World Health Organization

Thursday, 14 March 2013

Time	Session	Purpose of session, target outcomes and questions for MPAC	Type
	Session 5		open
09:00	RTS,S/AS01 Update **(D Kaslow/P Smith)**	For information	
09:55	Malaria Vaccine Technology Roadmap Update **(V Sathiyamoorthy)**	For information and input into target product profiles	
10:30	**Coffee/tea break**		
	Session 6		open
11:00	Financing malaria control **(R Cibulskis)** • Global resource allocation priorities • Guidance to countries on achieving highest impact with limited resources including prioritization among multiple interventions	For discussion and endorsement For discussion and input	
13:30	**Lunch**		
	Session 7		open
14:30	Malaria surveillance and proposed SME TEG **(R Cibulskis)**	For discussion and decision	
15:30	**Coffee/tea break**		
	Session 8		open
16:00	Criteria and classification related to elimination **(A Shapira/ A Rietveld)**	For discussion	
17:00	Intermittent Preventive Treatment in pregnancy **(A Bosman)**	For information re: second ERG meeting in July 2013	
17:30	**End of day**		

SUMMARY FOR MALARIA POLICY ADVISORY COMMITTEE RE: RTS,S/AS01 MALARIA VACCINE

February 2012. Written by WHO secretariat with input from JTEG Chair

For an introduction on the design of the Phase III trial, and an overview of the timings of availability of different data packages, please refer to the Briefing document on RTS,S/AS01 prepared for the September 2012 MPAC meeting[1].

There was an in-confidence Joint Technical Expert Group (JTEG) on Malaria Vaccines meeting on 9-10 October 2012. At this meeting GSK (GlaxoSmithKline) and PATH Malaria Vaccine Initiative (MVI) presented the second set of results from the Pivotal Phase 3 trial of RTS,S/AS01.

These results were published in a New England Journal of Medicine article[2], available online from 9 Nov 2012. The article reports data from 6,537 infants aged 6-12 weeks of age randomized 2:1 who received RTS,S/AS01 or Meningococcal C conjugate vaccine (control) in co-administration with DTwP/HepB/Hib and OPV. The duration of follow-up reported is 12 months post dose 3.

Efficacy & Immunogenicity: Summary Table of Per Protocol Analyses for RTS,S/AS01 Phase III Trial.

	6-12 week age group **(published Nov 2012)**	5-17 month age group **(published Oct 2011)**
Efficacy, first or only episode of clinical malaria	31%(97.5% CI 24-38)	56% (97.5% CI, 51 to 60)
Efficacy, all episodes of malaria	33% (95% CI 26-39)	55% (95%CI 50-59)
Efficacy, severe/ hospitalized malaria	37% (95% CI 5-58)	47% (95% CI 22-64)
Immunogenicity (antibody, elisa units per ml to malaria antigen).	209 (95%CI 197-222)	621 (95% CI, 592 to 652).

No new safety concerns are raised by this set of results, and it remains the case that the full Phase III data will be reviewed by the Global Advisory Committee on Vaccine Safety prior to the SAGE/MPAC decision session in 2015.

While much of the discussion following publication is likely to focus on the apparent difference between the efficacy figures in the 2 age groups, JTEG advised that the two age groups are not strictly comparable. This is because the numbers enrolled by site across the 11 sites differs between the two age groups, as does the number of malaria events. Malaria transmission intensity varies greatly across the sites. JTEG advised that site or transmission strata specific efficacy analyses are necessary to interpret the new results, and this was communicated to GSK/PATH Malaria Vaccine Initiative (MVI).

[1] Available from http://www.who.int/entity/malaria/mpac/sep2012/breifing_rtss_mpac_sep2012.pdf
[2] N Engl J Med 2012; 367:2284-2295. December 13, 2012. www.nejm.org/doi/full/10.1056/NEJMoa1208394

In 2012, GSK/MVI stated that they could not perform such analyses until a protocol amendment was passed by ethical committees. The site-specific analyses will proceed during 2013 as the protocol amendment had passed as of March 2013.

A potentially important finding is the three-fold lower antibody concentrations by ELISA to the malaria antigen in the younger age group. The apparent difference in efficacy between the two age groups may relate to some or all of the following factors: interference from co-administration with EPI vaccines, maternally acquired antibodies to the malaria antigen in RTS,S/AS01 and differences in the prior exposure of the children to malaria. If efficacy varies with transmission intensity, and the distribution of enrolled cases between sites with various transmission intensities is different between the 2 age groups, this could be a contributory factor. The time over which enrolment was completed was longer for the younger age group. Thus seasonality of transmission could also have impacted vaccine efficacy differently in the 2 age groups. A further factor raised by the GSK/MVI partnership is that the children in the 5-17 month age category had almost all received three prior doses of hepatitis B vaccine, and this may act to prime for higher malaria antibody responses given that RTS,S is a fusion malaria-hepatitis B vaccine.

WHO is starting preparatory work to inform policy discussions on choice of immunization schedules for RTS,S/AS01. This is expected to be a major policy question. It is planned that the age patterns for given malaria transmission settings, will be combined with immunization coverage data to provide modeled estimates of the percentage of severe malaria disease burden that would be missed by different possible schedules within the age ranges of immunization covered by the pivotal Phase 3 trial. The outcome of this work will be presented to SAGE and MPAC as part of the 2015 session at which a decision on a policy recommendation will be made. There is an ongoing discussion as to whether available published data from a recent systematic review and meta-analysis is sufficient to provide the severe malaria age patterns in sub-Saharan Africa as the basis for this planned work, or WHO should extend the previous systematic review by performing an assessment of whether additional datasets should be included, and by incorporating health facility data on hospitalized confirmed malaria cases in addition to published epidemiological studies.

Expected Policy Timings

The new results re-emphasize the previously stated WHO policy timings: WHO will issue policy recommendations in 2015 based on advice from JTEG through SAGE and MPAC. These recommendations will be based on all data available up to 2014, including the site-specific efficacy data and 18-month booster dose data. GSK/MVI have agreed that additional analyses requested by WHO will be performed in late 2014.

The initial WHO policy decision on RTS,S/AS01 is now tentatively scheduled for Q4 2015 at a planned joint MPAC/SAGE “for decision” session. The change in timing from Q2 2015 is due to a planned change in the GSK/MVI partnership’s regulatory submission timing. A scientific opinion from the European Medicines Agency is necessary prior to policy recommendation.

October 2012 JTEG Recommendations to WHO
JTEG indicated that the new data that have become available in Q4 2012 do not change the previously communicated policy timings. WHO policy recommendations can be expected in 2015, depending on the data available in 2014 and on the timing of regulatory submission.
RTS,S/AS01 will be evaluated as an addition to, not a replacement for, existing malaria prevention, diagnostic and treatment measures. There is a range of policy decisions possible in the 2015 timeframe, depending on the 2014 results.
JTEG highlights the following to be considered as part of the additional analyses for late 2014. These will also be revisited in review of the analysis plan for the 2013 analyses: • Site-specific and transmission strata specific efficacy analyses • Rates of disease in the vaccine vs. control group broken down by time since vaccination • Explorations of correlation between immunogenicity and efficacy • Exploration of the interaction between seasonality and vaccine efficacy • Correlation between pre-existing maternally acquired antibody to CS and immunogenicity • Correlation between anti-CS and anti-Hepatitis B antibody titres
Given the results to date, contingency plans for alternative schedules should be included, minimizing the number of additional routine immunization visits whilst maximizing expected efficacy. However it is unlikely that policy recommendations for use can be made on alternative schedules without clinical trial data on those schedules.
JTEG recommends the Secretariat present to MPAC and SAGE: • Available data (as soon as embargo period is over) • Summary of issues JTEG has identified • Pipeline of additional work that is ongoing or planned
JTEG supports WHO's effort on communication about these results. JTEG could be included in such communication efforts by provision of slides.
JTEG supports in concept a systematic review of the age pattern of severe malaria in sub-Saharan Africa if possible to do, noting that age-spectrum of hospitalizations can change at the same location as transmission changes, and this must be taken into account. This work may support considerations of alternate schedules during the 2014-2015 policy discussions.

RTS,S/AS01: JTEG Assessment and Preparations for Policy Recommendations

Peter Smith, Chair JTEG

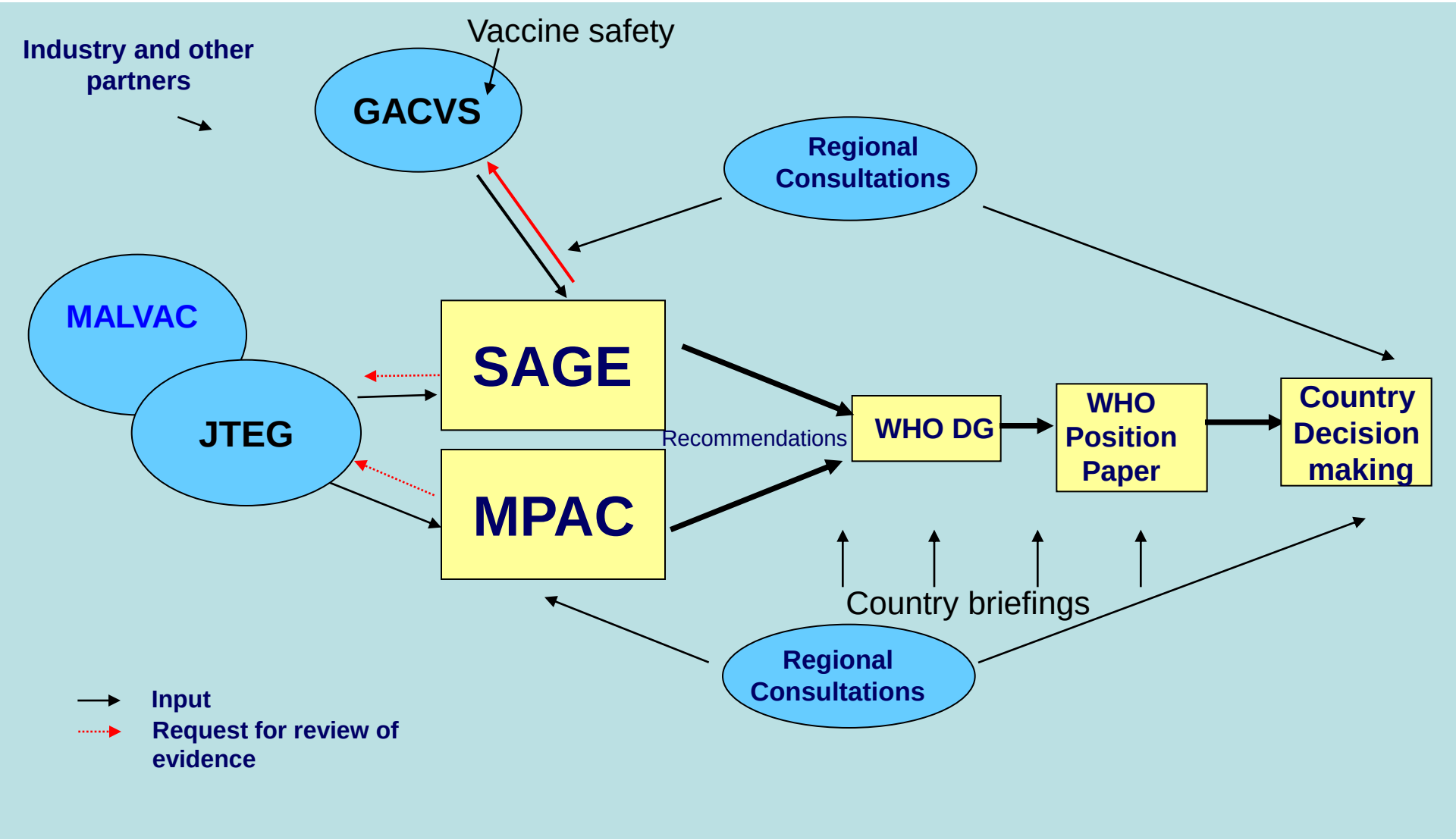
MPAC
14 Mar 2013

JTEG members

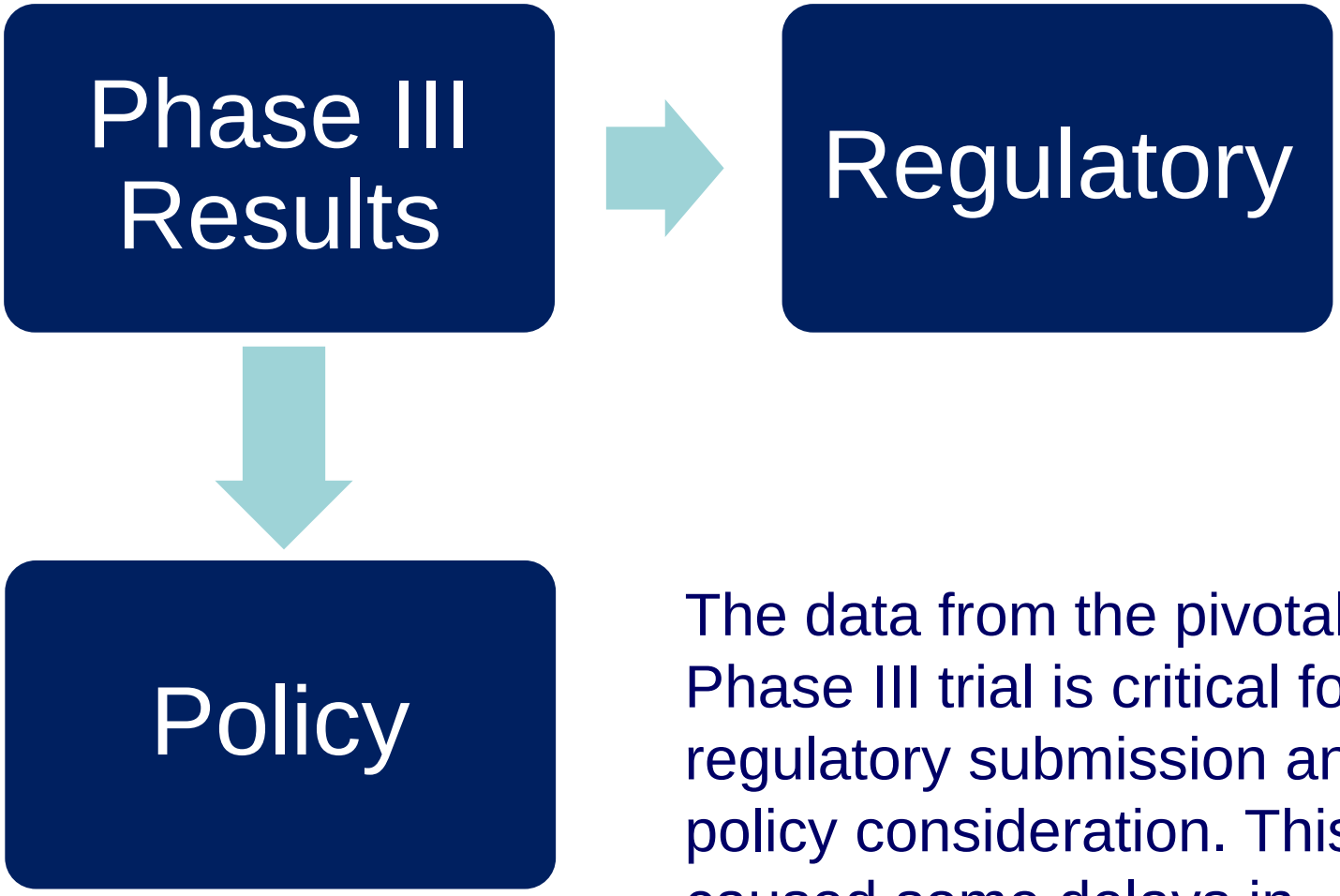
- Chair, Peter Smith
- **Fred Binka (MPAC member)**
- **Kamini Mendis (MPAC member)**
- Malcolm Molyneux
- Paul Milligan
- Kalifa Bojang
- Mahamadou Thera
- Blaise Genton
- Janet Wittes
- Robert Johnson
- Zulfiqar Bhutta (SAGE member)
- Claire-Anne Siegrist (SAGE member)

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

Pathways for WHO Policy Recommendations on Malaria Vaccines



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



The data from the pivotal Phase III trial is critical for both regulatory submission and policy consideration. This has caused some delays in GSK/MVI partnership in responding to WHO/JTEG requests in interim analyses

WHO/JTEG dialogue with GSK/MVI

The JTEG process has facilitated WHO's technical discourse with GSK/MVI.

GSK/MVI has agreed to conduct some of the key analyses that JTEG requested during the 2013 analyses of the 18 month follow-up data.

JTEG Assessment of One Year Follow up Results

The distribution of children and cases between sites is different in the 2 age groups and thus the pooled VE results for each of the 2 age groups are not strictly comparable (if there is heterogeneity of efficacy).

Pooled results are usually presented which is reasonable if some sites do not have markedly different efficacy to others.

JTEG advised that site or transmission strata specific analyses are required to aid interpretation of the results: GSK/MVI have agreed to provide these during 2013

Scientific questions raised by the recent results

- How does efficacy change with time since vaccination?
- Does efficacy vary with transmission intensity?
- Does the presence of marked seasonality affect measured efficacy, especially if efficacy declines rapidly?
- Does co-administration with pentavalent vaccine reduce efficacy?
- Does maternally acquired antibody present during vaccination affect efficacy?
- Does prior Hepatitis B immunization increase RTS,S efficacy?
- Does age or prior exposure to malaria affect efficacy?

WHO encourages exploration of all these questions as a high priority to guide policy discussions in 2015

Overview of analysis timepoints

Q4 2011 12 m follow-up post dose 3	Safety, Immunogenicity & Efficacy 6,000 children aged 5-17 months.
Q4 2012 12 m follow-up post dose 3	Safety, Immunogenicity & Efficacy 6,537 infants aged 6-12 weeks in co-administration with DTwP/Hep B/Hib
2013 18 m follow-up post dose 3	Both age groups
2014 30 m follow-up post dose 3	Both age groups, including 18 month booster dose

Key analyses expected in 2013 after 18mo follow up

- Duration of protection, including JTEG request to analyse all episodes of malaria in 6 month time intervals post vaccination
- Site-specific efficacy analyses
- Associations of efficacy with immunogenicity
- Association between pre-existing maternal antibodies and immunogenicity
- Cases averted analyses

Key data expected during 2013 from additional Phase III trials

- Pneumococcal & rotavirus vaccine co-administration
- Safety in HIV infected children

Key analyses expected in 2014

- As for 2013 with 30 months follow-up
- Effect of a booster dose at 18 months
- Analyses of the effect of seasonality
- Further analyses requested by WHO not yet confirmed, but including after seeing initial analyses.

