the segment of the private sector *(e.g positive incentives)*
- Find mechanisms for supervision
- Elaborate surveillance methods
- Find mechanisms for Quality Assurance (and measurement) of care and products
- Empower consumers and the demand *(e.g 'branding' of the shops)*
- Understand the microeconomics of running private sector outlets

→ in fact, attention to what is done for the public sector…

Section V – Research Agenda

Recommendation 7

Research looking at new strategies for effective diagnostic and treatment of febrile illness should be encouraged, using clinical outcomes* as primary study endpoints rather than laboratory results, in order to modify or expand the current WHO algorithms.

* a common definition needs to be found

Section V – Research Agenda

Recommendation 7

New strategies for effective diagnostic & treatment of febrile illness

Emerging research findings

- Withholding antimalarials in patients with a negative RDT is safe even in high endemic areas (several studies)
- Proportion of RDT negative patients treated with ACTs is decreasing over time
- IMCI leads to overtreatment with antibiotics (poor specificity of RR for pneumonia)
- In Pakistan, the clinical outcome of children with non-severe pneumonia as defined by WHO was not different when receiving amoxicillin or placebo (Hazir *et al*)
- Management of severe (but not very severe) pneumonia as defined by WHO is safe at community level (several studies) → update of IMCI ongoing
- Management of children according to iCCM is safe at community level (sev. studies)

Ref: Reyburn, Williams, Msellem, Bisoffi, Hamer, Skarbinski, D'Acremont, Ansah, Hopkins, Mawili-Mboumba, Yeboah, Chanda, Tiono, Anyorigiva, Akogun, Thiam, Bastiaens, Mukanga, Bari, Hazir, Soofi …

Section V – Research Agenda

Recommendation 7

New strategies for effective diagnostic & treatment of febrile illness

Recommended areas of research

- Safety of withholding antibiotics for non-severe pneumonia in children under five
- Best management of non-specific fevers in children and adults
- Benefit of specific classes of antibiotics in patients with non-specific fevers
- Risk factors for disease progression, severe illness and drug resistance
- Development and use of Disease severity vs Pathogen-specific lab tests
- Benefit of using new respiratory rate counters and pulse oximetry
- Best way to modify current algorithms for management of febrile patients
- Potential of new tools (e.g. electronic guides) for compliance and data collection
- Modelling to inform target product profiles of new diagnostics

Summary of recommendations

1. Studies on **etiologies of fevers** should be undertaken.
2. **Malaria** diagnosis and treatment should be deployed as part of **integrated management of fevers** (WHO algorithms).
3. **Evidence and lessons learned** from implementation should be taken into account when scaling-up **iCCM**.
4. The **core of the generic iCCM algorithm** should not be modified when used in countries programs.
5. **iCCM** programs should be implemented **together with** strengthening quality of care in **health facilities**.
6. When subsidizing malaria medicines and RDT for the **private sector**, also provide diagnosis and treatment for **common non-malaria causes of fever**.
7. **Research on new strategies** for effective diagnostic and treatment of febrile illness should be encouraged, using **clinical outcomes** as primary study endpoints.

Updating the WHO Guidelines for the Treatment of Malaria (MTGs) Pre-read for MPAC March 2013 Meeting

Introduction: The WHO Guidelines for the Treatment of Malaria (MTGs), the current edition of which is available in English, French and Spanish, provides comprehensible, global and evidence-based guidelines for the formulation of policies and protocols for the treatment of malaria. It was first published in 2006 with the 2nd edition published in 2010. The guidelines are available both in hard and electronic (web-based) versions. The MTGs have been produced under the guidance of the Technical Expert Group (TEG) on Malaria Chemotherapy, convened by the WHO Global Malaria Programme. Major comprehensive review for an updated edition of the Guidelines is undertaken after at least 3 years following the most recent publication. In between this review period, specific section updates can be undertaken on an ad-hoc basis when sufficient evidence supports this, and it is of major public health significance. A draft plan for revision and update was endorsed at the last meeting of the Malaria Policy Advisory Committee (MPAC) in September 2012. The purpose of this pre-read is to inform the MPAC of the progress since their last meeting on the process of reviewing and updating the Guidelines.

Proposed Scope of review (3rd edition): During a meeting of the Scoping Sub-committee of the TEG on Antimalarial Chemotherapy in Geneva on 25-26 February 2013, consensus was reached on the proposed scope of revisions and updates planned for the production of a 3rd edition (See Table 1, below). This will include a comprehensive review of existing recommendations in the light of any new evidence that might affect each recommendation in its totality, or with regard to the strength of the recommendation. A new section will be included to guide the use of antimalarials in the prevention of malaria: Intermittent preventive treatment, Seasonal malaria chemoprevention, and Chemoprophylaxis in travelers. In addition, a number of specific areas have been identified for in-depth / systematic review, including the section on drug quality.