Public Health Impact/Cost Effectiveness

- Second WHO meeting to assess status of malaria vaccine health economic models: 7-8 May 2013
- Will document status of multiple modeling groups working in this area
- Will propose role for such work in policy process
- Policy recommendations will be based on clinical trial data. In some areas a contribution from modeling may be beneficial e.g. guidance for Phase IV design

Key policy question: age group and schedule

- While original target group was infants aged 6,10,14 weeks, the published results raise the question of implementation in children aged 5-17 months
- WHO is commissioning work to model the proportion of malaria hospitalizations “missed” by schedules ending at different ages. Range from DTP3 up to 18 months of age being explored.
- Costing of adding new visits will also be requested in health economic work

Key policy question: role of RTS,S in context of other malaria control measures

- Available data indicates that efficacy is in addition to high level insecticide-treated bednet use
- Also possible that efficacy will be higher at low to moderate transmission levels
- Thus policy recommendations are highly likely to encourage sustained LLIN use together with any RTS,S introduction

Timing for policy recommendations

- Following review of the 2014 analyses, JTEG will draft candidate policy recommendations for review by MPAC and SAGE in joint session in Q4 2015
- The joint session has been deferred by 6 months due to a change in the planned regulatory submission timings by GSK/MVI

Messages from WHO

- Detailed Q&A available on WHO website
- RTS,S/AS01 will be evaluated as an addition to, not a replacement for, existing preventive and treatment measures
- It is too early to draw conclusions about the public health role of RTS,S/AS01
- Depending on the results expected in 2014, and on the regulatory submission timings, WHO will make the first malaria vaccine policy recommendations in late 2015.

Conclusions & Key Question for MPAC

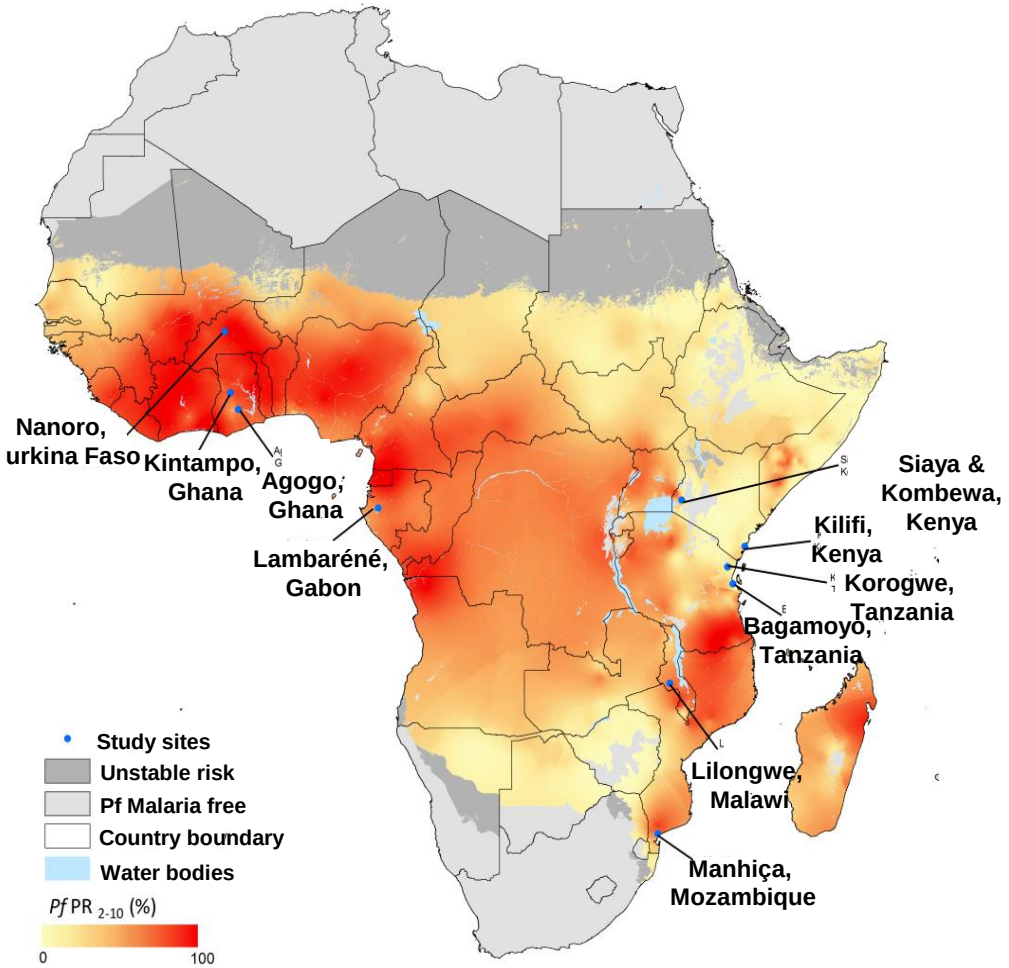
- GSK/MVI have proved responsive to WHO's requests for data and analyses needed to formulate policy recommendations
- JTEG is now confident we will have information necessary for MPAC and SAGE to make a decision in Q4 2015 (assuming regulatory timings allow).
- Do you have suggested additional work for WHO & JTEG in preparation for the 2015 "For Decision" session?

Discussion, Questions and Comments

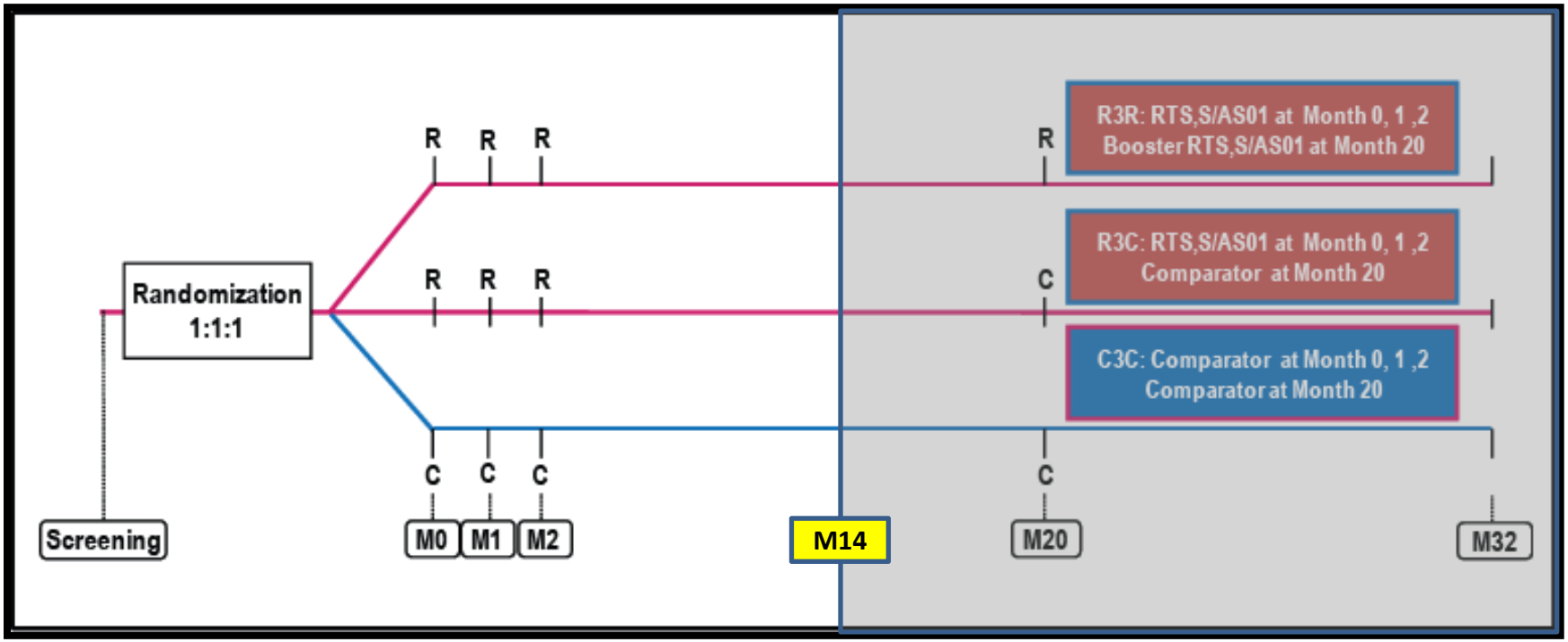
Status of RTS,S/AS01 malaria vaccine candidate

Multi-center RTS,S malaria vaccine efficacy trial

- Phase 3, randomized, controlled, double-blind trial conducted in 11 centers in 7 African countries
- 15,460 children enrolled in two age categories:
  - Children aged 5–17 months
  - Infants aged 6–12 weeks
- Co-primary endpoint:
  Vaccine efficacy against clinical malaria during 12 months of follow-up in each age category.
- Wide range of malaria transmission intensities (0.01 to 2.0 clinical episodes per child per year)
- Efficacy measured in presence of other malaria control interventions



Study design pivotal RTS,S efficacy trial



C = Rabies for 5-17 or Men C conjugate for 6-12 weeks

5-17 months old at 1st dose: **4296 children***

6-12 weeks old at 1st dose: **6003 infants**

- **1° endpoint**: Efficacy against clinical malaria disease, 1 year follow-up
- **2° endpoint**: Efficacy against severe malaria
- Safety

* Total enrolled = 8,923

5-17 months old at 1st dose: **1,561 children**

6-12 weeks old at 1st dose: **1,938 infants**

- Immunogenicity for anti-CS
- Reactogenicity

Key Phase 3 efficacy and immunogenicity results: 5-17 months and 6-12 weeks age categories

Endpoint	%VE (with 95%CI)	
	5-17 mo	6-12 wk
First episode clinical malaria (ATP, adjusted, co-primary endpoint) (ITT, unadjusted)	**55.8%** (97.5%CI: 50.6; 60.4) **50.4%** (45.8; 54.6)	**31.3%** (97.5%CI: 23.6; 38.3) **30.1%** (23.6; 36.1)
All clinical malaria episodes (ATP, adjusted) (ITT, unadjusted)	**55.1%** (50.5; 59.2) **53.9%** (49.6; 57.8)	**33.0%** (26.4; 38.9) **32.9%** (26.7; 38.5)
Severe malaria (ATP) (ITT)	**47.3%** (22.4; 64.2) **45.1%** (23.8; 60.5)	**36.6%** (4.6; 57.7) **26.0%** (-7.4; 48.6)
Anti-CS antibodies GMTs (EU/mL)	**621.2** (591.7-652.1)	**209.2** (196.8-222.4)
	NEJM 2011; 365: 1863-1875	*NEJM 2012; 367: 2284-95*

ATP: According to protocol
ITT: Intent to treat
CI: Confidence Intervals
GMT: Geometric Mean Titers

Comparison of incidence and RTS,S/AS01 efficacy between Phase 2 and Phase 3 studies in 6–12 weeks age category

	Phase 2*	Phase 3**
Study center	Kintampo, Bagamoyo, Lambarene	11 study centres
Incidence in control group	**0.62**	**1.25**
DTPwHepB/Hib co-admin	Yes	Yes
HepB vaccine priming	No	No
Anti-CS GMT (95% CI)	**190.3** (154.3-234.7)	**209.2** (196.8-222.4)
% VE (95% CI) (FU time)	**62** (36-77) (12m)	**32** (25-38) (12m)

Anti-CS = anti-circumsporozoite
GMT = geometric mean antibody titer calculated on all infants
95%CI = 95% confidence interval
VE = vaccine efficacy
FU = follow-up

Asante et al. Lancet Infect Dis, 2011
***The RTS,S Clinical Trials Partnership, NEJM, 2012 November 9, 2012DOI: 10.1056/NEJMoa1208394*

Safety profile of the RTS,S malaria vaccine candidate

- **Serious Adverse Events (SAEs):**
  - Overall reporting comparable between RTS,S and control vaccine groups
  - Fatal SAEs balanced between groups; none considered causally related to study vaccines
- **Reactogenicity:**
  - Injection site reactions and fever reported more frequently in RTS,S than control vaccine groups, but only few reactions were of severe intensity
  - Less local reactogenicity reported at RTS,S than DTwP-HepB/Hib site of injection
- **Generalized convulsive seizures within 7 days after vaccination:**
  - 5-17 month age category: more frequently reported in RTS,S (1/1000 doses) compared to control (0.6/1000 doses) vaccine group
  - 6-12 week age category: reported in RTS,S (0.2/1000 doses) compared to control (0.5/1000 doses) vaccine group
- **Meningitis:**
  - Reported more frequently in the malaria vaccine group, but was considered unlikely to be vaccine-related.

These events will continue to be monitored and full safety review will be conducted by GACVS before the SAGE/MPAC decision session.

Estimated Public Health Impact of RTS,S in Phase III

The absolute number of malaria cases averted depend on **baseline malaria incidence**:

- Given the wide range of transmission intensities across the clinical trial sites involved the Phase III efficacy trial, the number of malaria cases averted will likely vary largely.
- Overall, across all trial sites in the Phase III efficacy trial:

	Number of malaria cases averted (per 1,000 person years at risk)		
	Severe malaria**	Clinical* >5,000 parasites	Clinical **[3] >0 parasites
6-12 weeks[1]	9	269	414
5-17 months[2]	23	733	1088

*primary case definition

**secondary case definition

Calculated from : 1. NEJM 2011;365:1863-75 – 2. NEJM 2012;367:2284-95 and 3. GSK data on file

Impact of RTS,S and that of other vaccines

- **RTS,S**: **Number of malaria cases averted** (per 1,000 person years at risk)

	Severe malaria	Clinical >0 parasites
6-12 weeks[1]	9	414
5-17 months[2]	23	1088

- **PCV**: **Pneumonia cases averted** (per 1,000 PYAR)

	Severe	Clinical
in the Gambia[3]	2	17
in South Africa[4] (HIV-)	1.6	2.7
(HIV+)	20.5	23.0

- **HRV**[5]: **Rotavirus gastroenteritis cases averted** (per 1,000 PYAR)

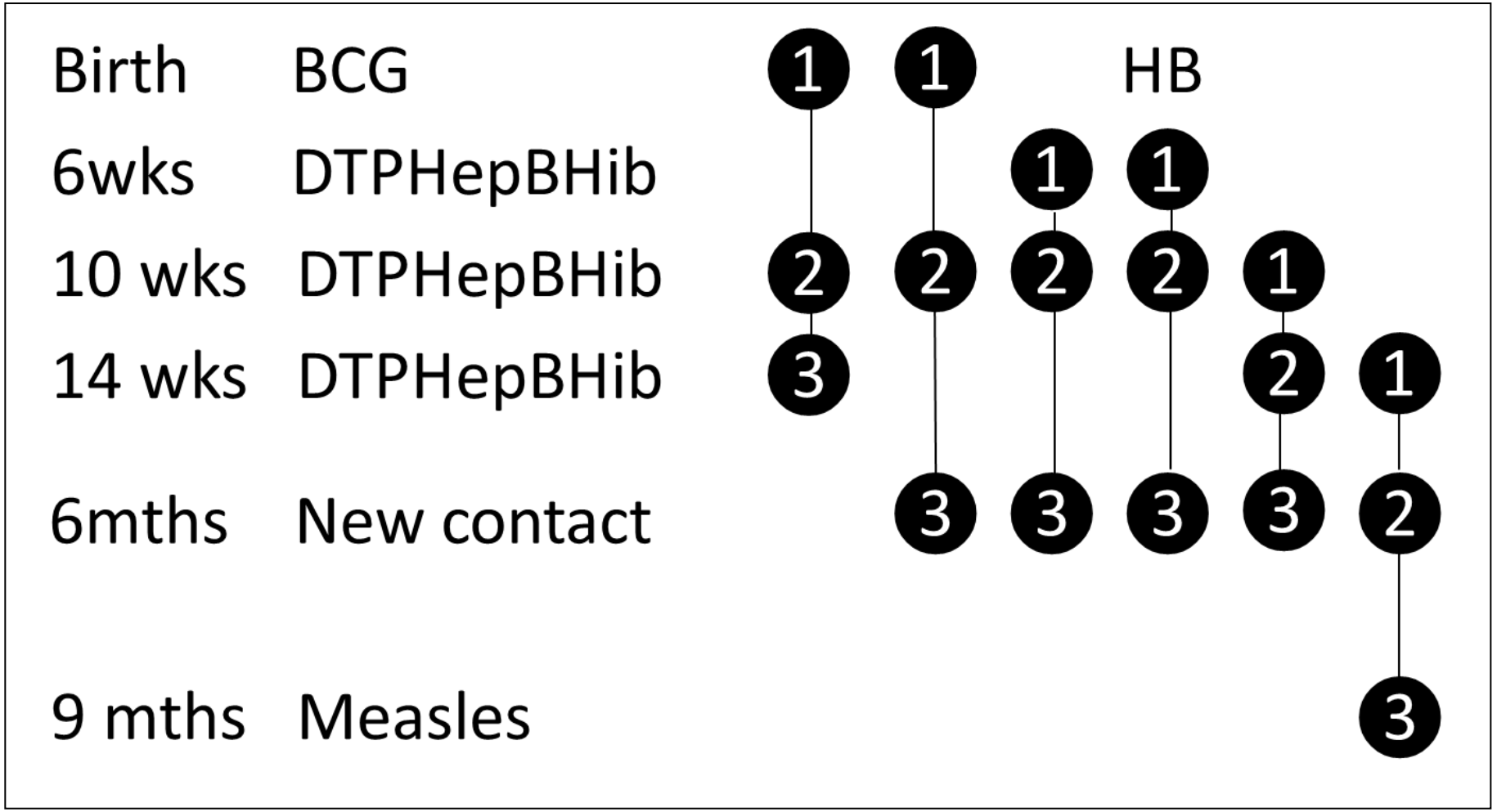
Severe	Clinical
50	117

Calculated from : 1. NEJM 2011;365:1863-75 – 2. NEJM 2012;367:2284-95 and GSK data on file
3. Lancet 2005;365:1139-46 – 4. CID 2005;40:1511-8 – 5. NEJM 2010;362:289-98

Update on other clinical activities

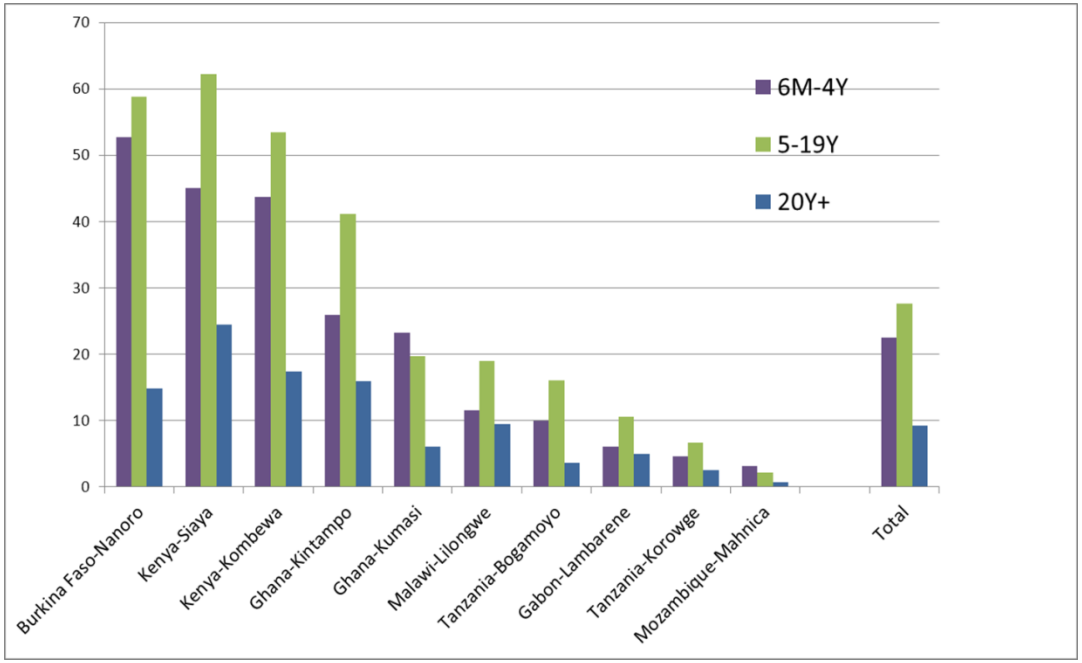
- **Lot-to-lot consistency study (Nigeria)**
  - Healthy 5-17 month olds (80/group)
  - **Results:**
    - Demonstrated equivalence of three consecutive commercial scale lots
    - Demonstrated non-inferiority of commercial to pilot scale lots
    - No safety signal observed - all vaccines were well tolerated
- **Co-administration with Rotavirus and Pneumo-conjugate vaccines**
- **Safety/ Immuno study in HIV+ children**
- **Genotyping (co-sponsored by Harvard School of Public Health)**
  - Selective pressure on the parasite: Specific parasite variants? Change of the number of parasite types?
- **Explore immune correlates of RTS,S-induced protective immunity**
- **Explore new schedules**

Phase 2 (Malawi): Exploring new schedules v 6, 10 and 14 weeks



Malaria Transmission Intensity: 6405 subjects (ATP)

- **Annual cross-sectional survey (2011-2014)**
  - Target peak of malaria season (~ 8 weeks)
  - Collect blood: RDT-Slides-AMA1-MSP1 Antibodies-Hb
  - Individual and house questionnaire
- **Primary endpoint: *P. falciparum* parasitemia**
- **First year results:**
  - Recruitment in 8 sites
  - Mean Age 12.6 yrs [min: 6 M; max 90.75 yrs]
  - Female: Male – 3672:2736
  - From the ATP cohort: 1314 (20.5%) were infected



Acknowledgments

Participants and families

Study staff

PATH Malaria Vaccine Initiative

GlaxoSmithKline

Malaria Clinical Trials Alliance

Research Centers and Partners

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Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique

Ifakara Health Institute, Bagamoyo, Tanzania

Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso

KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya

KEMRI-Walter Reed Project, Kombewa, Kenya

KEMRI - Wellcome Trust Research Program, Kilifi, Kenya

Kintampo Health Research Center, Kintampo, Ghana

National Institute for Medical Research, Korogwe, Tanzania

School of Medical Sciences, Kumasi, Ghana

University of North Carolina Project, Lilongwe, Malawi

University of Tübingen, Germany

Prince Leopold Institute of Tropical Medicine, Belgium

University of Copenhagen, Denmark

University of Barcelona, Spain

Swiss Tropical Institute, Switzerland

London School of Hygiene and Tropical Medicine, UK

US Centers for Disease Control and Prevention, USA

University of North Carolina at Chapel Hill, USA

Walter Reed Institute of Research, USA

2013 Update to the Malaria Vaccine Technology Roadmap

Introductory text

This text represents the result of a review process facilitated by WHO, and working with the malaria vaccine funders group, to update the vision and strategic goal of the Malaria Vaccine Technology Roadmap. Originally launched at the 2006 WHO Global Vaccine Research Forum, and supported by the malaria vaccine funders group, the roadmap has formed a strategic framework underpinning the activities of the global malaria vaccine R&D community.

Substantial changes in malaria epidemiology are now being observed in many, but not all, settings following reduction in malaria transmission(1) in association with scaling-up of malaria control measures. Reduced transmission is associated with a shift in the peak age of clinical malaria to older children(2) and therefore the median age of hospitalization due to malaria has increased(3, 4) in some settings**.**

In response to the recognition that the epidemiological and malaria control status have changed markedly since 2006, and acknowledging substantial changes in the strategic direction for malaria research, the roadmap has been updated to encompass the current goals of prevention of malaria disease and deaths, accompanied by consideration of the accepted goals of incremental malaria elimination and ultimately global eradication. The expanded vision and strategic goals reflect these ambitious aims of the global malaria community.

The 2015 Landmark goal remains in place, unchanged, as follows “By 2015, develop and license a first generation malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year.” Furthermore, the 11 priority areas in research, vaccine development, key capacities, policy and commercialization, all remain in place unchanged.

The priority areas outlined in the Malaria Vaccine Technology Roadmap will be updated only as necessary to reflect the new Vision and Strategic Goals, and taking into account the major progress in many of the areas since 2006.

It is noted that the following goal has been set as an indicator of success for the Global Vaccine Action Plan of the Decade of Vaccines by the 2012 World Health Assembly “Proof of concept for a vaccine that shows greater than or equal to 75% efficacy for HIV/AIDS, tuberculosis, or malaria by 2020”.

Keeping the roadmap up-to-date in future

Further reviews of the vision and strategic goals will occur at least every 5 years in light of the epidemiological and control situation at that time and progress in the development of new tools and technologies. Changes will be made only if necessary.

The malaria vaccine community should work with the malaria control and elimination communities to ensure products under development are suitable for use alongside current WHO recommended malaria prevention, diagnostic and treatment measures.

Vision

Safe and effective vaccines against *Plasmodium falciparum* and *Plasmodium vivax* that prevent transmission, disease and death to enable malaria eradication

Strategic Goals

By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* and encompassing the following two objectives, for use by the international public health community[1]:

1) Malaria vaccines with a protective efficacy of at least 70-80%[2] against clinical malaria, suitable for administration to appropriate at-risk groups in malaria-endemic areas.[3]
2) Malaria vaccines that reduce transmission[4] of the parasite and thereby substantially reduce the incidence of human malaria infection to achieve elimination in multiple settings. The vaccines should be suitable for administration to people of all ages in mass campaigns[5]

[1] While vaccines that meet or exceed these targets are acknowledged as being of major public health significance, those that do not fully meet these targets may still have substantial value. Any licensed, available malaria vaccine will undergo assessment for evidence-based policy recommendation by WHO.

[2] Relative efficacy estimates may be provided where a vaccine is tested against a licensed, available first generation malaria vaccine. In this case WHO will evaluate whether the relative efficacy estimates can be considered analogous to absolute efficacy of >70-80% (ie analogous to >70-80% efficacy from trials conducted with a traditional control arm)

[3] The efficacy measure will be an absolute reduction in incidence of all episodes of clinical malaria over at least 2 years. Booster doses will be required no more frequently than annually.

[4] The new transmission-related strategic goal does not apply only to sexual stage/mosquito antigen vaccines but to any vaccine capable of interrupting malaria transmission .

[5] For this goal the endpoints will be set through the process for development of preferred product characteristics for malaria vaccines. Although these metrics are centrally important to this goal, there is no consensus available to set the criteria at the time of this update.

Background to WHO malaria vaccine Preferred Product Characteristics

Vaccine R&D should address an unmet public health need. To do this, the unmet need must be identified and defined, and product development plans put in place. The strategic goals above provide guidance on the two highest priorities in terms of public health need for malaria vaccines.

Two sets of WHO preferred product characteristics (PPCs) will be developed in 2013-2014. The WHO PPCs will provide guidance on the characteristics of malaria vaccines that could meet the two strategic goals of the Roadmap, and could be programmatically suitable for use in malaria-endemic settings. Any malaria vaccine which becomes available for use in malaria-endemic countries will undergo evidence-based policy assessment by WHO through the standard policy processes. Those vaccines not meeting the WHO PPCs are not excluded from consideration for policy recommendation and pre-qualification by WHO. However the PPCs provide information on the desired characteristics of vaccines to meet the public health need, and to lower the burden on developing country immunization and malaria control programmes.

Target audience for this update:

- The Vision and Strategic Goals are aimed at senior leadership within international and national donor, financing and public health agencies, as well as governments of malaria-endemic countries.
- The Strategic Goals are also of interest to malaria vaccine developers in academia, government agencies, public-private partnerships and industry.
- The WHO malaria vaccine Preferred Product Characteristics are aimed at a technical audience in research & development in industry, public-private partnerships, academia and government agencies, who have an interest in development of malaria vaccines to meet the public health need in developing malaria-endemic countries.

Malaria Vaccine Technology Roadmap Priority Areas

Re-stated below are the original 11 Priority Areas. Those which are out of date will be reworded through a joint process between WHO and the malaria vaccine funders group.

Research

1. Develop a standard set of immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines.

2. Standardize clinical trial design and assessment to allow comparison of data and to determine correlates of protection.

3. Use state-of-the-art approaches, including functional genomics, to characterize the biological functions of proteins at the interface of host-parasite interactions and to identify novel potential antigen candidates.

4. Develop web-based information-sharing tools to strengthen connections between the laboratory and the clinic.

Vaccine Development

5. Establish a systematic approach for prioritizing sub-unit vaccine candidates using accepted pre-clinical criteria.

6. Pursue multi-antigen, multi-stage, and attenuated whole-parasite vaccine approaches.

Key Capacities

7. Establish readily accessible formulation and scale-up process development capacity for malaria vaccines.

8. Build and broaden good clinical practice (GCP) clinical trial capacity in Africa and other malaria-endemic regions to accommodate the growing number of trials required for malaria vaccine development.

Policy and Commercialization

9. Establish and maintain country-level dialogues to facilitate decision-making on malaria vaccine policy.

10. Secure sustainable financing for future procurement of vaccines.

11. Develop novel regulatory strategies to expedite approval while ensuring safety.

References

1. WHO. World Malaria Report. 2011. Available from: www.who.int/malaria.
2. Carneiro I, Roca-Feltrer A, Griffin JT, Smith L, Tanner M, Schellenberg JA, et al. Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. PLoS ONE. 2010;5(2):e8988.
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Updating the Malaria Vaccine Technology Roadmap

Vasee Moorthy MRCP PhD

MPAC 14 March 2013

World Health Organization

Purpose of this MPAC session

- MPAC to be updated on the strategic R&D framework for malaria vaccines, including new Vision & Strategic Goals
- Input into plans for WHO Preferred Product Characteristics
- Process for agreement of efficacy criterion for elimination vaccines is a challenging element

Vision

The malaria vaccine community will develop an effective vaccine that prevents severe disease and death caused by *Plasmodium falciparum* malaria in children under five in sub-Saharan Africa and other highly endemic regions. Efficient global coordination and collaboration will stimulate the malaria vaccine pipeline and accelerate progress towards this achievement.

Strategic Goal

By 2025, develop and license a malaria vaccine that has a protective efficacy of more than 80% against clinical disease[1] and lasts longer than four years.

Process for update

- Public consultation process for updates to Vision and Strategic Goal
- Agreement on final wording between WHO and Malaria Vaccine Funders Group.
- Development of Preferred Product Characteristics for the new Strategic Goals to follow the Update. This will be a WHO process.

Process for update

- First public consultation in September 2012 – 45 written comments from agencies and vaccine development groups
- Second public consultation in November 2012 – few comments. Timeframe and efficacy threshold main discussion points.
- WHO Meeting on 5 February 2013 with 40 participants, including five MPAC members
- To be finalized on April 24 at meeting of funding agencies

Vision

The malaria vaccine community will develop an effective vaccine that prevents severe disease and death caused by *Plasmodium falciparum* malaria in children under five in sub-Saharan Africa and other highly endemic regions. Efficient global coordination and collaboration will stimulate the malaria vaccine pipeline and accelerate progress towards this achievement.

Vision post 5 Feb meeting

- Safe and effective vaccines against *Plasmodium falciparum* and *Plasmodium vivax* that prevent transmission, disease and death to enable malaria eradication.

Strategic Goal

By 2025, develop and license a malaria vaccine that has a protective efficacy of more than 80% against clinical disease[1] and lasts longer than four years.

Draft wording for update: Strategic Goals

- By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* and encompassing the following two objectives, for use by the international public health community:

Updated Strategic Goal on vaccines to prevent clinical malaria

- POST FEB 5: Malaria vaccines with a protective efficacy of **at least** 70-80% against clinical malaria, suitable for administration to **appropriate at-risk groups** in malaria-endemic areas.

New Strategic Goal 2: vaccines to reduce transmission & achieve elimination

- Malaria vaccines that inhibit transmission of the parasite and thereby substantially reduce the incidence of human malaria infection to achieve elimination in multiple settings. The vaccines should be suitable for administration to people of all ages in mass campaigns
- Key message: Goals focus on desired outcomes of vaccination, not the antigenic target of the vaccine
- Product development pathway differ by desired outcome, and by antigenic target

Development of WHO Preferred Product Characteristics

- The strategic goals above provide guidance on high priorities in terms of public health need for malaria vaccines.
- Two sets of WHO preferred product characteristics (PPCs) will be developed in 2013-2014
- These PPC will provide technical guidance about the desired characteristics of malaria vaccines to meet the strategic goals
- What we want to see developed to achieve priority public health goals. Should enable and guide product development, not restrict it.

Outline workplan for development of WHO PPCs

- Consult with funders group representatives, vaccine developers and WHO advisory committees
- Aim: Ensure common understanding of intended purposes, and agree use for PPCs.
- Use will differ for different agencies. Primary audience is vaccine developers and product development focused agencies

Purpose of WHO Preferred Product Characteristics (PPC) for Malaria Vaccines

- Guidance on key performance characteristics (safety, efficacy) for new malaria vaccines
- Guidance on key target groups
- Guidance on minimum programmatic suitability criteria to enable delivery of vaccines once available.
- Support strategic discussions on vaccine development

	Morbidity	Transmission/Elimination
Indication	+	++
Target Population	++	+++
Dosage	++	++
Route of Immunization	+	+
Presentation	++	++
Storage	++	++
Safety	++	++
Efficacy	+	+++
Lack of interference	+	+
Packaging	+	+
Registration/PQ	+	+

Outline workplan for development of WHO PPCs

- Efficacy & target age groups for transmission/elimination PPC:
  - Q3-4 2013 Multidisciplinary consultation involving modellers, biologists, statisticians, epidemiologists, clinical trialists, representatives from regulatory and malaria endemic country authorities.
  - Include summaries of existing work from other agencies
  - Consider whether different criteria will be essential for different transmission settings
  - Include guidance on surrogate endpoints
  - Include MPAC input

Outline workplan for development of WHO PPCs

- Programmatic Suitability:
  - Review existing WHO Programmatic Suitability for Prequalification document and include criteria, with changes only if necessary.
  - Consultation with relevant WHO advisory groups on specific criteria for malaria vaccines
  - Keep this light, as guidance already available

Criteria for transmission/elimination PPC (WHO 2003 draft document as starting point)

1. Indication: Prevention of transmission of P. falciparum and/or P. vivax (according to epidemiological setting)

2. Target Population: Total population in malaria-endemic setting

3. Dosage: Preferably one or two immunizations, maximum of three immunizations. Preferably one dosage level regardless of age.

Criteria for transmission/elimination PPC 2

5. Route of Immunization: Any route implementable on a large scale without the need for extensive health provider's training

6. Presentation: Large multidose vials; preferably liquid

7. Storage: Shelf-life at least 2 years. Preferably ambient, minimally 2-8°C. A vaccine vial monitor should be attached.

8. Safety: Preferably superior to that of currently licensed paediatric vaccines. Minimally non-inferior

Criteria for transmission/elimination PPC

9. Efficacy: ???

10. Interference: No significant interference with other vaccines planned for co-administration

11. Packaging: Ensure minimal storage requirements

12. Product registration and prequalification: The product must be WHO pre-qualified

Conclusion

- Updated Roadmap to be launched during 2013:
  - Please assist with communication to vaccine R&D agencies
- Input from MPAC into plan for development of WHO Preferred Product Characteristics
  - Delegate 1-3 members to working group, to join 1-3 members from SAGE?
  - Provide feedback on certain aspects that must be taken into account
- To be discussed at SAGE in April, and PPCs in other disease areas may follow

How should funds for malaria control be spent when there are not enough?

March 2013 – note for MPAC discussion

The MPAC advises WHO on the most effective interventions for malaria control and elimination. However, current funding levels do not allow for full implementation of all interventions globally[1]. Therefore guidance from MPAC is sought on what strategies should be used to allocate limited funds. It is important that decisions on resource allocation are based on transparent, clearly defined criteria rather than being driven by political expediency or by those with the loudest voice. Guidance is needed in two areas: (i) how external finances should be allocated between countries; and (ii) how should funds be allocated within countries.

1. Which countries or populations should be prioritized for malaria control funding?

This question primarily affects international funding for malaria control since there is little scope for reallocating domestic government funds to another country[2]. For international funding the choice of countries that should benefit from a donor's resources will be influenced by two principal factors:

a) The funds already available or potentially available to a country i.e. the ability of domestic governments to pay for malaria control themselves and commitments made by other donors.

b) The equity and health objectives of international funding i.e. who should benefit and what impact is sought (which is influenced by the epidemiological setting and the capacity of endemic countries to utilize funds).

When considering funds available it is generally accepted that countries with lower levels of available funds should receive priority – a donor is reluctant to provide money to a country that can afford to pay for malaria control itself or is already benefiting substantially from other external resources. In considering equity and health objectives it is helpful to consider five hypothetical ways in which funding for malaria control could be allocated between countries[3].

---

[1] Total domestic spending on malaria control was estimated to be US$ 625 million in 2011, while international disbursements were estimated to be US$ 1.67 billion, yielding a total of US$2.3 billion. Global resource requirements for malaria control are estimated to exceed US$ 5.1 billion per year between 2011 and 2020 (1), resulting in a gap of US$ 2.8 billion. Projections indicate that total funding for malaria control will remain at less than US$ 2.7 billion between 2013 and 2015.

[2] Exceptions may be for cross border control initiatives which may prove to be a more beneficial investment than spending money domestically.