Table 1: Proposed major revisions for the 3rd Edition of the Guidelines for the Treatment of Malaria

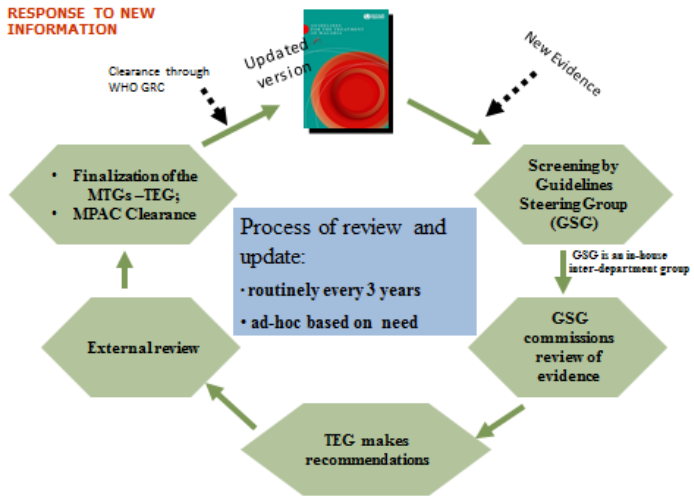
Key topic / Recommendation	Evidence
Title – Revise based on inclusion of preventive treatment and chemoprophylaxis.	
Resistance to antimalarial medicines – Expanding guidance on containing artemisinin resistance (together with TEG on DRC).	B
Antimalarial drug quality – New chapter (expanding section 7.8.4)	B
Antimalarial treatment policy	
Strategies to improve adherence to policies in the private and informal sectors.	B
Role of multiple first line therapies to slow the spread of antimalarial resistance.	B
Diagnosis of malaria	
Comparison of RDTs, microscopy and PCR for *P. falciparum* diagnosis, including the number of cases missed by false negative tests.	A
Comparison of RDTs, microscopy and PCR for the diagnosis of *P. vivax* malaria.	A
Risk: benefit assessment of limiting ACT treatment to definitively diagnosed patients.	B/C
Is systematic malaria testing needed in children presenting with moderate - severe anaemia in high-risk malaria areas?	B
Treatment of uncomplicated P. falciparum malaria	
Update on safety, and efficacy of available ACTs (including comparison of cardiotoxicity across quinolone antimalarials).	A*
Update review of the effect of ACT treatment duration of efficacy.	A*
Review published and other data in public-domain on novel antimalarial molecules / combinations that have been pre-accredited / registered recently, and consider against agreed criteria whether any should be systematically reviewed and graded.	A
Drug interactions between antimalarials and antiretrovirals.	A*
Interactions between malaria and iron supplementation.	A
Review the safety and efficacy of ACTs in the treatment of uncomplicated malaria in pregnancy, with separate analyses for first trimester, and for 2nd / 3rd trimesters; and for *P. falciparum* and *P. vivax* treatment.	A
Refine dosage recommendations in vulnerable target populations. Review recommendations for treatment of newborns, infants, malnourished and obese patients.	B
Refine definition of treatment failure, and indications for 2nd line treatment.	C
Emphasise importance of follow up and notification of confirmed cases to inform targeting of control / elimination strategies.	C

Treatment of severe P. falciparum malaria	
Is parenteral artemether superior to parenteral quinine in severe malaria?	A
Efficacy of rectal artesunate as pre-referral treatment, stratified by age, parasite density.	A
The role of antibiotic use in management of severe malaria, stratified by age.	A / B
Fluid therapy in severe malaria.	A / C
Risk of haemolysis following severe malaria treated with injectable artesunate.	B
Treatment of non-falciparum (P vivax, ovale, malaria, knowlesi) and mixed infections	
Is ACT or CQ preferred treatment for uncomplicated *P. vivax / ovale* treatment (stratified by primaquine co-administration)?	A*
Define minimum age when primaquine considered safe to use	A
Add section on treatment of *P. knowlesi.*	B/C
Case management in the context of malaria elimination	
Safety and effectiveness of mass drug administration in cluster randomised trials.	A
Safety and efficacy of 0.25 vs. 0.75 mg/kg primaquine as gametocytocidal agent for reducing *P. falciparum* transmission.	B
Role of RDTs in malaria elimination programmes.	C
Intermittent Preventive Treatment - New Chapter	
Safety and Efficacy of mefloquine as IPTp, compared to available antimalarials (together with ERG).	A
Minimum number of SP doses required for effective use as IPTp, stratified by HIV and of quintuple *dhfr/dhps* mutation prevalence.	A
Safety and Efficacy of IPTi.	A
Seasonal Malaria Chemoprophylaxis – New chapter	A*
Chemoprophylaxis in Travellers – New chapter	A
Safety and Effectiveness of available chemoprophylaxis options, including primaquine	A
General – Colour code to distinguish treatment and prevention sections; Condense where possible; More graphics and images to be included; Better use of online annexes and weblinks; Consider Portuguese translation.	
Legend on Levels of Evidence	
A: Systematic Review and Grade Table; (A* - Grade Table available - to be updated if necessary)	
B: Systematic Review and modelling (PK / economic) - for evidence not suitable for GRADE Table	
C: TEG Consensus decision	