[3] Culyer AJ and Wagstaff A (1992) Need, equity and equality in health and health care. Centre for Health Economics, Discussion Paper 95. University of York

i. *Allocating equal amounts of money per person at risk of malaria*. This scheme allocates external funding in proportion to the number of people at risk in each country. It is ostensibly equitable but does not fully take into account health need (i.e. the degree of risk) or the health impact attainable.

ii. *Allocating funds in order to provide equal access to interventions*. This scheme assesses how much it would cost to provide universal access to vector control, diagnostic testing and treatment to each person at risk in a country, and allocates resources in proportion to country totals. It takes into account health need in that it considers populations at risk, and the cost of providing services to those that are sick, but does not consider fully the extent to which populations will benefit. The scheme is in line with UN and other declarations of universal access to prevention, diagnostics and treatment. Given that the cost of malaria control in most settings is dominated by vector control, in which the costs are driven by the size of the population at risk, this scheme results in an allocation similar to that of equal funding per capita even though the principles of its derivation are different. Two features of this model are that: (i) the allocation of funds is not influenced by a country's malaria mortality rates, but funds are allocated simply in proportion to the resources required to achieve universal access to malaria interventions; and (ii) each person at risk is given equal opportunity to receive malaria interventions.

iii. *Allocating funds according to disease burden* e.g. in proportion to number of deaths or death rates. This scheme is in line with "allocating resources to where they are most needed" but does not take into account the extent to which health status can be improved (and resources are arguably not needed if health status cannot be improved). This scheme is also not explicitly linked to resources needed to deal with the burden.

iv. *Allocating funds to maximize lives saved*. This scheme takes into account the fact that ITNs or other interventions may have different impacts depending on where they are used e.g. more lives will be saved by deploying 1,000 ITNs in Africa than in Philippines. It is in line with considerations of "value for money" and may be in line with allocating resources to where they are most needed if need is defined as capacity to benefit. In this model funds are first allocated to the country where malaria mortality rates are highest (this is also where the benefit per unit of investment is likely to be greatest or where the cost of saving a life is lowest). After disbursing sufficient funds to achieve universal coverage of interventions in that country, funds are allocated to the country with the second highest mortality rate (and second lowest cost per life saved). This pattern is repeated until all funding for has been exhausted. The effect of this scheme is to maximize the total number of cases averted and lives saved. Other than focusing on countries with the highest initial disease burdens it does not explicitly take into account equity considerations. Thus, populations with the highest disease burdens that benefit from investments first may end up with lower death rates than others they initially ranked behind (e.g. after a certain number of ITNs have been distributed resources would not be going to where the greatest burden is), and inequalities may persist.

v. *Allocating funds to equalize health status*. This scheme is similar to that of *maximizing lives saved* in that it assigns funds preferentially to countries with highest disease burdens. As with the *maximizing lives saved* option it starts by allocating funds to the country with the highest death rates but it only allocates funds to this country until death rates are reduced to the same

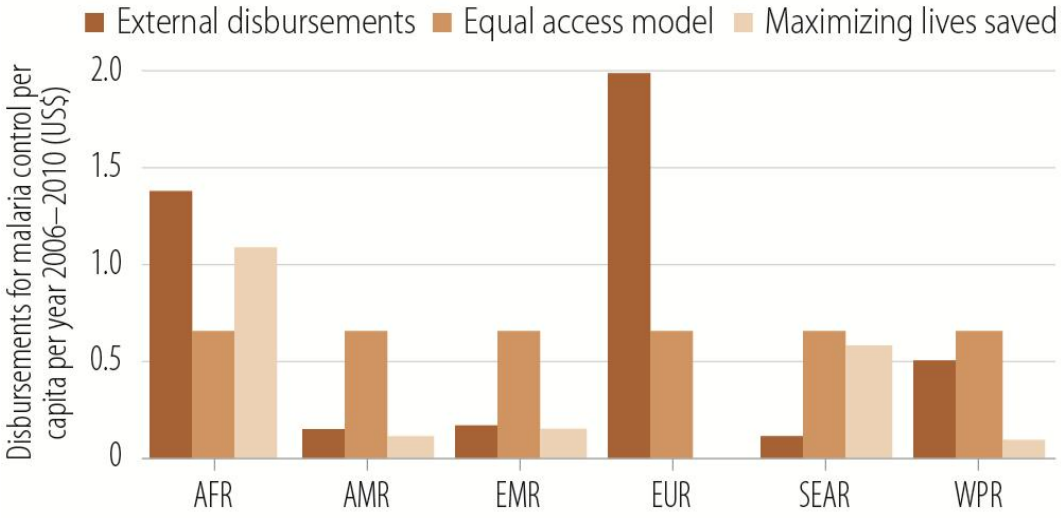
level as the country with the next highest death rates. Funds are then allocated to both countries until they are reduced to those of the next country, then funds are allocated to three countries and so on. The effect of this scheme is to reduce and equalize the level of the highest death rates as much as possible within a given budget constraint.

In the first three schemes the proportion of funds allocated to a country remains constant irrespective of the total budget envelope. A feature of the *maximizing health gain*, and *equalizing health status* models is that as funds become more constrained, a greater proportion of funds go to countries with the highest mortality rates.

It is instructive to compare each of the models with historical patterns of external funding (2006-2010) in order to assess how closely they correspond. Given that malaria programme funding in most settings is dominated by the cost of vector control (ITNs and IRS), which is driven by population at risk, the schemes (i) and (ii) are similar. Thus only scheme ii is presented and is given the label *equal access*. Scheme (iii) is only loosely related to resource need and is not explored further (a high number of deaths or a high death rate does not necessarily translate into a specific resource need except for care of the dead). Schemes (iv) and (v) yield similar results for most funding scenarios which are applicable today and are therefore presented as a single option with the label "maximizing health gain".

With the equal access model it can be seen that funds would flow equally to each WHO Region according to the size of population at risk (Figure 1). With the maximizing lives saved model, funds would flow preferentially to the African and South-East Asia Regions. Historical funding patterns have prioritized the African Region, providing fewer funds to the South-East Asia Region.

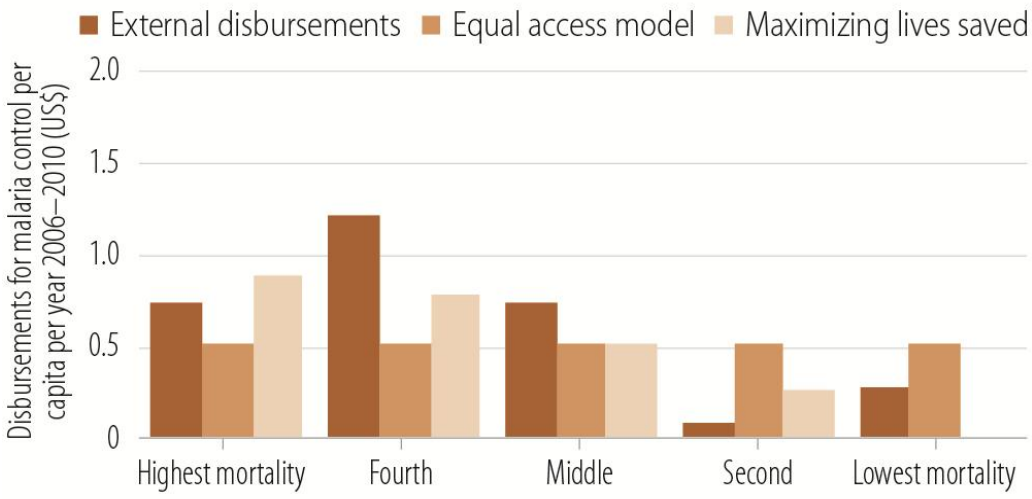
Figure 1. External funding per capita by WHO Region: historical disbursement patterns versus two alternative resource allocation models (*equal access* and *maximizing lives saved*)[4].



[4] The total amount of funds available for the alternative funding models is the same as in the historical patterns of external funding.

In the equal access model funds are assigned equally to countries irrespective of mortality rates (funding allocations are driven by population at risk) (Figure 2). With the maximizing lives saved model, external funds are assigned preferentially to countries with the highest mortality rates, with no resources going to those with the very lowest rates. Historically, external funds have tended to be allocated to countries with the highest mortality rates. However, countries with the very highest mortality rates have not benefited as much as would be expected if funds were being targeted to maximize health gains, while countries with the lowest mortality rates have received a higher than expected proportion.

Figure 2. External funding per capita by disease burden: historical disbursement patterns versus two alternative resource allocation models (*equal access* and *maximizing lives saved*)[5].[6]



Advice is sought from MPAC on two questions:

- Should external funds be allocated to maximize health gain or some other criteria?
- What external funds should be allocated to containment of drug resistance, malaria elimination?

[5] The total amount of funds available for the alternative funding models is the same as in the historical patterns of external funding.
[6] Malaria endemic countries are ranked by malaria mortality rates in 2000 and divided into five quintiles.

2. How should limited resources be allocated within countries?

Few countries have sufficient resources to achieve universal coverage of all malaria control interventions (vector control, diagnostic testing, treatment, surveillance, management support etc). As a consequence, they make decisions on what blend of interventions should be used, their scale of deployment and on the populations that should benefit. They make such choices with little guidance.

Two questions are of particular relevance:

a) What interventions should a country invest in if resources are not sufficient to achieve universal coverage of vector control, diagnostic testing and treatment?

b) To which populations should interventions be targeted? There are at least three options.

   i. No targeting – all populations at risk get an equal share of resources
   ii. Targeting to highest transmission areas
   iii. Targeting to demographically vulnerable groups such as pregnant women and children.

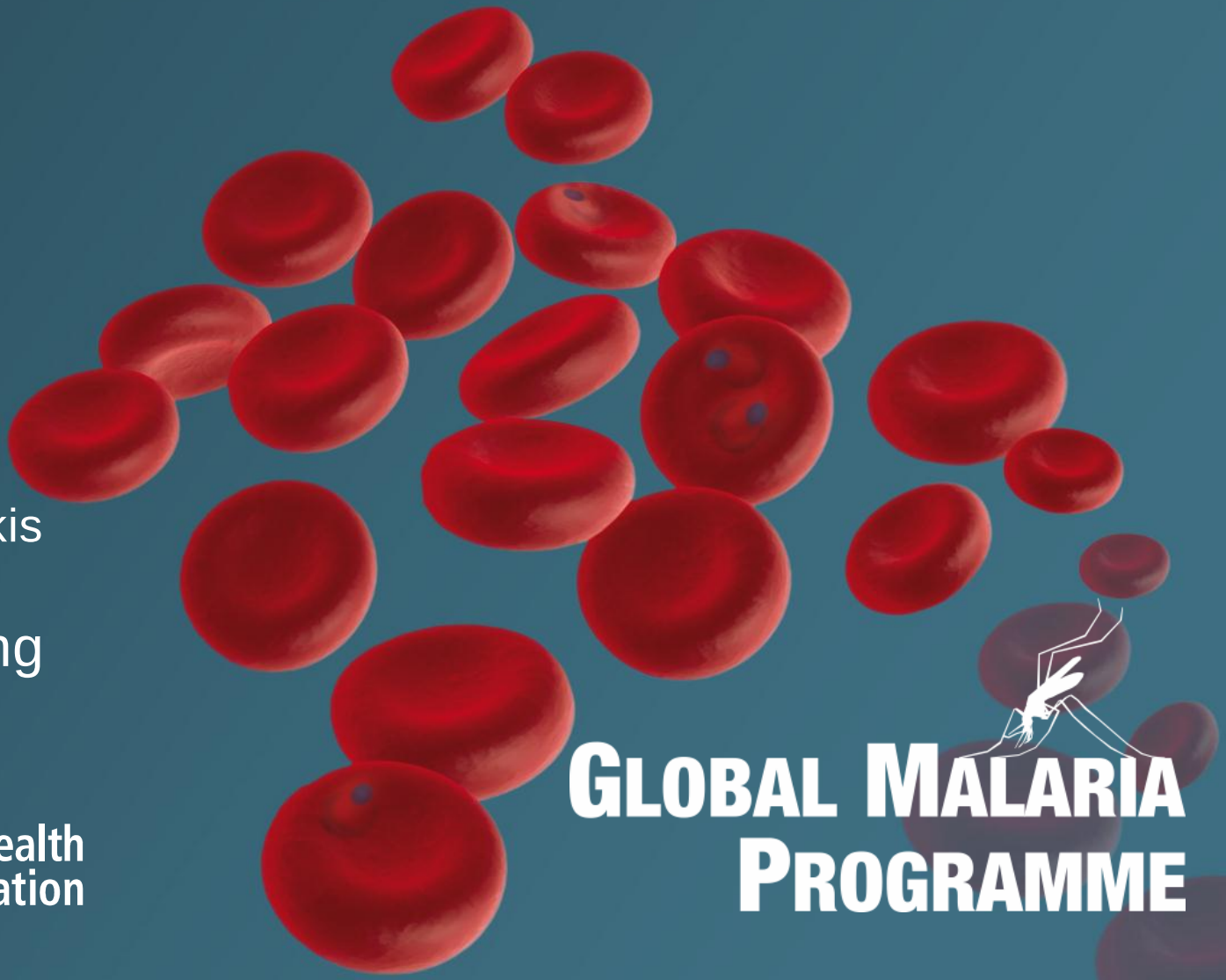
The first two options are analogous to the equal access and maximizing health gain options in the between country resource funding scenarios. Option 2 is likely to result in a larger number of cases and deaths averted than option 1. Option 3 could yield higher health gains than option 2 (although this is sensitive to what assumptions are made) but conflicts with guidance on achieving universal coverage.

Advice is sought from MPAC on two questions:

- Faced with a resource constraint, should malaria programmes prioritize certain interventions e.g. diagnosis and treatment given that they account for a small proportion of the malaria control budget?

- Faced with a resource constraint, should malaria programmes prioritize certain populations e.g. those with highest morbidity and mortality rates?

Financing Malaria Control – allocating limited resources



Richard Cibulskis

MPAC meeting
March, 2013

World Health Organization

GLOBAL MALARIA PROGRAMME

Allocating limited resources

1. How to allocate (international) resources between countries?
2. How should limited resources be allocated within countries?

Why ask?

- Domestic malaria spending US$ 625 million in 2011
- International disbursements US$ 1.67 billion, yielding a total of US$2.3 billion.
- Global resource requirements > US$ 5.1 billion per year

- WHO is asked to advise on which countries should receive priority

- WHO recommends particular interventions but there is not always enough money to implement fully

Resource allocation between countries depends on:

1. Funds potentially available
   - Domestic government's ability to pay
   - Other donor funding

2. Equity or health objectives
   - Who should benefit (rich/ poor)
   - Maximizing health lives saved/ cases averted, achieving elimination
   - (influenced by absorptive capacity, previous performance)

3. Political objectives

Prefer to have clear principles for allocating resources otherwise they will be driven by those with the loudest voice.

Global Fund Eligibility/ Prioritization

Pre 2008: Countries qualify if latest malaria specific death rates >1/1000

2008: WHO recommended should consider death rates for 2000

2009: GF proposed formula that would consider case incidence as well as mortality rates so countries with *P.vivax* could benefit.

If considering mortality and incidence *rates* Solomon Islands given higher rank than India – WHO suggested to also look at proportion of global burden a country represents.

WHO modified formula and produced four tiers of countries: Very Low, Low, Medium, High

Global Fund Eligibility/ Prioritization

Step A
A parameter based on (a) mortality rate per 1,000 persons at risk of malaria; and (b) morbidity rate per 1,000 persons at risk of malaria was established. Cut-off points and scores are shown in the table below.

Table 3: Malaria: first parameter, values and scores

Parameter 1	Value	Score
Combination of mortality rate and morbidity rate per 1,000 persons at risk of malaria	Mortality rate ≥ 0.75 and morbidity rate ≥ 10	4
	(Mortality rate ≥ 0.75 and morbidity rate <10) OR Mortality rate ≥ 0.1 and <0.75 regardless of morbidity rate	3
	Mortality rate <0.1 and morbidity rate ≥1	2
	Mortality rate <0.1 and morbidity rate <1	1

Step B
A second parameter based on the country's contribution to the global number of malaria deaths was established. Cut-off points and scores are shown in the table below

Table 4: Malaria: second parameter, values and scores

Parameter 2	Values	Score
Contribution to global deaths	≥ 1%	4
	≥ 0.25% and <1%	3
	≥ 0.01% and < 0.25%	2
	< 0.01%	1

Step C
The final score is then given by the arithmetic average of the two scores for a country, rounded to the nearest integer where needed.

While "transparent" and provides a spread across the world while prioritizing higher burden countries
It does not reflect any particular principals in resource allocation – or indicate how much should go to each band.

Alternatives for allocating resources between countries

1. Equal amounts of money per person at risk – does not take into account need
2. Allocating fund in proportion to disease burden e.g. number of deaths
3. *Equalizing access* - Allocating funds according to resource need - to provide equal access to interventions
4. *Maximizing lives saved* - Allocating funds according to capacity to benefit - to achieve universal coverage in countries with highest death rates and maximize lives saved
5. *Equalizing death rates* - Allocating funds so as to reduce and equalize the highest death rates

With schemes 4 and 5, as funds become more constrained a greater proportion of funds are directed to countries with the highest mortality rates

Example of resource allocations – USD 100 million

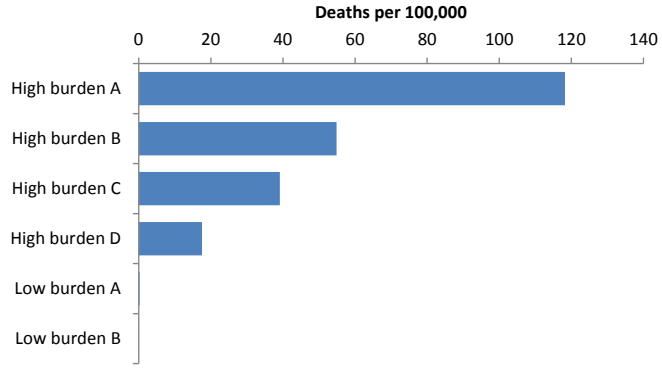
Country data		Population	Fevers	Cases	Deaths	USD needed for universal access	Deaths per 100,000
High burden	A	13,000,000	16,000,000	6,000,000	15,000	30,000,000	115
High burden	B	32,000,000	25,000,000	14,000,000	17,000	66,000,000	53
High burden	C	39,000,000	35,000,000	15,000,000	15,000	80,000,000	38
High burden	D	8,000,000	4,000,000	2,000,000	1,400	13,000,000	18
Low burden	E	55,000,000	9,000,000	64,000	122	74,000,000	0
Low burden	F	7,000,000	1,000,000	43,000	0	9,000,000	0
		154,000,000	90,000,000	37,107,000	48,522	272,000,000	

USD (millions) allocated		Equal amount per person	In proportion to no. of deaths	In proportion to resource need	Until resource need fulfilled	Until death rates equalized
High burden	A	9	31	11	30	10
High burden	B	21	35	24	66	43
High burden	C	25	31	29	4	30
High burden	D	5	3	5		18
Low burden	E	36	0	27		
Low burden	F	4	0	3		
						100

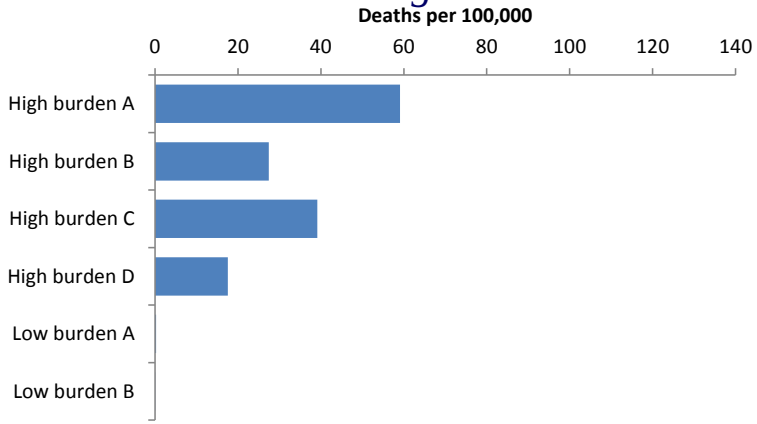
The type of scheme used for resource allocation can greatly affect which countries benefit, the health impact and impact on equity

Example of resource allocations – USD 100 million

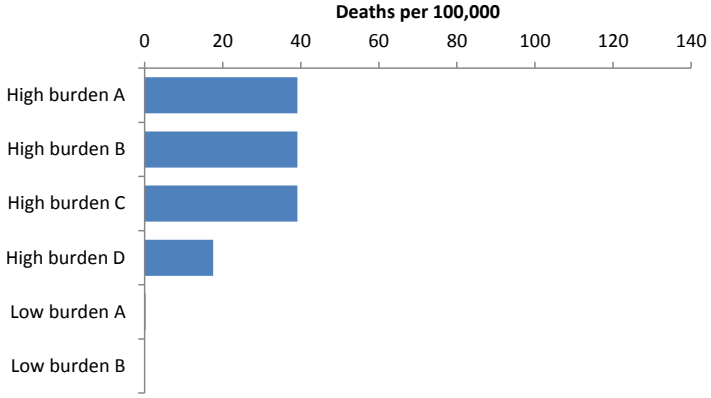
Initial malaria death rates



Malaria death rates after "maximizing lives saved"