Review process and timelines*

September 2012	Establishment of a WHO Guideline Steering Group (GSG). This is a WHO in-house committee comprised of members from relevant WHO departments involved in development of guidelines related to case management of malaria.
February 2013	Meeting of WHO GSG with the MTG TEG Scoping sub-committee to define the likely revisions needed in terms of new sections, and substantial revisions to existing sections, for which systematic evidence reviews are required.
March 2013	Commission of reviews of available evidence.
September 2013	Completion of Systematic Reviews and construction of GRADE Tables by LSTM Cochrane review group.
October 2013	Completion of 1st draft of 3rd Edition of the Guidelines.
November 2013	Full TEG meeting to review and reach consensus on recommendations in 1st draft of 3rd Edition of Guidelines.
December 2013	Revise 1st draft of 3rd Edition of Guidelines to capture recommendations of the TEG and GSG, and ensure consistency throughout all sections.
January 2014	Review by External experts and potential end/users of the guidelines.
February 2014	Finalization of the guidelines and submission to MPAC.
March 2014	Approval from MPAC.
Q2 2014	Final clearance through the WHO GRC and other WHO in-house processes.
June 2014	Ready for Printing, Web Publication, translations and dissemination.

A simplified illustration of the process is presented below.



* *The timeframe included above is the anticipated minimal projections based on the previous experience of the Malaria Treatment Guidelines development process. The GRC advises that a minimum of 24 months is required to produce or update a standard comprehensive Guideline.*

Updating the Guidelines for the Treatment of Malaria

Meeting of the Malaria Policy Advisory Committee
Geneva, 13-15 March, 2013

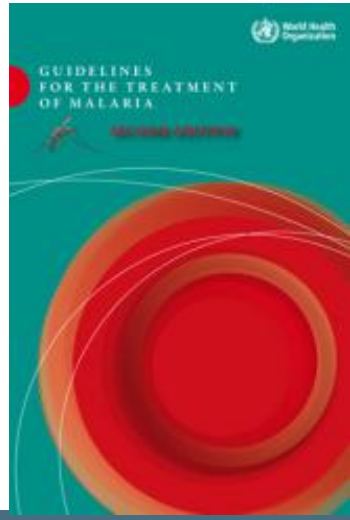
Prof. Nick White
Co-chair, Chemotherapy Technical Expert Group
With thanks to Peter Olumese

World Health Organization

GLOBAL MALARIA PROGRAMME

WHO Guidelines for the Treatment of Malaria (MTGs)

- **The WHO Guidelines for the Treatment of Malaria (MTGs),**
  - **provide comprehensible, global and evidence-based guidelines for the formulation of policies and protocols for the treatment of malaria.**
  - **was first published in 2006, and a revised edition (2nd edition) published in 2010.**
  - **is available in hard and web-based versions.**
  - **the current edition of which is available in English, French and Spanish.**



Target audience

- **primarily policy-makers in ministries of health, who formulate national treatment guidelines.**
- **in addition, the other groups working in public health and institutions should also find them useful**

Update of the review process

- **A draft plan for revision and update for the 3rd edition was endorsed at the Malaria Policy Advisory Committee (MPAC) in September 2012. This included**
  - The proposed scope and development timelines
- **This presentation highlights the outcome of a meeting of the scoping sub-committee of the TEG on malaria chemotherapy (25-26 February 2013). The main objective of the meeting were:**
  - Identify and list: 1). priority topics and /or sections of the current Guidelines to be updated; and 2). new priority topics/ area that need to be included in the Guidelines.
  - Develop potential recommendations on identified areas and formulate draft questions using the population, intervention, comparison, outcome (PICO) format for evidence collation and review

Outcome of the scoping meeting

Highlights of the outcome of the meeting were:

- **Consensus on conducting a comprehensive review of existing recommendations in the light of new evidence that might affect each recommendation in its totality, or with regards to the strength of the recommendation.**
- **A *new section* on the use of antimalarials in the prevention of malaria will be included in the new edition.**

Specifics

A few specifics are presented below, the extensive list in in the pre-read

- **General**
  - ?Title revision (with inclusion of preventive chemotherapy)
  - Expand sections on
    - Resistance to antimalarial medicines
    - Antimalarial drug quality
    - Antimalarial treatment policy
- **Diagnosis**
  - Comparison of RDTs, microscopy, and PCR
  - Is systematic malaria testing needed in all children presenting with anaemia in high transmission areas

Specifics (contd)

- **Treatment of uncomplicated *P. falciparum* malaria**
  - Update on safety, and efficacy of recommended ACTs
  - Review data (public domain) on novel antimalarial molecules /combinations with a view of inclusion or not in the MTGs.
  - Review safety and efficacy of ACTs in the treatment of malaria in pregnancy (all trimesters)
  - Refine dosage recommendations, particularly in vulnerable populations
  - Refine indications for 2nd line treatment
- **Severe malaria**
  - Is parenteral artemether superior to parenteral quinine
  - Efficacy of rectal artesunate as pre-referral treatment
  - The role of antibiotic use in the management of severe malaria
  - Fluid therapy
  - Risk of post treatment haemolysis following the use of injectable artesunate
- **Treatment of non non-falciparum malaria**
  - Is ACT or CQ preferred treatment for vivax / ovale
  - Add section on *P.knowlesi*

Specifics (contd)

- **Case management in the context of malaria elimination**
  - Safety and effectiveness of mass drug administration
  - Safety and efficacy of 0.25 vs. 0.75mg/kg primaquine as gametocytocidal agent for *P. falciparum*
  - Role of RDTs in malaria elimination programmes
- **New chapters**
  - Intermittent preventive treatments (IPTp; IPTi)
  - Seasonal malaria chemoprevention
  - Chemoprophylaxis in travelers
    - Safety and effectiveness of available chemoprophylaxis options, including primaquine

Review timelines

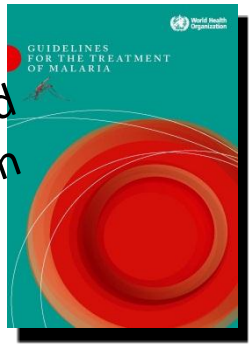
- **Commission of reviews of available evidence – *March 2013***
- **Completion of the systematic reviews and Grade tables – *September 2013***
- **TEG meeting to review and reach consensus on the draft recommendations *(November 2013)***
- **Finalisation and submission to MPAC *(March 2014)***
- **Final clearance through the WHO GRC and other WHO in-house processes *(second quarter 2014)***
  - Publication, translations and dissemination ***(June 2014)***

***** *Major rate limiting step is the availability of evidence in a format suitable for systematic review to which the GRADE methodology can be applied.*

RESPONSE TO NEW INFORMATION

Clearance through WHO GRC

Updated version



New Evidence

- **Finalization of the MTGs –TEG;**
- **MPAC Clearance**

Screening by Guidelines Steering Group (GSG)

GSG is an in-house inter-department group

GSG commissions review of evidence

TEG makes recommendations

External review

Process of review and update:

- **routinely every 3 years**
- **ad-hoc based on need**

Technical Expert Group (TEG) on Malaria Vector Control – Update, March 2013

During its last meeting in September 2012, the Malaria Policy and Advisory Committee (MPAC) requested the establishment of a Technical Expert Group (TEG) on malaria vector control. The TEG was tasked with reviewing and providing guidance and making draft recommendations to the MPAC on the implementation of malaria vector control including issues related to programme management.

The responsibilities of the TEG is to review and recommend to MPAC the predicted effectiveness and appropriate mix of vector control interventions for particular situations, including: the adoption of new forms of vector control following recognition of "proof of principle" from the Vector Control Advisory Group (VCAG); the formulation of evidence-based norms, standards and guidelines for the implementation and management of malaria vector control; policy issues related to building capacity for entomological monitoring and optimization of vector control investments; and identify gaps in evidence and specific areas of research to improve the management and implementation of malaria vector control.

As the challenges of implementing malaria vector control at country level are changing rapidly, especially the threat of insecticide resistance and maintaining coverage in financially constrained programmes, MPAC also requested the TEG to provide advice directly to the Global Malaria Programme (WHO/GMP) when necessary.

Following a call for candidate vector control experts to serve and support the two both the WHO Vector Control TEG and VCAG, a total of 147 curriculum vitae were received. These were scored by two WHO-assigned external experts (MPAC members) and two WHO staff, in the following areas of expertise: malaria vector biology and control; insecticide resistance; epidemiology of malaria transmission; vector control - including impact of interventions; planning and management of vector control programmes; and health systems - including health economics. Pre-established criteria for scoring were used.

The consolidated list of scores by the above-mentioned experts were used to rank the candidates. The same pool of 147 candidates were reviewed by GMP and the Neglected Tropical Disease (NTD) to score and identify potential members for the newly established VCAG on new forms/tools of vector control. Note that VCAG, focused on vector control *tools* including those for other vector-borne diseases, such as dengue, will be jointly managed by GMP and the Neglected Tropical Disease Department. The TEG, focused on malaria vector control strategies is managed by GMP and reports to the MPAC. In order to maximize the contribution of the experts to the work of the two advisory committees where possible, assignment of the same individuals to both committees was avoided.

The following candidates accepted an invitation to serve as members of VC TEG. The nomination took into consideration their expertise, geographical and gender distribution. Of the fifteen proposed members, five are women.

No.	Name	Gender	WHO Region
1	Chioma Amajoh	Female	AFRO
2	Pierre Carnevale	Male	EURO
3	John Chimumbwa	Male	AFRO
4	Maureen Coetzee	Female	AFRO
5	Josiane Etang	Female	AFRO
6	Marc Coosemans	Male	EURO
7	Jeffery Hii	Male	WPRO
8	Christian Lengeler	Male	EURO

9	Jonathan Lines	Male	EURO
10	Mark Rowland	Male	EURO
11	Robert Wirtz	Male	AMRO
12	Martha Quinones	Female	AMRO
13	Melanie Renshaw	Female	EURO
14	Joshua Yukich	Male	AMRO
15	Rajander Singh Sharma	Male	SEARO

Dr. Melanie Renshaw and Dr. John Chimumbwa have agreed to serve as co-chairs of the Vector Control TEG.