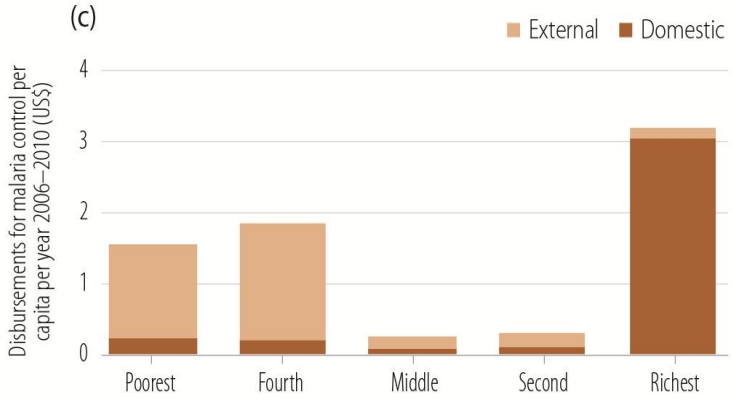
Malaria death rates after "equalizing death rates"

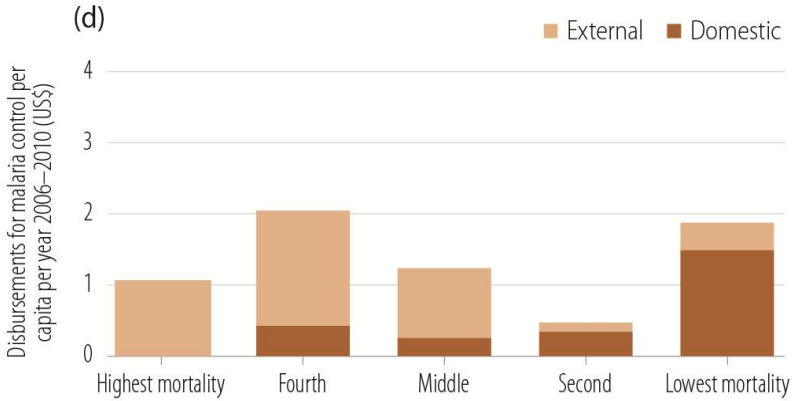


Allocation of domestic and international funding for malaria control

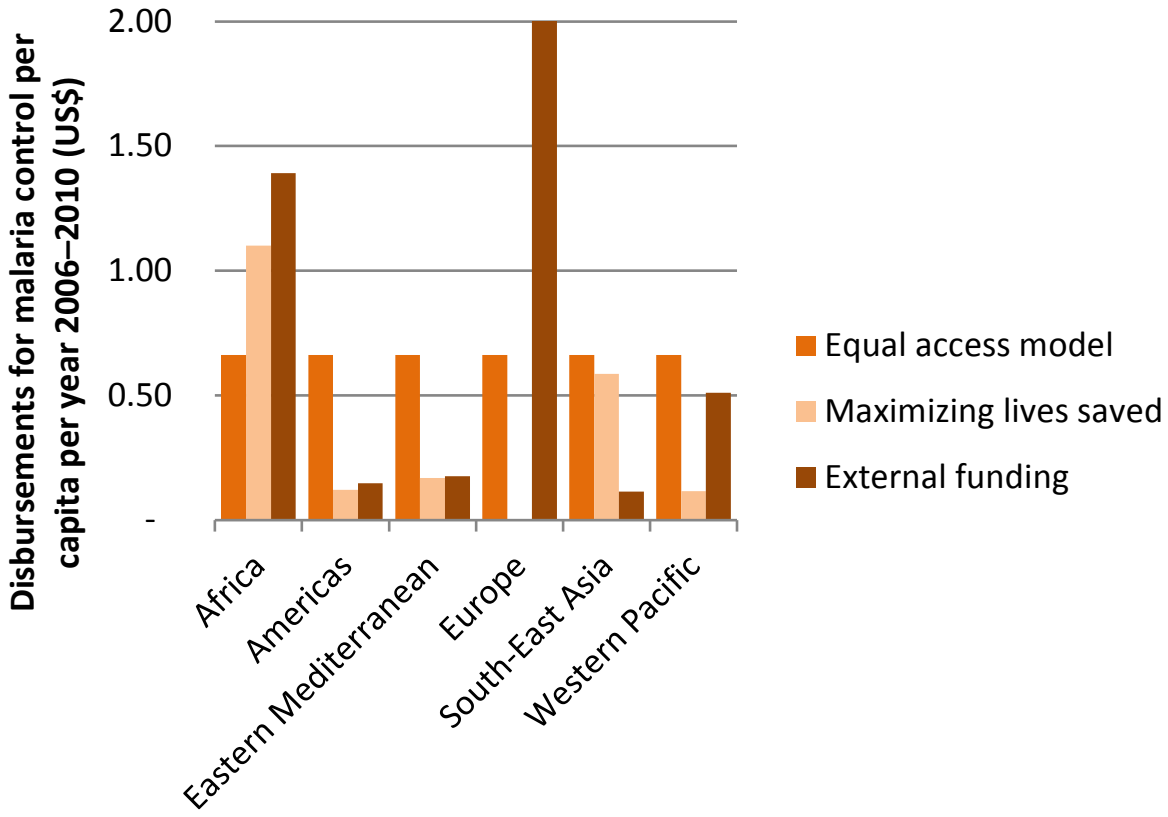
Domestic funding per capita is highest in the wealthiest countries and in countries with the lowest mortality rates, mostly in the European Region and the Region of the Americas.

International funding for malaria control has been targeted to countries with lower GNI per capita and higher mortality rates, particularly those in Africa i.e. going to where the need is greatest.

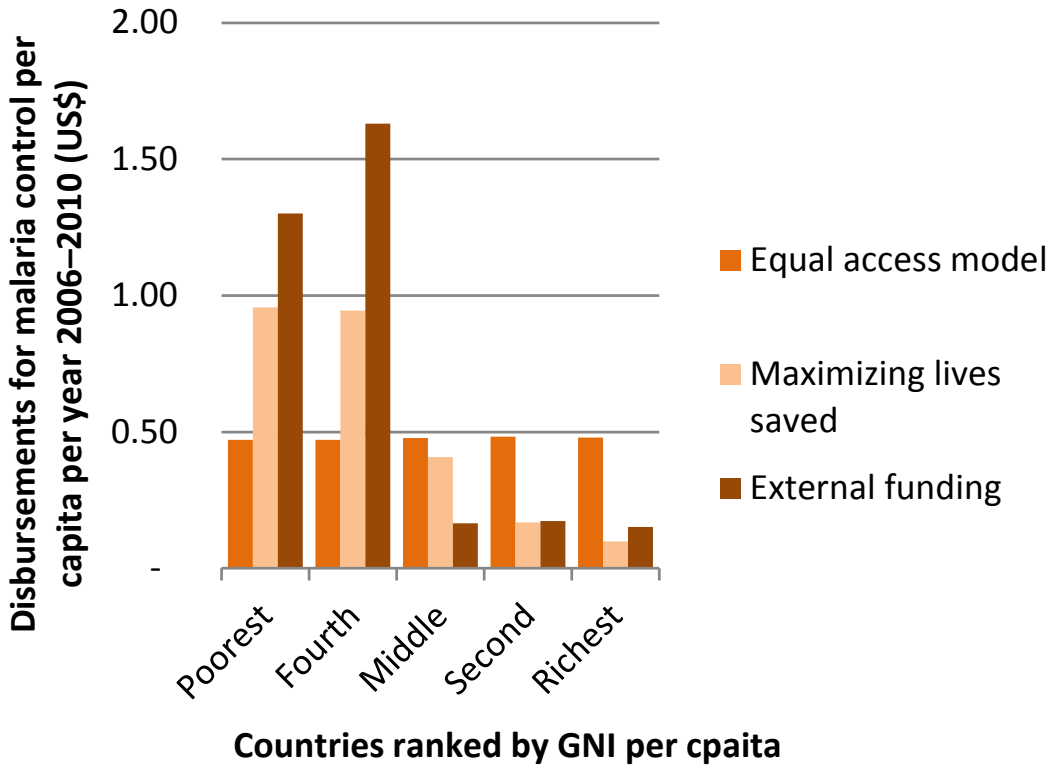




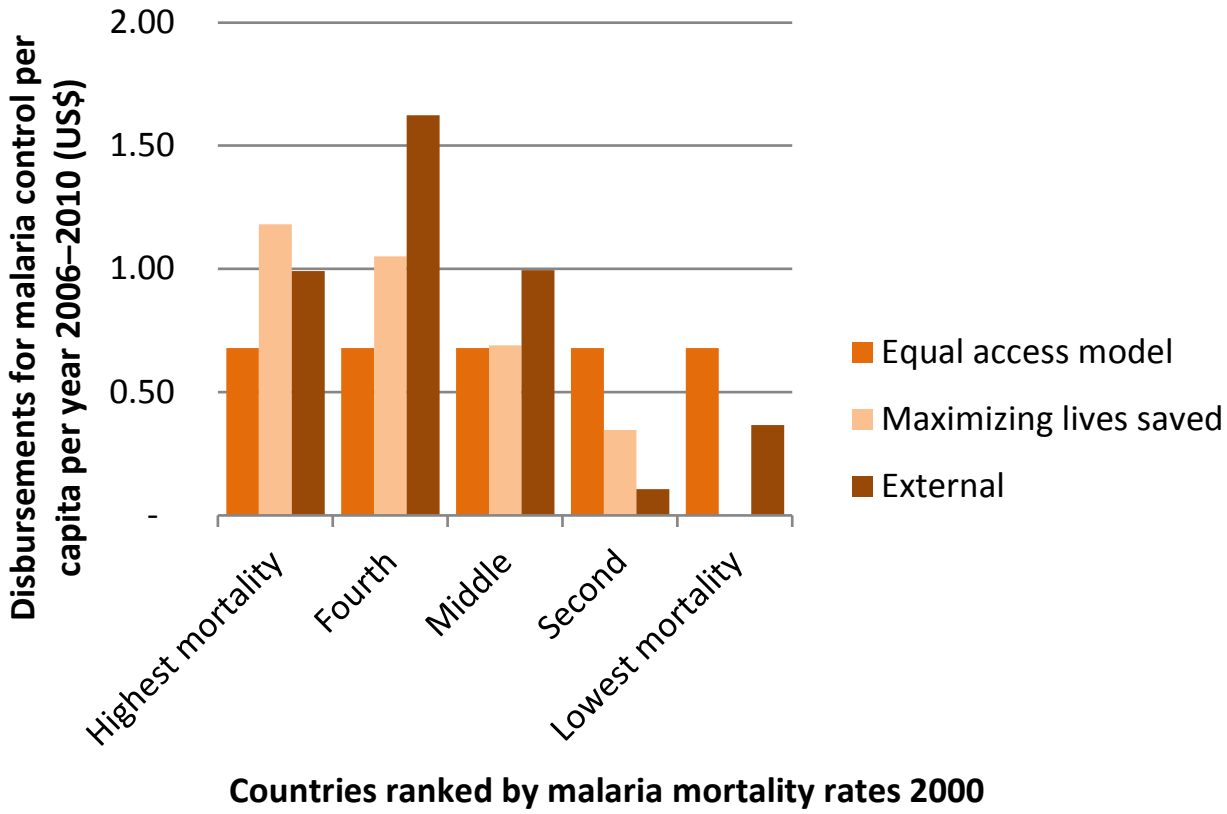
Existing patterns of resource allocation



Existing patterns of resource allocation

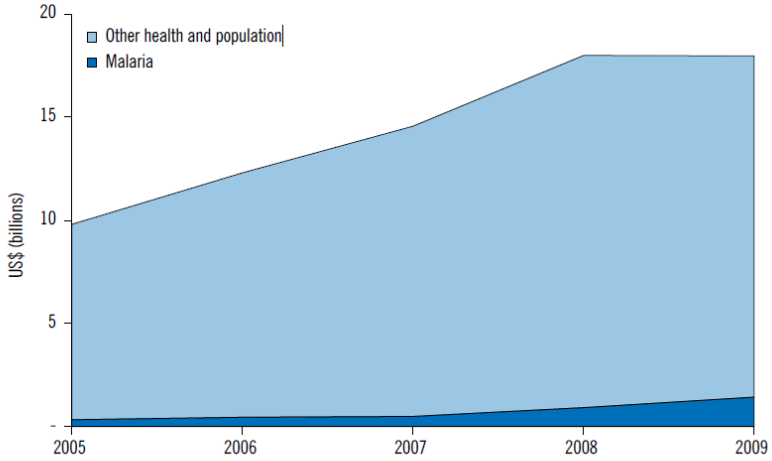


Existing patterns of resource allocation



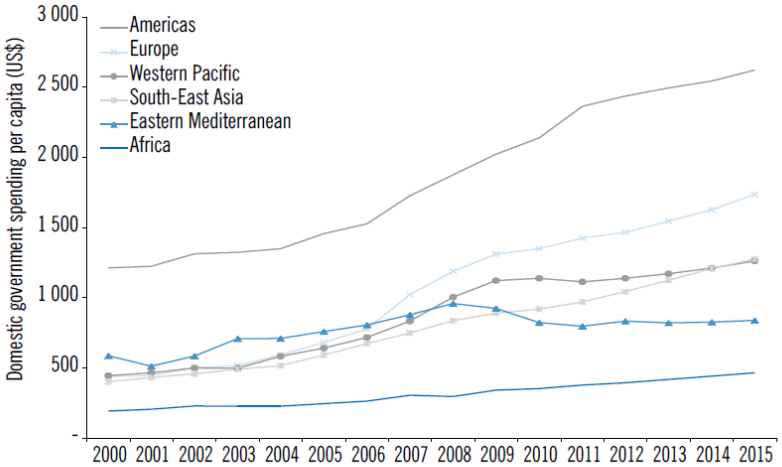
Trends in financing

Figure 3.11 Official development assistance for malaria and other health and population activities



Source: OECD database on foreign aid flows http://stats.oecd.org/qwids/

Figure 3.12 Median total domestic government spending in malaria-endemic countries by WHO Region



Source: International Monetary Fund World Economic Outlook Database, September 2011

Future international funding for malaria may be stagnant – malaria endemic countries are growing

Questions for MPAC

Between countries:

1. Should external funds be allocated to maximize health gain or some other criteria
2. What external funds should be allocated to containment of drug/ insecticide resistance or elimination?

Investing limited resources within countries

Few countries have sufficient resources for achieve universal coverage of all interventions. Therefore they make decisions on what blend of interventions should be used, their scale of deployment and on the populations that should benefit. Two questions:

1. a) What interventions should a country invest in if resources are not sufficient to achieve universal coverage of vector control, diagnostic testing and treatment?

2. b) To which populations should interventions be targeted? There are at least three options.
   i. No targeting – all populations at risk get an equal share of resources
   ii. Targeting to highest transmission areas
   iii. Targeting to demographically vulnerable groups such as pregnant women and children.

Questions for MPAC

Between countries:

1. Should external funds be allocated to maximize health gain or some other criteria
2. What external funds should be allocated to containment of drug/ insecticide resistance or elimination?

Within countries:

1. Faced with a resource constraint, should malaria programmes prioritize certain interventions, e.g. diagnosis and treatment, given that they account for a smaller part of the malaria control budget?
2. Faced with a resource constraint, should malaria programmes prioritize certain populations e.g. those with highest morbidity and mortality rates.

Proposal for the Establishment of a Technical Expert Group for Surveillance, Monitoring and Evaluation

March 2013 – note for MPAC discussion

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1. Background

The past decade has witnessed tremendous expansion in the financing and coverage of malaria control programmes which has led to significant decreases in malaria cases and deaths: 50 countries are on track to meet World Health Assembly (WHA) and Roll Back malaria (RBM) targets to reduce malaria case incidence by 75% by 2015. However, while there has been much progress in programme implementation our ability to track programme financing, coverage and impact remains weak particularly in countries where both burden and malaria control investments are greatest. For example, of 99 countries with on-going malaria transmission 41 countries were unable to submit sufficiently complete and consistent data to reliably assess trends in malaria cases. These countries account for 85% of estimated malaria cases.

Weaknesses in surveillance, monitoring and evaluation stem partly from the fragmented availability of guidance to countries on how to monitor and evaluate programmes. There has been some progress in the development of such guidance in the past decade, notably:

1. Household surveys – the RBM Monitoring and Evaluation Reference Group (MERG) has worked to harmonize indictors that can be derived from households, principally for insecticide-treated net (ITN) coverage, uptake of intermittent preventive treatment in pregnancy (IPTp), parasite prevalence and, more recently, diagnostic testing.

2. Surveillance manuals – in 2012 WHO released 2 manuals on malaria surveillance covering programmes in the control and elimination phases, respectively. See http://www.who.int/malaria/surveillance_monitoring/operationalmanuals/en/index.html

However, significant gaps remain, such as how to monitor the extent of diagnostic testing and the appropriate use of antimalarial medicines (key components of the *T3: Test. Treat. Track* initiative). Overall guidance on what strategies a country should use to monitor programmes, and how data can be used to support decision-making, is also lacking (such as the respective role of household surveys, health facility surveys and routinely derived information).

A principal reason for the gap is that there is no single body with a dedicated interest in developing comprehensive guidance that is genuinely useful to national programme managers and other national and subnational public health staff. The RBM MERG was established at a time when investments in malaria programmes were low and the availability of information was scarce, and made considerable advances in ensuring that approaches used in the Demographic and Health Surveys (DHS), Multiple Indicator Cluster Surveys (MICS) and Malaria Indicator Surveys (MIS) are consistent. However, the RBM MERG's focus has been on deriving information for international monitoring rather than developing guidance on establishing systems that can be used to support programmes, and hence has focussed on household surveys rather than routine systems. The RBM MERG has also worked according to the agendas of its constituents and its advice has at times been at variance with that of WHO potentially leading to confusion at country level. For example, following WHO's recommendation to ensure ITNs are supplied to all age groups, MERG continued, until recently, to recommend the proportion of children under 5 years of age sleeping under and ITN as its lead indicator.

As a result of the need to develop more comprehensive guidance on monitoring and evaluation, it is proposed that an technical expert group be established called the Surveillance, Monitoring and Evaluation (SME TEG) The SME TEG would develop guidance on what strategies endemic countries can employ to monitor and evaluate malaria programmes which covers financial tracking, programme coverage, and disease trends -- including burden estimation. Such guidance should be reviewed on a regular basis, in conjunction with latest MPAC recommendations or methodological developments in order that it reflects current best practice.

2. Membership of SME TEG

Members of SME TEG will be expected to provide GMP with high quality, well considered advice on matters related to malaria surveillance, monitoring and evaluation. The provisional plan is that SME TEG will comprise up to 12 members, who will serve in their personal capacity and will be drawn from persons who have specific expertise in monitoring finances, vector control, diagnostic testing and treatment, morbidity and mortality, elimination as well as methodologies for generating information including health information systems, household surveys and demographic surveillance systems. As far as possible, members will be selected on the basis of the principles of equitable geographical representation from developed and developing countries and be balanced with regard to gender.