The TEG is working with the Secretariat in the following three areas to develop policy recommendations for MPAC at its next meeting in September 2013:

1. Position Statement on Methods for Maintaining Coverage with Long-lasting Insecticidal Nets (LLINs)

A first draft of this paper was shared with TEG members on 25 February 2013. This was the last day members were requested to confirm their acceptance. Comments were received on March 4. The consensus from TEG members was that the document needed further refinement before presentation to MPAC. The TEG recommended that universal coverage remain the goal, with implementation of mass campaigns every three years, coupled with continuous routine distribution through multiple channels according to the specific country context. The paper needs to be concise, with clear, practical recommendations for national programmes that reflect the experiences accumulated over the years on the implementation of different distribution channels.

2. Technical guidance for countries and partners on how to estimate the survival of LLINs from field data on durability

The second critical area where national programmes have asked for guidance, is how to estimate the durability of LLINs after deployment. This information is critical for budgeting, for the timing of distribution campaigns, for procurement decisions for specific country contexts as well as an incentive to manufacturers for more durable and innovative products. The paper is currently being drafted. It will be shared with TEG members for their review and recommendations before being presented to MPAC in September 2013 for decision.

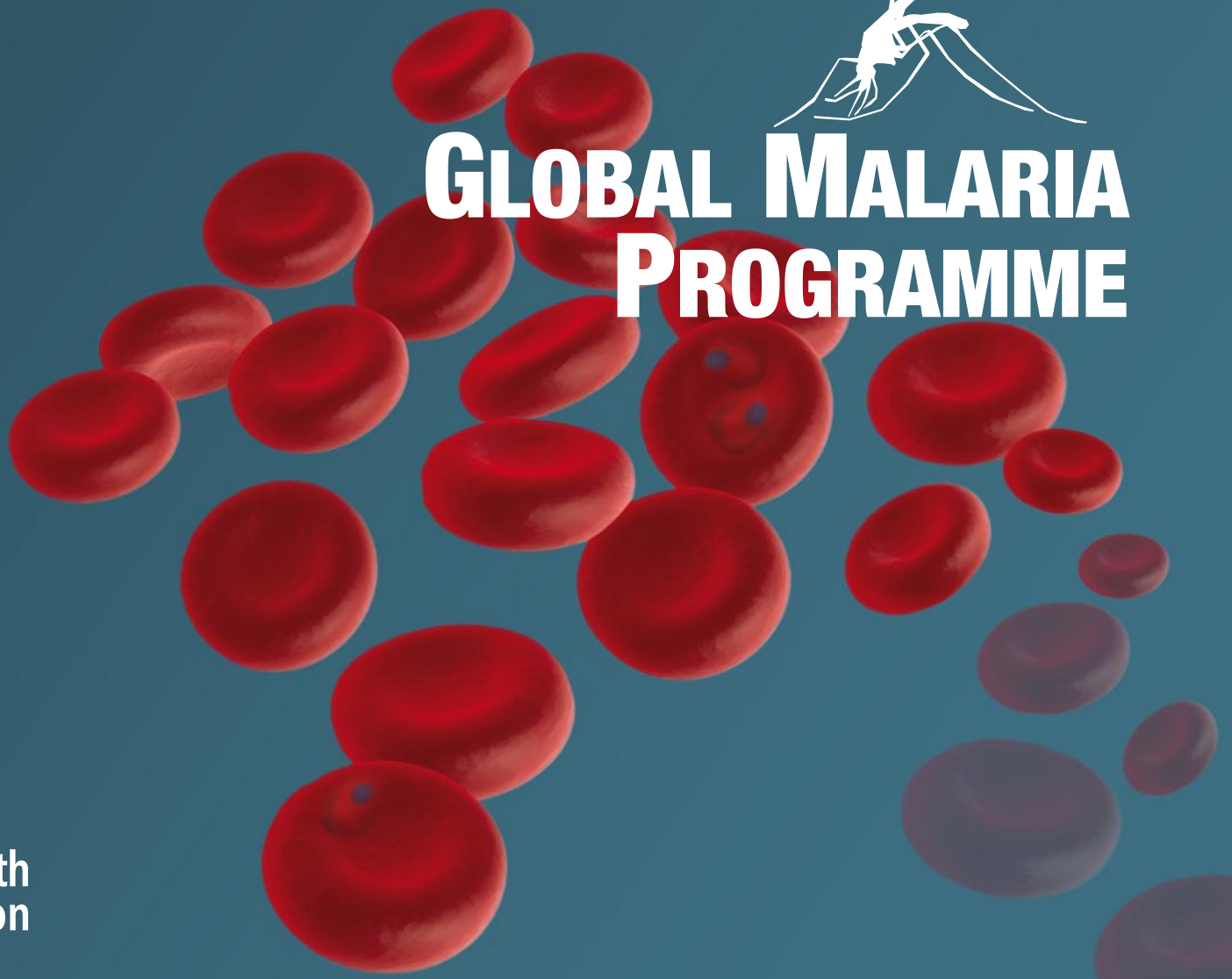
3. Technical guidance for countries to prioritize malaria vector control interventions when faced with constrained or unstable resources

The third critical area where national programs have asked for guidance is how to prioritize interventions, including indoor residual spraying and LLIN distributions, when the program is faced with constrained or unstable resources. The paper is currently being drafted and will be shared with TEG members for their review and recommendation before being presented to MPAC in September 2013 for decision.