An open call for inviting submissions and/or nomination of experts to serve on SME TEG will be posted on the WHO web site and sent out through other appropriate channels. SME TEG members, including the Chairperson, will be appointed by Director of the Global Malaria Programme based upon the recommendations from a panel composed of the Coordinator of the Strategy, Economics, and Elimination unit, a regional WHO malaria advisor, the MPAC Chairperson, and one additional MPAC member. The panel may also consult with other relevant WHO departments. Members of SME TEG, including the Chairperson, will be appointed to serve for an initial term of three years, renewable once, for a period up to an addition three years. The Chairperson of SME TEG will be invited as a resource person to all MPAC meetings at which surveillance, monitoring and evaluation issues are being discussed.

Membership of SME TEG may be terminated for any of the following reasons:

• failure to attend two consecutive SME TEG meetings;

• change in affiliation resulting in a conflict of interest; and

• lack of professionalism involving, for example, a breach of confidentiality.

WHO Regional Offices and other WHO departments will be invited as members of the Secretariat to participate in SME TEG meetings and deliberations as appropriate. Additional experts will be invited to participate in meetings, also as appropriate, to ensure that a sufficiently broad base of expertise is available for the specific agenda items at each meeting.

3. SME TEG Operating Procedures

The SME TEG will meet at least once a year in open and closed meetings. Open meetings can be attended by anyone interested in SME issues and are intended for discussion of new tools, technologies and approaches and issues related to the agenda item(s) of the closed meeting. Closed meetings will follow the open meetings and will be restricted to SME TEG members and the other independent experts to be invited by GMP. Recommendations from the SME TEG will be referred to the MPAC for consideration.

A web page will be established for SME TEG which will be used to allow access to supporting documentation and the agenda of SME TEG, and to disseminate the recommendations and meeting reports of SME TEG.

Technical Expert Group for Surveillance Monitoring and Evaluation

GLOBAL MALARIA PROGRAMME

Geneva, 14 March 2013

World Health Organization

Outline

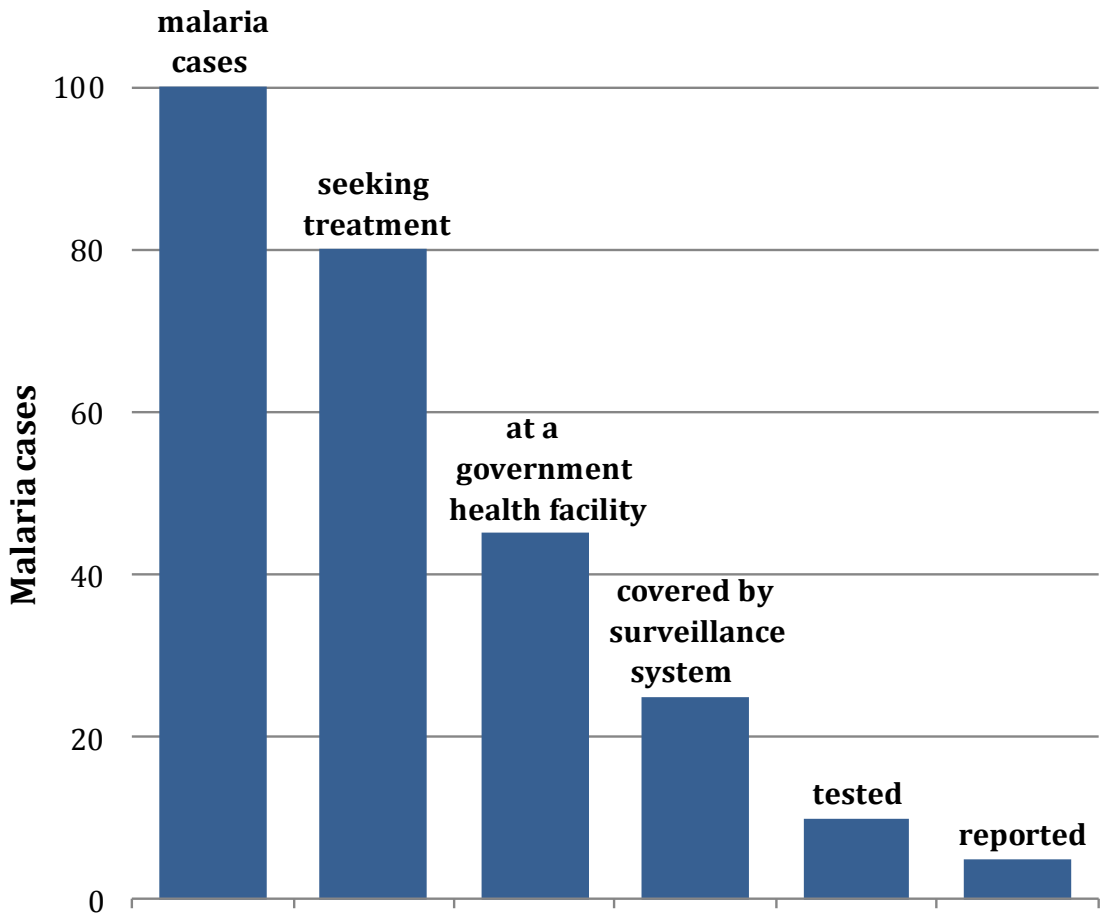
- Status of systems for surveillance, monitoring and evaluation
- Existing guidance
- Proposed Surveillance, Monitoring and Evaluation TEG

Proportion of cases detected by surveillance systems

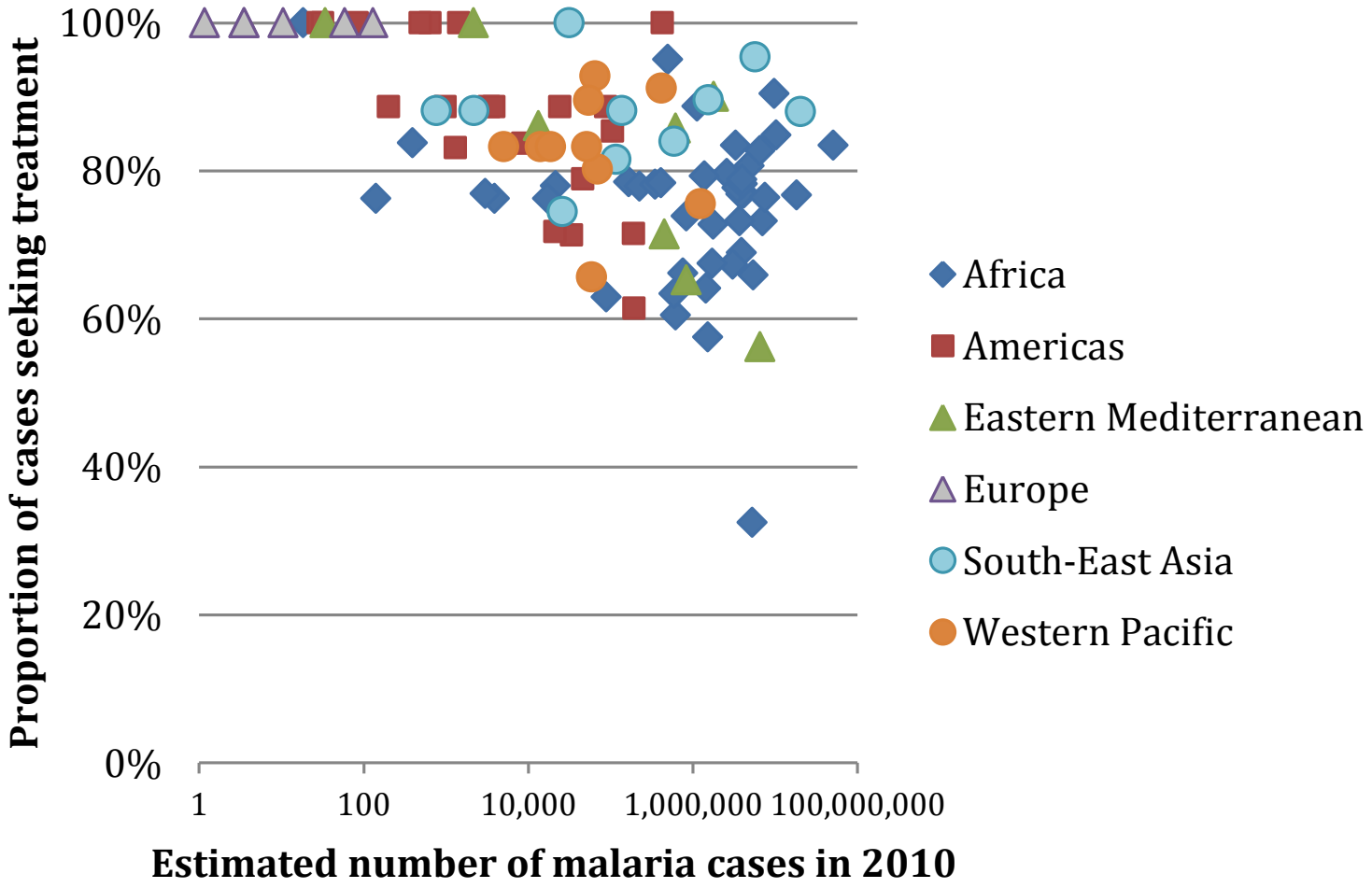
Region	Estimated number of cases 2010	Reported number of cases 2010	Reported/ estimated
Africa	174 000	18 000	11%
Americas	1 100	700	59%
Eastern Mediterranean	10 400	1 000	10%
Europe	0.2	0.2	87%
South-East Asia	32 000	2 400	9%
Western Pacific	1 700	260	13%
World	219 000	22 500	10%

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

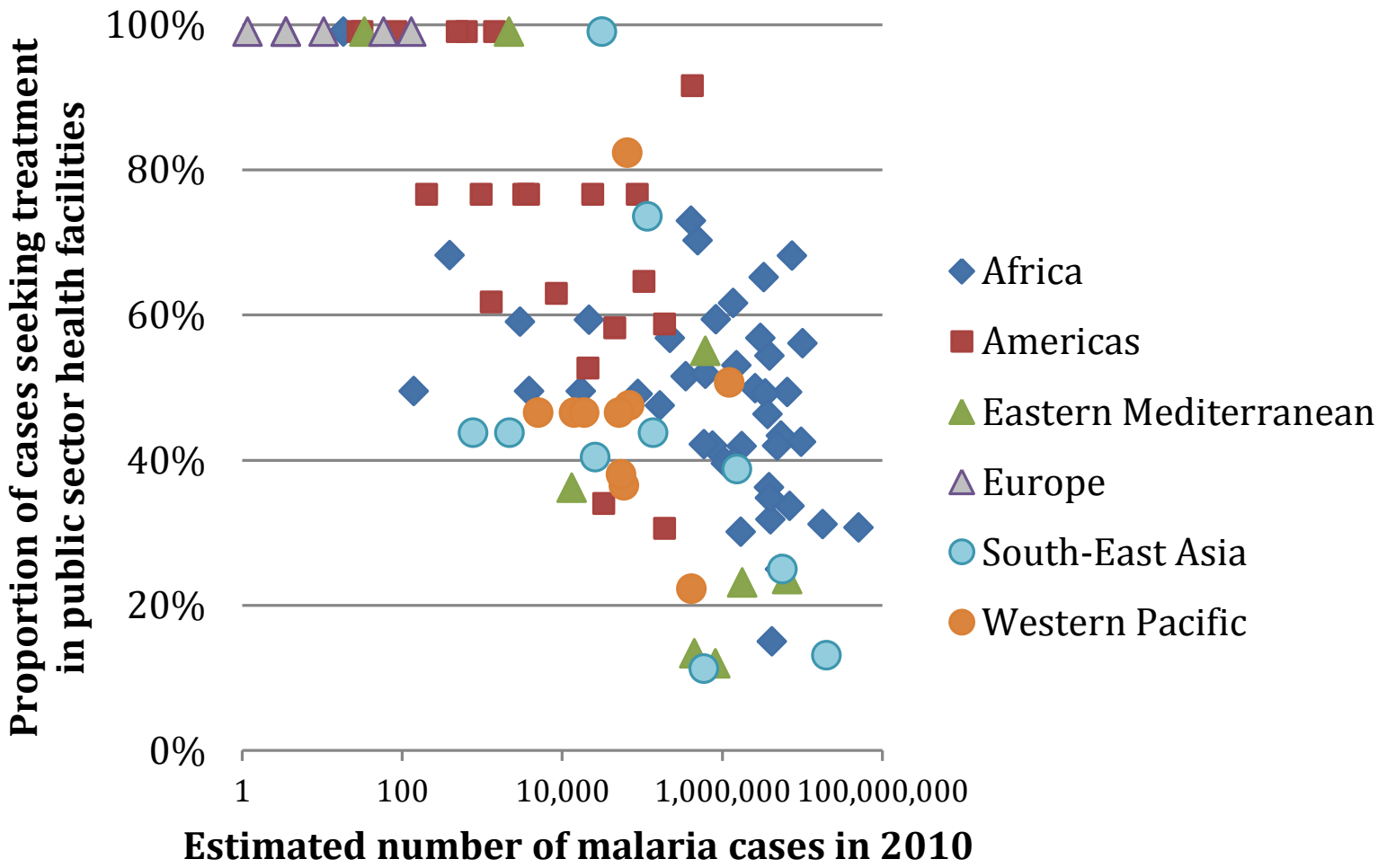
Bottlenecks in case detection



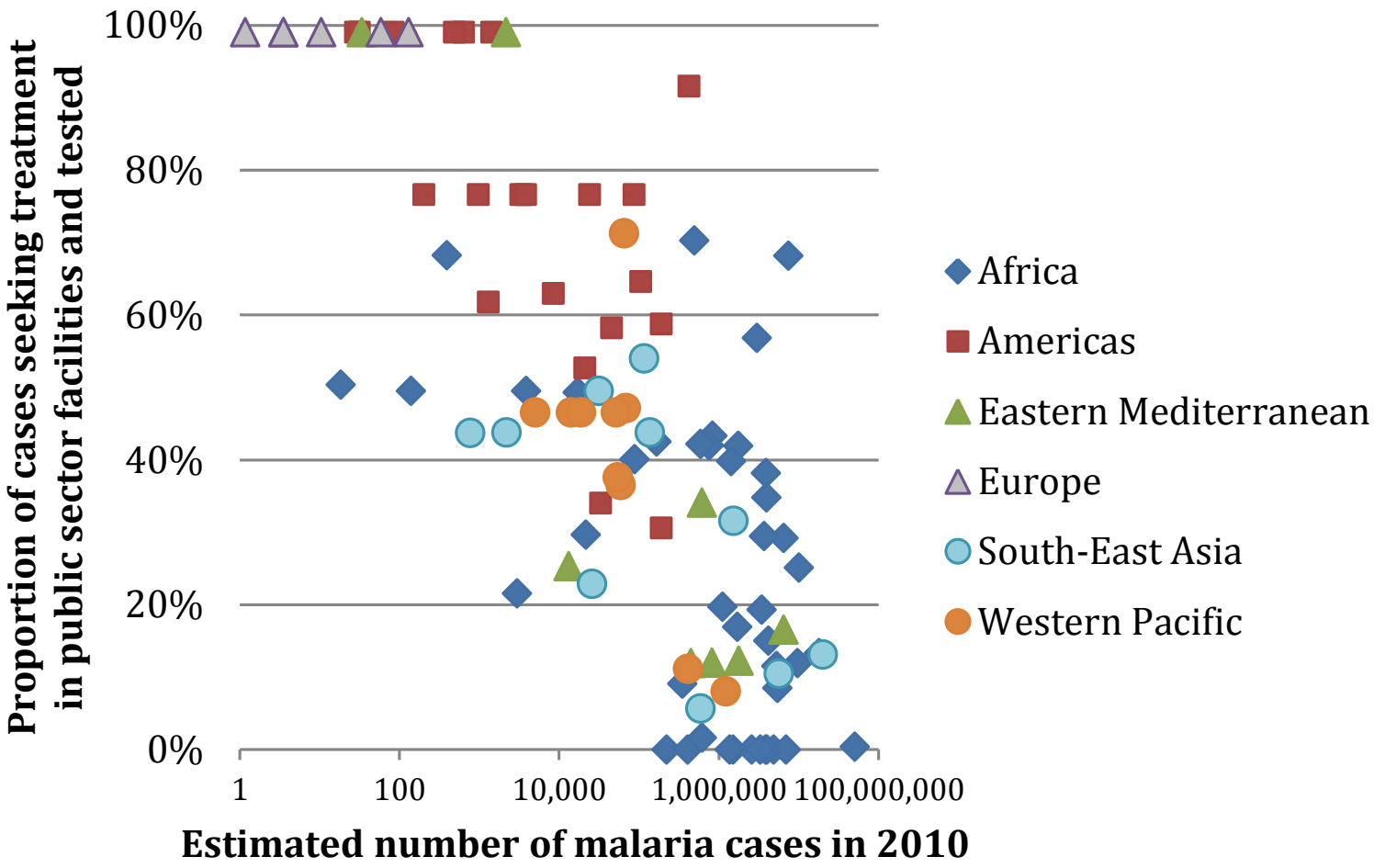
Proportion of cases seeking treatment



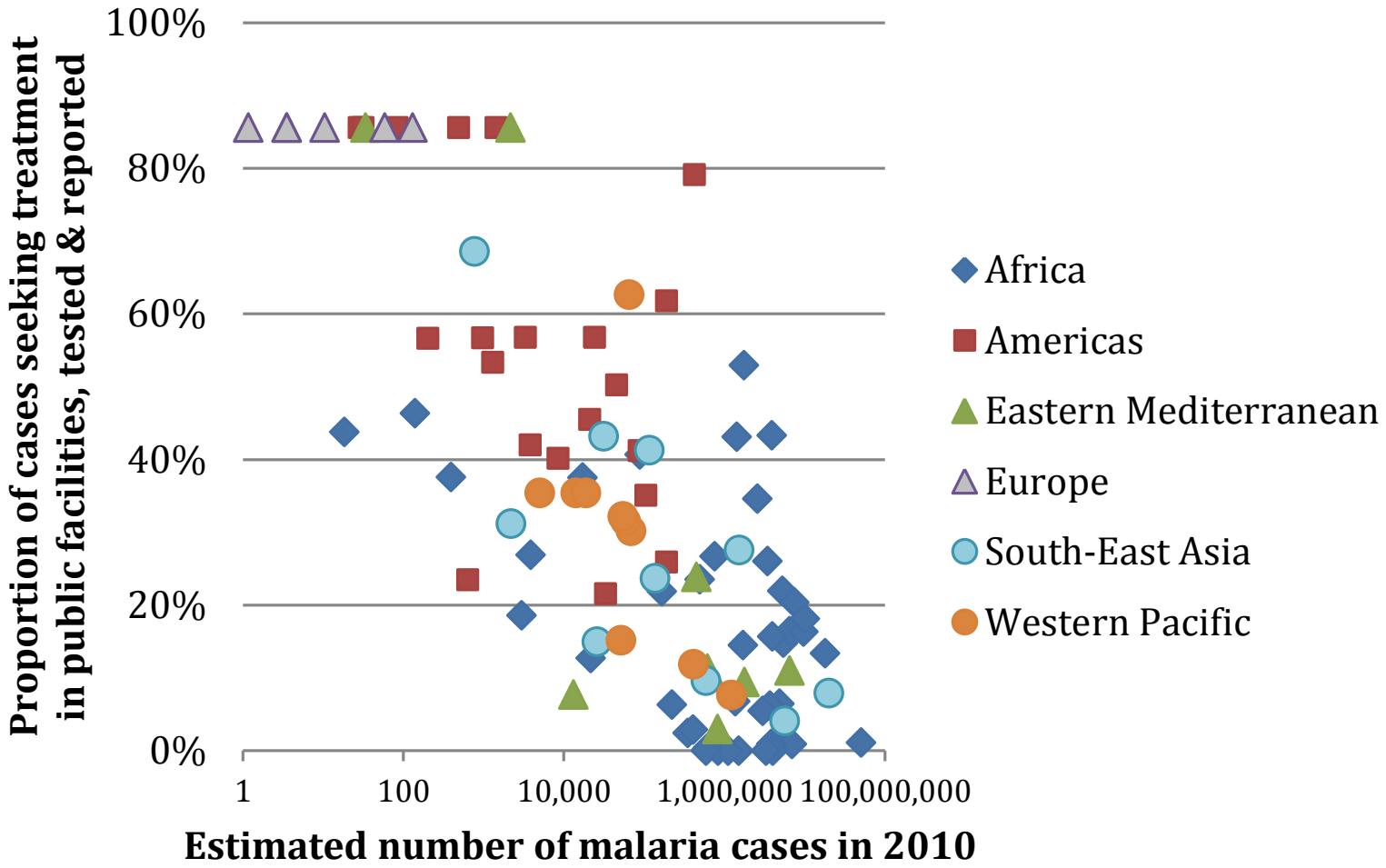
Proportion of cases seeking treatment at a government health facility