A meeting of TEG is planned for 15-17 July 2013 to discuss and finalize these papers and propose recommendations for MPAC in September 2013 for a decision.

The MPAC is invited to provide input to the three topics under consideration above, as well as to suggest other areas of focus or specific question for the Vector Control TEG to address in the near future.

VC TEG updates for MPAC Meeting, March 2013



GLOBAL MALARIA PROGRAMME

World Health Organization

Outline

- Call to establish a malaria vector control Technical Expert Group (TEG)
- Process to constitute the Technical Expert Group
- What are the immediate issues requiring TEG's attention?
- Next steps to address the gaps in policy/guidance
- Way forward

Call to establish a TEG on malaria vector control

- **September 2012, MPAC requested the establishment of a Technical Expert Group (TEG) on malaria vector control.**
- **The TEG was tasked with:**
  - Reviewing and providing guidance on the implementation of malaria vector control
  - Drafting recommendations to the MPAC on vector control including issues related to programme management
  - When necessary, provide advice directly to the Global Malaria Programme (WHO/GMP)

Responsibilities of TEG

- **Review and recommend to MPAC the predicted effectiveness and appropriate mix of vector control interventions for particular situations, including:**
  - the adoption of new forms of vector control following recognition of "proof of principle" from the Vector Control Advisory Group (VCAG);
- **Formulate evidence-based norms, standards and guidelines for the implementation and management of malaria vector control;**
- **Propose policy recommendations for building capacity on entomological monitoring and optimization of vector control investments;**
- **Identify gaps in evidence and specific areas of research to improve the management and implementation of malaria vector control**

Request for CVs from Vector Control Experts

- A call for candidates to serve on the TEG and VCAG
- Response was overwhelming – received a total of 147 CVs
- For VC TEG, these were scored by two external experts (MPAC members) and two WHO staff

Areas of expertise and criteria for scoring candidates

- **The focus was on the following areas of expertise:**
  - malaria vector biology and control;
  - insecticide resistance;
  - epidemiology of malaria transmission;
  - vector control - including impact of interventions;
  - planning and management of vector control programmes;
  - and health systems - including health economics.
- **Pre-established criteria for scoring were used as follows:**
  - 0 = no experience; 1 = 2 years or less experience
  - 2 = 3-5 years of experience; 3 = 6-9 years of experience
  - 4 = 10-14 years of experience; 5 = more than 15 years of experience
  - Relevant skills and experience

No.	Name	Gender	WHO Region
1	Chioma Amajoh	Female	AFRO
2	Pierre Carnevale	Male	EURO
3	John Chimumbwa	Male	AFRO
4	Maureen Coetzee	Female	AFRO
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12	Martha Quinones	Female	AMRO
13	Melanie Renshaw	Female	EURO
14	Joshua Yukich	Male	AMRO
15	Rajander Singh Sharma	Male	SEARO

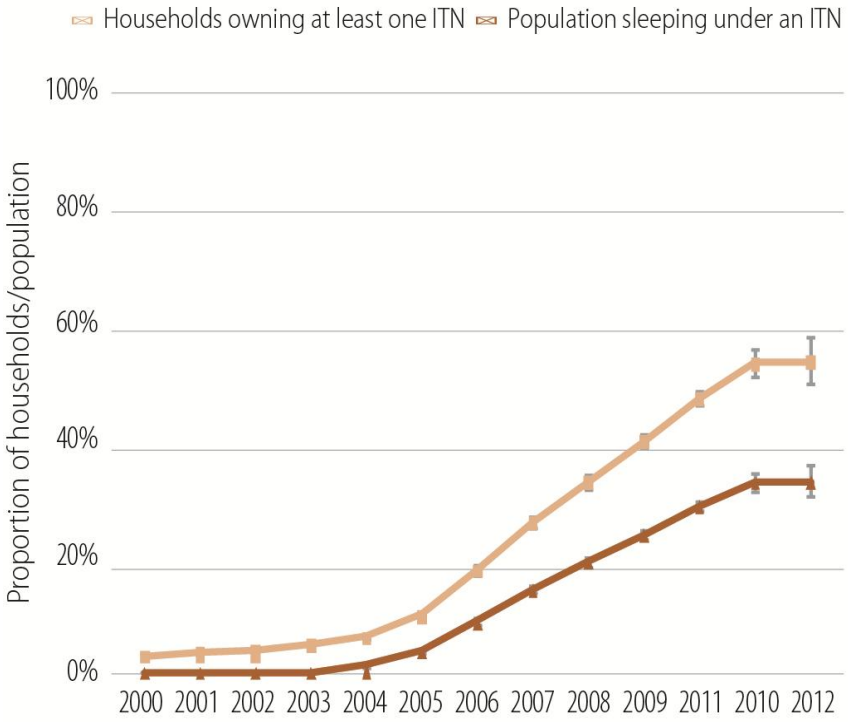
Challenges requiring policy guidance by TEG

- Unstable financial resources to ensure universal access to interventions
- Need for more durable nets
- Capacity to implement GPIRM technical recommendations

Trend in estimated households with at least one ITN and population sleeping under an ITN in sub-Saharan Africa

The percentage of households owning at least one ITN in sub-Saharan Africa rose from 3% in 2000 to 53% in 2011, and remained at 53% in 2012.

The proportion of the population sleeping under an ITN also increased from 2% in 2000 to 33% in 2011, and remained at 33% in 2012.

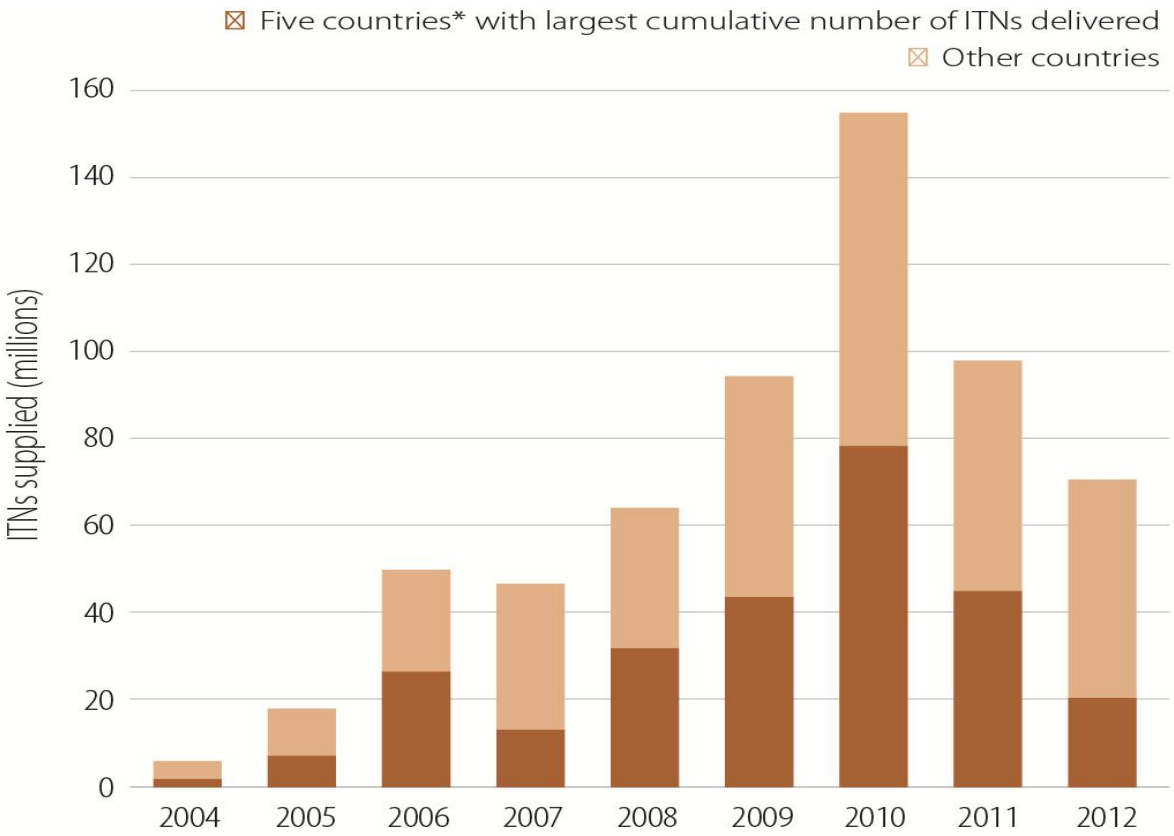


Proportion of population sleeping under an ITN derived from relationship with household ownership of at least one ITN analyzed by linear regression in 48 household surveys 2001-2011, y= 0.67x - 0.03.

Source: ITN coverage model from the Institute for Health Metrics and Evaluation, which takes into account ITNs supplied by manufacturers, ITNs delivered by NMCPs and household survey results (1). Includes Djibouti, Somalia and Sudan which are in the WHO Eastern Mediterranean Region.