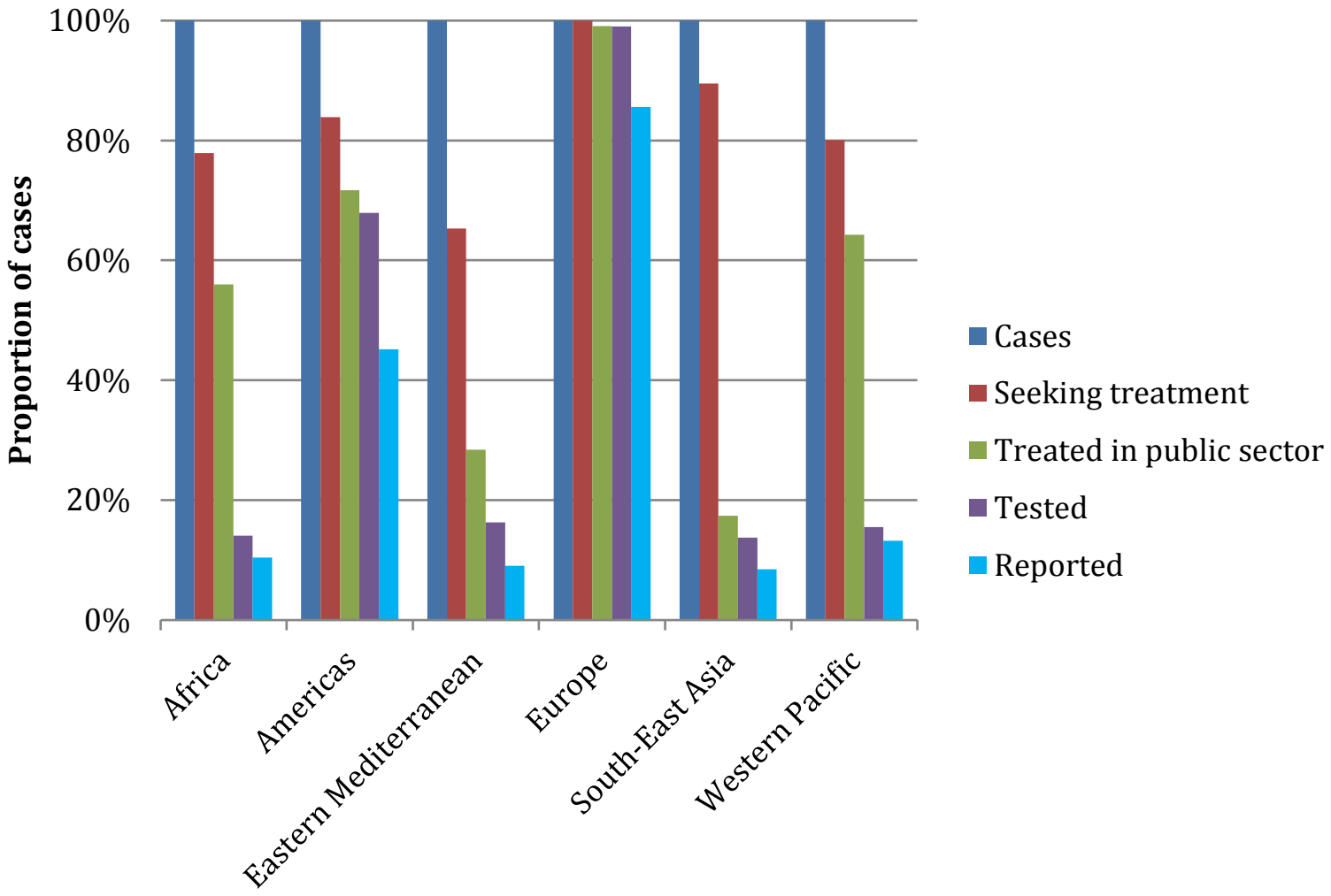
Proportion of cases seeking treatment at a government health facility and tested



Proportion of cases seeking treatment at a government health facility, tested and reported



Bottlenecks in case detection by WHO region

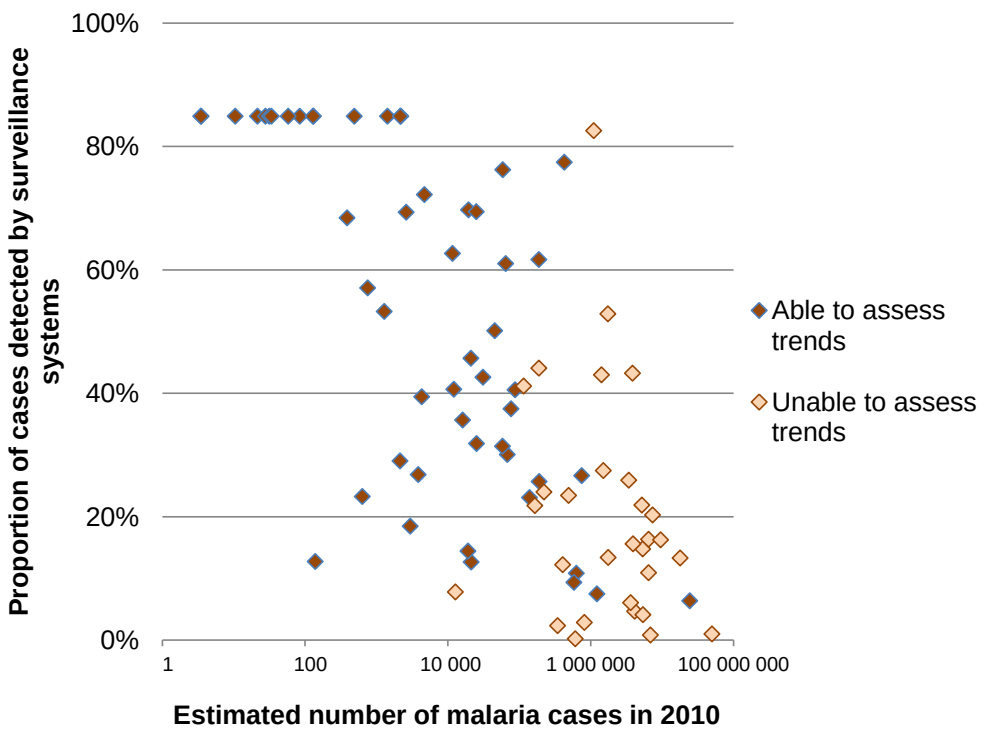


Assessing trends in malaria through surveillance systems

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.



Number of household surveys (DHS, MICS, MIS)

Region	2007	2008	2009	2010	2011	Total
AFR	7	8	4	11	5	35
AMR	2	1	1	1		5
EMR	1	1	1			3
EUR						0
SEAR	2		2		1	5
WPR		1		1		2
World	12	11	8	13	6	50

Issues for Surveillance Monitoring and Evaluation

Surveillance and Impact

- Case detection rates are 10% and lowest in countries with the highest number of malaria cases. A reliable assessment of trends can not be made in 41 countries out of 99 with ongoing transmission using data submitted to WHO. These countries account for 85% of total estimated cases in 2010.
- Not more than 15 household surveys conducted per year.

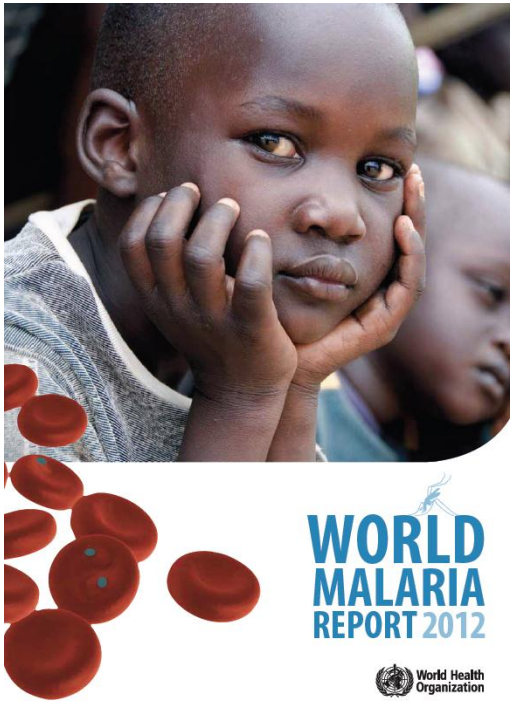
Programme coverage

- ITN coverage is modelled as recent household survey data are not always available. Estimates problematic when mass campaigns are done.
- Routine data on diagnostic testing not reported reliably for many countries. Household survey data sparse. Biased estimates.
- Difficult to track the extent to which confirmed malaria cases receive an antimalarial medicine because diagnostic test results are not usually linked to the treatment given to patients (in routine systems or household surveys) – Tracking the number of antimalarials procured or distributed is unsatisfactory.

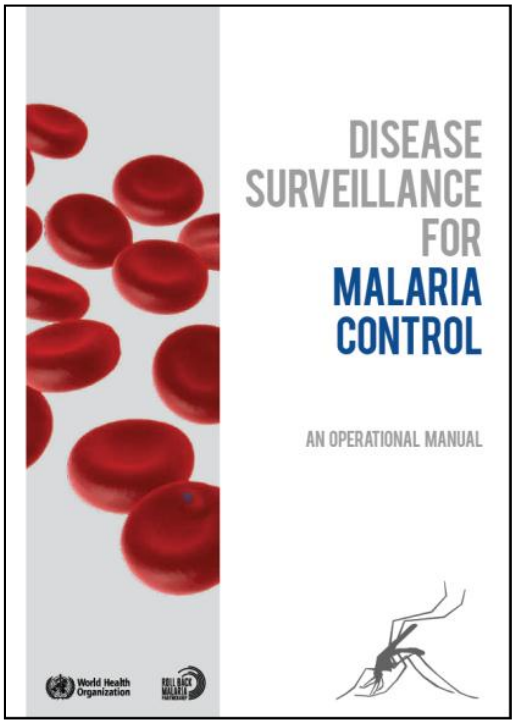
Financing

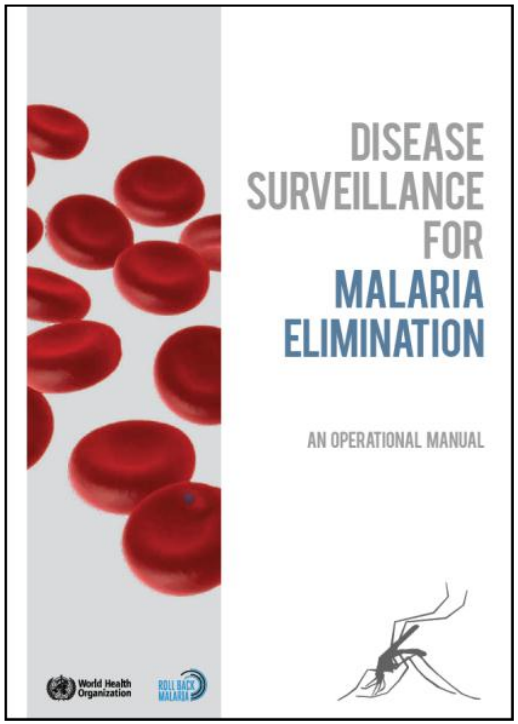
- For most donors data on external financing for malaria control is only up to 2010.
- Domestic financing data are difficult to gather

Guidance provided by WHO



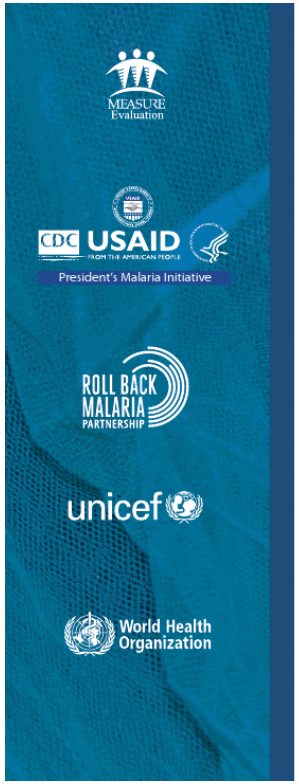
Indicators





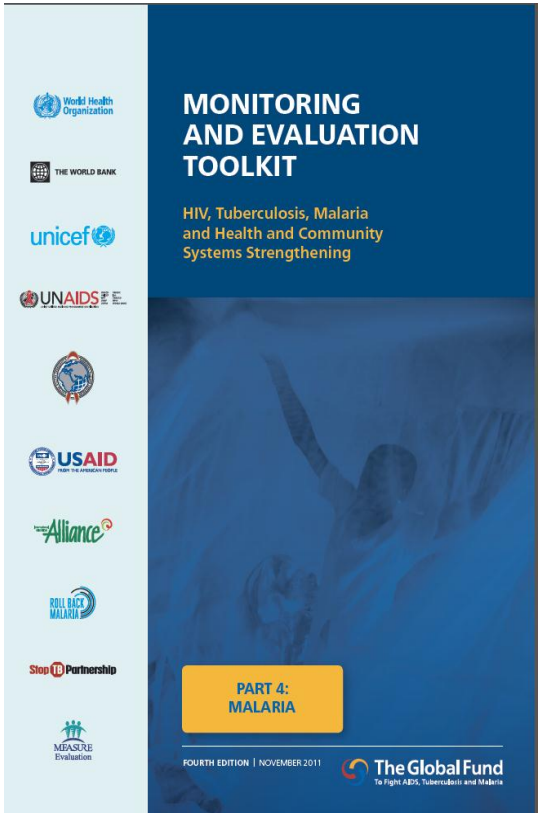
Indicators, reporting systems, data use etc

Guidance provided by other partners



Household Survey Indicators for Malaria Control

Indicators,



Indicators, reporting systems, data use etc

Indicators recommended by WHO/ RBM

Table 2.2 Indicators for measuring progress towards GMAP objectives and targets

GMAP Objective or Target	Key Indicator	Further Analysis	Supporting Indicator
Objective 1 Reduce global malaria deaths to near zero* by end 2015	→ Inpatient malaria deaths per 1000 persons per year	→ Has health facility reporting completeness changed over time?	→ Completeness of monthly health facility reports
	→ **All-cause under 5 mortality rate**	→ What factors are responsible?	→ **Program coverage (detailed below)**
Target 1.1 Achieve universal access to case management in the public sector	→ Proportion of suspected malaria cases that receive a parasitological test		
	→ **Proportion of children under 5 years old with fever in the last 2 weeks who had a finger or heel stick**	→ Are people seeking advice or treatment for fever and from where?	→ **Proportion of children under 5 years old with fever in the last 2 weeks for whom advice or treatment was sought**
Target 1.2 Achieve universal access to case management, or appropriate referral, in the private sector	→ Proportion of confirmed malaria cases that receive first-line antimalarial treatment according to national policy	→ Are adequate quantities of antimalarial medicines available?	→ Proportion of health facilities without stock-outs of key commodities by month
Target 1.3 Achieve universal access to community case management (CCM) of malaria	→ **Proportion receiving first-line treatment among children under 5 years old with fever in the last 2 weeks who received any antimalarial drugs**		
Objective 2 Reduce global malaria cases by 75% by end 2015 (from 2000 levels)	→ Confirmed malaria cases (microscopy or RDT) per 1000 persons per year	→ Has diagnostic effort changed over time?	→ Annual blood examination rate
		→ Has health facility reporting completeness changed over time?	→ Completeness of monthly health facility reports
		→ Have test positivity rates changed over time?	→ Malaria test positivity rate
	→ Parasite prevalence: proportiion of children aged 6–59 months with malaria infection	→ Is there other evidence of morbidity change?	→ **Proportion of children aged 6–59 months with a hemoglobin measurement of <8 g/dL**

Gaps in Guidance

- Monitoring access to diagnostic testing and treatment – household surveys, health facility surveys, routine systems

- Overall monitoring and evaluation guidance – when and how often to use household surveys, the role of routine systems.

- MERG guidance
  - Does not necessarily reflect latest guidance of WHO
    - ITN indicators
  - Does not necessarily respond to latest MPAC recommendations
    - IPTp
    - SMC
    - Primaquine single dose for *P. falciparum*
  - Tends to focus on data for international monitoring rather than programmes

Proposed Surveillance, Monitoring and Evaluation TEG

Role

To advise GMP/MPAC on matters related to malaria surveillance, monitoring and evaluation

Topics

- finances
- vector control
- diagnosis and treatment
- morbidity and mortality,
- elimination

Methodologies

- health management information systems
- household surveys
- demographic surveillance systems

Some of the same people as MERG

Malaria elimination – definitions, criteria and possible variants

For discussion

A.Schapira

WHO Malaria Policy Advisory Committee meeting 13-15 March 2013

Topics

1. Definition and criteria for elimination
2. Current WHO classification of countries
3. Is de-certification needed?
4. A proposed “new” category: Non-endemic controlled malaria
5. Species-specific elimination and *P.knowlesi*
6. Sub-national elimination

Definition and criteria for elimination

- **Malaria elimination**: "a reduction to zero of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts. Continued measures to prevent re-establishment of transmission are required."
- **Malaria-free**: "an area, where there is no continuing local mosquito-borne malaria transmission, *and the risk of acquiring malaria is limited to introduced cases only"*
- "**Certification of malaria elimination**: granted by WHO after proving beyond reasonable doubt that the chain of local malaria transmission by *Anopheles* mosquitoes has been fully interrupted in an entire country for at least three consecutive years." … "When a country has zero locally acquired malaria cases for at least three consecutive years, it can request WHO to certify its malaria-free status".

WHO (2007). Malaria Elimination. A field manual for low and moderate endemic countries

"Elimination: nationwide per year fewer than three 'epidemiologically linked' cases of malaria infection, without an identifiable risk factor other than local mosquito transmission, for three consecutive years."

(WHO (2006). Informal consultation on malaria elimination: setting up the WHO agenda). This was quoted almost verbatim in WHO (2007). United Arab Emirates certified malaria-free. *Weekly Epidemiological Record* **82**, 25-32.