Number of ITNs delivered by manufacturers to countries in sub-Saharan Africa

- 150 million ITNs are needed annually
- Only 66 million delivered in 2012
- Down from 145 million delivered in 2010
- Situation needs urgent attention



* Democratic Republic of the Congo, Ethiopia, Kenya, Nigeria, United Republic of Tanzania

Source: *Alliance for Malaria Prevention. Data for the first three quarters of 2012 have been multiplied by 4/3 to provide an annual estimate.*

Evidence that LLIN longevity is variable and 2 years or less in some settings

- Multi-country analysis by A. Kilian et al found average 50% survivorship after 3 years
- Madagascar preliminary analysis of 3-year follow-up data:
  - survivorship of 51% of polyester and 41% of polyethylene LLIN
  - most holes caused by sparks from fire and rodent damage
- Nigeria: AMP household surveys report high loss after 1 year
- Mentor Initiative: report high 3-year failure of 2 major current LLIN types in eastern Chad (mechanical damage)
- WHO guidelines on monitoring LLIN durability since 2010
- WHO procurement guidelines in 2012 – emphasizing on local data on durability

➢ **There is a need to invest in developing more durable nets and guidance on how to estimate the median life span of LLINs to support effective coverage at country level**

Immediate strategies - where LLINs are main vector control intervention, and no increase in malaria cases

Areas with	Monitoring Response	Vector Control Response
No resistance yet	• Frequent monitoring to check for appearance of resistance	• No change

Resistance unknown	• Introduce resistance monitoring immediately and identify mechanisms (genes)
	• Close monitoring for
	  • increase in R-gene frequency
	  • spread to new locations
	• Check/reinforce surveillance for increases in cases
		• Continue promoting LLINs
		• Ensure quality, extent, completeness of LLIN coverage;
		• Timely replacement of worn-out nets

If resistance reported	• Identify mechanisms (genes)
	• Close monitoring for
	  • increase in R-gene frequency
	  • spread to new locations
	• Check/reinforce surveillance for increases in cases
		• Continue promoting LLINs
		• Add, if possible, IRS with non-pyr (with rotation) in all resistance areas or at least in areas of concern.
		• Review and revise when mechanism(s) known

Immediate strategies - where LLINs are the main vector control intervention, and malaria cases seem to be increasing

Areas with	Monitoring Response	Vector Control Response
No resistance yet (so IR not the cause of the increase)	• Frequent monitoring to check for appearance of resistance • Monitor VC coverage closely to establish cause of increase	• Ensure quality, extent, completeness of LLIN coverage; • Timely replace worn-out nets.

Resistance mechanism unknown	• Identify mechanisms (genes)
	• Close monitoring for
	  • increase in R-gene frequency
	  • spread to new locations
	• Check/reinforce surveillance
		• Continue promoting LLINs
		• Add, if possible, IRS with non-pyr (with rotation) in all resistance areas or at least in areas of concern.
		• Review and revise when mechanism(s) known

Immediate strategies - where IRS is the main vector control intervention

Areas with	Monitoring Response	Vector Control Response
No resistance yet	Frequent monitoring to check for appearance of resistance	Pre-emptive rotations (annual)
Resistance present	• Close monitoring for increase in R-gene frequency and spread to new locations • Identify R mechanisms (genes) • Reinforce surveillance for increases in cases	• Stop use of current insecticide (and others to which there is also resistance) • Introduce rotations with other classes

Next Steps to address the challenges

1. Technical paper on methods to sustain UC with LLINs

- **A draft paper was shared with TEG members on 25 February 2013 and comments received on March 4**
  - Consensus that the document needed further refinement before presentation to MPAC
  - Universal coverage remains the goal, with implementation of mass campaigns every three years
  - Coupled with continuous routine distribution through multiple channels according to the specific country context
  - Guidance should be concise, with clear, practical recommendations for national programmes
  - Guidance should reflect experiences and local context on the implementation of different distribution channels

2. Technical guidance on how to estimate median LLIN durability

- **National programmes have asked for guidance on how to estimate the median durability of LLINs after deployment**
- **Information is critical for**
  - Overall budgeting of LLIN implementation
  - Timing of distribution campaigns
  - Procurement decisions for specific country contexts
  - Encouraging manufacturers for more durable and innovative products

➢ **The paper is currently being drafted and will be shared with TEG members for their review and recommendation. It will be presented to MPAC in September 2013 for decision.**

3. Technical guidance for countries to prioritize vector control interventions when faced with resource contraints

- National programs have asked for guidance on how to prioritize interventions when faced with constrained or unstable resources
- Is prioritizing/targeting of vector control interventions the way forward?
- What is the criteria – biological or geographical targeting?
- How feasible is this in countries where the malaria surveillance system is weak?

➢ **The paper is currently being drafted and will be shared with TEG members for their review and recommendation. It will be presented to MPAC in September 2013 for decision.**

4. Technical guidance and rationale for capacity building for vector control

- Policy guidance has focused on commodities (LLINs and insecticides) – also need human and infrastructural guidance
- Increased demand for routine entomological surveillance and for insecticide resistance monitoring and management – requires well trained people
- How do we develop a training programme/curriculum that is tailored to the needs of control programmes?

➢ **Planning to draft a technical paper on capacity building to be reviewed by TEG and a possible decision by MPAC in March 2014.**

Way forward

- A meeting of the VC TEG is planned for 22nd-24th July 2013 to discuss and finalize these papers and propose recommendations for MPAC in September 2013 for a decision.

- **The MPAC is invited to provide input to the four topics under consideration above, as well as to suggest other areas of focus or specific question for the Vector Control TEG to address in the near future**