- Suggestion: Remove ambiguity: Malaria elimination and malaria-free status should be defined as no local transmission <u>without</u> mentioning "the risk of acquiring malaria is limited to introduced cases only". <u>Criterion</u> for certification: ZERO locally transmitted cases detected for 3 consecutive years (by good surveillance etc.).

The rules for **follow-up of certification**:

- "Because certification is the recognition of a considerable operational achievement, countries will remain listed as having achieved malaria elimination even if they subsequently suffer a temporary occurrence of local transmission.
- An indication of the re-establishment of transmission would be the occurrence of three or more introduced and/or indigenous malaria infections linked in space and time to local mosquito-borne transmission in the same geographic focus, for two consecutive years for *P.falciparum* and for three consecutive years for *P.vivax*."

Field manual (2007) and draft criteria from the informal consultation on malaria elimination in 2006.

Comment: This criterion is somewhat arbitrary, but appears to have worked well. It has been pointed out that it can only be fulfilled in a situation with very low malariogenic potential (Cohen et al., 2010) , but such low risk is anyway a pre-condition for certification.

Current WHO classification of countries (WMR 2011)

- Pre-elimination,
- Elimination,
- Prevention of re-introduction
- Certified malaria-free within last 5 years, or no local transmission reported for over a decade.

- The classification is based on a combination of operational and epidemiological criteria.
- This avoids commenting on the situation of countries, which were certified in the past.

Comments on this classification (1)

- Countries may be malaria-free without having been certified; this is normal for those, which never had malaria or became malaria-free without any deliberate efforts or with little deliberate effort before the GMEP. However, some countries, which did deliberately eliminate malaria, but were not certified, are not mentioned.

- There is no process for de-certification. What are the formalities if a certified country has sporadic malaria or if it becomes malaria-endemic?

Suggestions:

One possibility may be to de-certify countries. This might however be painful and unfair to countries, which boldly decided to undergo the scrutiny of certification compared to those, which decided that "they don't need certification."

An alternative possibility is to make a separation between certification as a medal obtained at a give point in time and obliging certain follow-up and the classification in categories, which may be changed any time based on epidemiological data. What would be needed then would be to make the classification comprehensive, so that every country in the world is classified. This would be more pragmatic, but reduces the prestige of certification.

What is the policy of other WHO programmes?

Comments (2): “Prevention of reintroduction” or “controlled non-endemic malaria”

- “Prevention of reintroduction” is problematic: Any country in which malaria has been eliminated needs to prevent reintroduction. The programme activities characterising these countries such as vigilance and case investigation of imported cases are the same as in malaria-free countries.
- “Controlled non-endemic malaria” has been proposed defined as: “a state where interventions have interrupted endemic transmission and sharply limited onward transmission from imported infections, but where high malariogenic potential means that some level of local transmission is inevitable; elimination would naturally follow if all malaria resulting from imported infections could be prevented.”

Cohen et al. (2010). How absolute is zero? An evaluation of historical and current definitions of malaria elimination *Malaria Journal*, **9**:213)

- Comment: The advantage is that this is a rational endpoint for a number of countries, where a high risk of importation combined with high receptivity makes elimination impossible – or unacceptably costly and almost impossible to maintain.

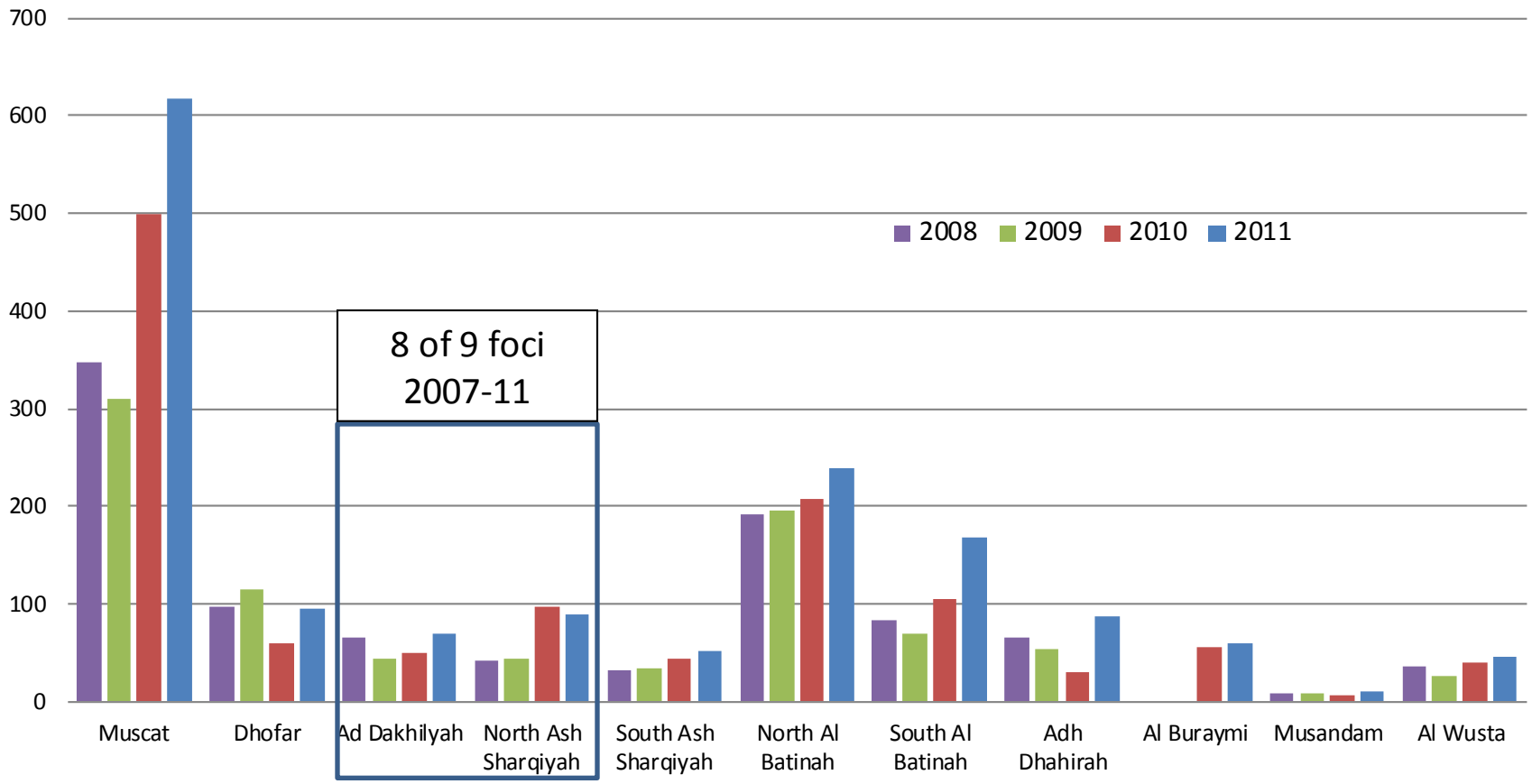
Proposed **operational criterion** to distinguish controlled non-endemic malaria from (controlled low-) endemic malaria:

- Ratio locally transmitted cases: imported cases < 1:1, would correspond to Rc=0.5 (each case gives rise directly to 0.5 cases), meaning that malaria is clearly not endemic.
- In a large country, many cases might be imported to areas with 0 receptivity; at the same time, some cases could be imported to areas with varying degrees of receptivity>0; it may be necessary to use stratification, when applying this criterion.

Example Oman

No. of foci **2007 -2011**	9
Total no. cases incl. imported	**64**
Nationality of probable source:	India: 2 Pakistan: 5 Unknown: 2
Other imported cases in same areas as the foci	6
Total imported cases in foci	**15**

Oman: All malaria cases 2008-2011 by governorate



Oman as an example of non-endemic controlled malaria

- If you count all the cases recorded in the two governorates with 8 of 9 foci, the ratio

  locally transmitted:imported is well < 1:1.
- If one would include all cases recorded in the country, the ratio would be much lower, but it would be meaningless epidemiologically to include imported cases for example in Muscat (capital city), where there is no receptivity.

Suggestion on “controlled non-endemic malaria”

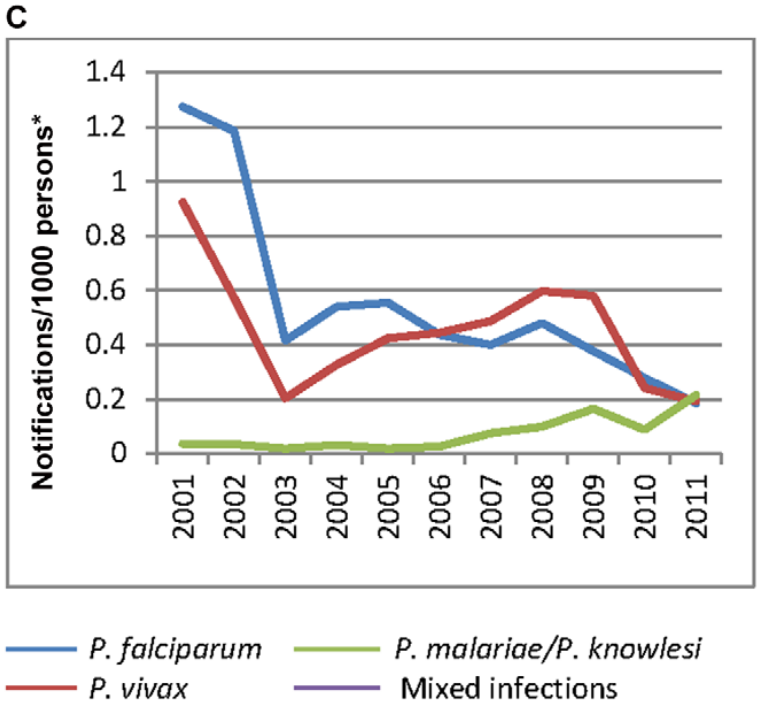
- The category of controlled non-endemic malaria would be similar to the present “prevention of reintroduction” category.
- It would have a more precise definition.
- It would be an acceptable endpoint for many countries, which could achieve elimination when vulnerability, which is determined by external factors, is greatly reduced.
- Maintenance may require considerable capacity and annual expenditure
- The classification could be recognized annually by WHO based on an epidemiological analysis; formal certification might be too onerous.

Species-specific elimination and zoonotic malaria

- There is a contradiction between malaria elimination according to WHO referring to all species of human malaria parasites, while malaria eradication refers to “infection by a specific agent”. However, this contradiction has little if any implication as long as we are far from the elimination of any species.

P.knowlesi

- In Sabah, Malaysia, "…, *P. malariae/P. knowlesi* notifications increased >10-fold between 2004 (n = 59) and 2011 (n = 703).
- The extensive deforestation …has led to encroachment of humans into previously forested areas, resulting in increased interaction with vectors and simian hosts. Removal of habitat and malaria control activities may have led to change in vector behaviour, or vector shift.
- *P.knowlesi* appears to have increased very recently, long after Sabah's most extensive period of deforestation during the 1970s and early 1980s



Williams T et al. (2013). Increasing Incidence of *Plasmodium knowlesi* Malaria following Control of P. *falciparum* and *P. vivax* Malaria in Sabah, Malaysia. *PLOS Neglected Tropical Diseases.* **7**, e2026

- Comment: Natural human-to-human transmission of *P.knowlesi* might be confirmed any time, although it is technically demanding.
- "Surveillance should be continued to detect human-to-human transmission of *P. knowlesi*. If it is confirmed and *P. knowlesi* becomes the fifth human malaria parasite, it then would be inconsistent with malaria elimination."

Report. Informal consultation on the public health importance of *Plasmodium knowlesi*. Convened by WHO/WPRO in Kuching, Sarawak, Malaysia, 22- 24 February 2011

- The conundrum is that once natural human-to-human transmission has been proven to occur, then elimination could be certified only if every *P.knowlesi* infection is proven to be zoonotic!

Are we witnessing a biological transition? Are we paying enough attention?

"Following current understanding of the evolutionary route of other human malaria vectors and parasites, an increasing human population in knowlesi malaria endemic regions will select for a more anthropophilic vector as well as a parasite that preferentially transmits between humans. Applying these adaptations, evolutionary invasion analysis yields threshold conditions under which this macaque disease may become a significant public health issue."

Yakob, L. et al. (2010) Modelling knowlesi malaria transmission in humans: vector preference and host competence. *Malaria Journal*, **9**, 329

Sub-national elimination

- Current WHO guidelines recognize sub-national elimination, but do not allow WHO certification of it.
- Elimination in some Indian states or Chinese provinces could be momentous milestones, also in an international perspective, but it would be hard to set the limits for where WHO should go.
- There is a need for WHO guidance to countries about handling sub-national elimination. Based on experience from the Philippines, it is suggested that:
  - such national processes should emulate WHO certification;
  - a clear distinction should be made by the certifying and the certified entities;
  - emphasis should be placed on the capacity of the certified entity to achieve and maintain malaria-free status with limited central financial and technical support. However, this might need to be applied with flexibility in the case of for example small island provinces.

Proposal for a second meeting of the WHO Evidence Review Group on Intermittent Preventive Treatment of malaria in pregnancy (IPTp) to be held on 9-11 July 2013, Geneva, WHO

Background

The Malaria Policy Advisory Committee has reviewed the policy on intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) in September 2012. On this basis, WHO recommends that SP should be given for IPTp to all pregnant women at each scheduled antenatal care visit, starting as early as possible during the 2nd trimester of gestation.[*] IPTp-SP is an integral part of WHO's strategy for prevention and control of malaria in pregnancy, which also includes the use of insecticide-treated nets, prompt diagnostic testing and effective treatment.

The new recommendation is based on the assessment by the Evidence Review Group in July 2012 of more recently available data, [†], including a meta-analysis of 7 trials on IPTp-SP, which showed that 3 or more doses of SP for IPTp were associated with a 20% reduction in low birth weight (LBW) compared to 2 doses of SP. The effect was consistent across a wide range of SP resistance levels, and there were no differences in serious adverse events between the two groups[‡].

In October 2012, WHO published the new recommendations on IPTp-SP,[*] and urged national health authorities to disseminate this update widely and ensure its correct application. Based on initial feedback from representatives of national programmes and several implementing partners, the Global Malaria Programme (GMP) and Reproductive Health and Research (RHR) Programme of WHO have also developed a policy briefing paper to offer additional background information, more explanations on operational aspects, a compilation of the scientific evidence, together with a set of frequently asked questions on the new IPTp-SP policy.

[*] http://www.who.int/entity/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf

[†] http://www.who.int/entity/malaria/mpac/sep2012/iptp_sp_erg_meeting_report_july2012.pdf

[‡] Kayentao K. *et al.* Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *JAMA,* 2013, 309: 594-604. doi: 10.1001/jama.2012.216231

Emerging new evidence

The Malaria in Pregnancy Consortium (MIPc) and the US President's Malaria Initiative (Centers for Disease Control and Prevention (CDC) and USAID) are conducting a series of IPTp-SP effectiveness monitoring studies (known as the IPTp-Mon(itoring) study). These studies involve HIV negative pregnant women from 8 sites in 6 countries (Burkina Faso, Kenya, Malawi, Mali, Uganda and Zimbabwe). This research is evaluating the contribution of SP resistance to IPTp effectiveness, with specific attention to: 1) *in-vivo* clearance of peripheral parasitaemia in pregnant women, 2) impact on maternal and neonatal outcomes, e.g. birth weight, placental infection, clinical malaria, maternal anemia and fetal anemia, and 3) prevalence of molecular markers of SP resistance. A manuscript will be available for WHO to review in June 2013.

In addition, to assess the situation in countries of Central and Western Africa with medium-to-low levels of resistance to SP, a meta-analysis of IPTp effectiveness is being undertaken by MIPc of all published observational studies (1995-2013) reporting LBW as a function of the number of doses received; this will also include DHS data. The study, named IPTp-AMA (aggregate meta-analysis), is being finalised and the manuscript will also be available for WHO to review in June 2013.

Studies on the efficacy and safety of mefloquine for IPTp, in the context of Insecticide-Treated Nets (ITNs), named the MiPPAD study (Malaria in Pregnancy Preventive Alternative Drugs) will be also be completed by June 2013. The MiPPAD study, co-funded by the EDCTP and MIPc, involves two clinical trials: i) a randomized open-label superiority 3-arm trial to compare 2-dose mefloquine (MQ) versus 2-dose SP for IPTp in preventing adverse effects of malaria during pregnancy and to compare the tolerability of 2 different MQ administration regimens (MQ full dose versus 2 doses split over 2 days); and ii) a randomized, double-blind, superiority trial to compare the efficacy of 3- dose MQ as IPTp with that of placebo-IPTp in HIV-infected pregnant women receiving co-trimoxazole (CTX) prophylaxis. The first trial is being conducted in Benin, Gabon, Tanzania and Mozambique, and has enrolled 4750 pregnant women attending antenatal clinics (ANC). The primary endpoint is the proportion of infants born with low birth weight; the study includes infant follow-up for one year. The second trial is being conducted in Kenya, Tanzania and Mozambique, and has recruited 1071 pregnant women. The primary endpoint is the proportion of women at deliver with microscopic or submicroscopic parasitemia;infants are thenfollowed-up for 2 months after delivery. For both studies, manuscripts will be available for WHO to review in June 2013.

In addition to the mefloquine safety data emerging from these two studies, WHO/GMP will seek access to the pregnancy registry on mefloquine of Hoffmann-La Roche (manufacturer of the Lariam brand of mefloquine) as well as to additional relevant safety data from research groups which have conducted trials on mefloquine use/exposures during pregnancy.

Based on the IPTp-Mon(itoring) study, and following the recommendations of the Evidence Review Group convened in 2012, a working group has been established to develop a simplified protocol template to monitor the impact of SP resistance on IPTp-SP effectiveness. The draft protocol will be finalized by May 2013 for review and finalization by the ERG meeting, which is being proposed for July 2013. In addition, a second working group has been established to develop a simplified protocol to monitor the programmatic determinants of IPTp-SP effectiveness. If work progresses well and the draft protocol is ready, it would be possible to also review and finalise this protocol at the ERG meeting in July 2013.

Objectives of the proposed IPTp ERG meeting

The specific objectives of the meeting of the Evidence Review Group will be to:

- Review the evidence regarding the contribution of SP resistance to IPTp effectiveness.
- Finalise the core protocol to monitor the impact of SP resistance on IPTp-SP effectiveness.
- Review evidence on efficacy and safety of mefloquine for IPTp compared to SP (for all women) and to daily co-trimoxazole prophylaxis (for HIV+ pregnant women).
- Develop draft policy recommendations on the contribution of SP resistance to IPTp effectiveness and monitoring methods, as well as on the efficacy and safety of mefloquine for IPTp for consideration by the MPAC in September 2013.

Interactions with the TEG of malaria chemotherapy

The recently published meta-analysis of 7 IPTp trials on 3+ doses of SP versus 2 doses, together with new evidence on the impact of SP resistance on IPTp effectiveness will be assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The new evidence from the randomized-controlled trials on efficacy and safety of mefloquine for IPTp compared to SP and to daily co-trimoxazole prophylaxis in HIV+ pregnant women will also be assessed using GRADE. Based on these assessments , new recommendations on SP and mefloquine for IPTp will be included in the 3rd edition of the WHO Guidelines for the Treatment of Malaria, that will be released in 2014.