Final 26.01.12

Malaria Policy Advisory Committee (MPAC) Inaugural Meeting Agenda

Dates: 31 January to 2 February 2012
Location: Crowne Plaza Geneva

Tuesday, 31 January 2012

Time	Session	Purpose of session, target outcomes and questions for MPAC	Type
09:00	Welcome - Introduction **K Marsh** - Chair of MPAC		**closed**
09:30	MPAC decision making process and outputs	For discussion (operational)	**closed**
10:45	**Coffee/tea break**		
11:00	ERGs, TEGs and their ways of work	For discussion (operational)	**closed**
12:30	**Lunch**		
13:30	Session 1 - Report from Director, GMP **R Newman** Global report including key updates and challenges from regions, and the GMP strategy	For information and discussion	**open**
15:00	**Coffee/tea break**		
15:15	Session 2 - Drug Resistance **P Ringwald** – Coordinator DRC Update on the situation, including the need for a TEG	For information and discussion - MPAC to review proposed ToR and consider creating TEG for drug resistance	**open**
17:00	**Reception**		

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Wednesday, 1 February 2012

Time	Session	Purpose of session, target outcomes and questions for MPAC	Type
09:00	Session 3 - RDT Procurement Criteria **A Bosman** – Coordinator DTV Update on current criteria, and why the threshold needs review	For discussion - MPAC to review current threshold and make recommendation	**open**
10:30	**Coffee/tea break**		
10:45	Session 4 - Larviciding **J Lines** – WHO GMP Consultant Update on the situation and a proposed position statement	For discussion - MPAC to review draft position statement and consider endorsement	**open**
12:00	**Lunch**		
13:00	Session 5 - Classification of countries for elimination **A Rietveld** – Medical Officer, SEE Update on current and proposed classification criteria	For discussion - MPAC to input on proposed criteria for country program classification	**open**
14:45	**Coffee/tea break**		
15:00	Session 6 - Estimating malaria cases and deaths **R Cibulskis** – Coordinator SEE Update on current estimates	For preliminary discussion - MPAC to advise on proposed evidence review process	**open**
17:00	**End of day**		

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Thursday, 2 February 2012

Time	Session	Purpose of session, target outcomes and questions for MPAC	Type
09:00	Session 7 - Seasonal Malaria Chemoprevention **N White & F Binka** – Chairs of TEG Report/Grade tables	For information - MPAC to review evidence and recommendation from TEG	**open**
10:30	**Coffee/tea break**		
10:45	Session 8 - Seasonal Malaria Chemoprevention (continued) Publications/Policy recommendation	For information - MPAC to review evidence and recommendation from TEG	**open**
12:00	**Lunch**		
13:00	Formulation of MPAC recommendations	For discussion - MPAC to make policy recommendations for WHO	**closed**
14:45	**Coffee/tea break**		
15:00	Priority activities Dates and agenda for future meetings Summary of actions and next steps	For discussion (operational) - MPAC to decide on establishment of ERGs for next MPAC meeting(s).	**closed**
17:00	**Close of meeting**		

Global Report to MPAC: Sustaining the gains in malaria control and elimination

Malaria Policy Advisory Committee
Inaugural Meeting
Geneva, Switzerland
31 January 2012

GLOBAL MALARIA PROGRAMME

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

World Health Organization

Objectives

- Overview of progress in malaria control, by intervention (data from World Malaria Report 2011)
- Roles of Global Malaria Programme
- Key deliverables: 2011-2015
  - Overview of MPAC
- Challenges
- Opportunities

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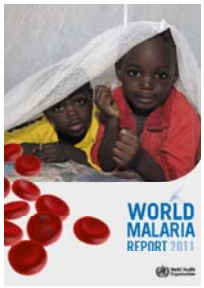
World Malaria Report 2011



- 2011 Report released on 13 December 2011
- Annual reference on the status of global malaria control & elimination. Data to 2010 and 2011
- Principal data source is national programs in 106 endemic countries with support from: WHO Regional offices, ACT Watch, AMFm, ALMA, CDC, CHAI, Columbia University, DFID, DHS/ Measure, FIND, GHG UCSF, Global Fund, IHME, ISGlobal, JHU, PATH, R4D, RBM, Tulane University, UNICEF, UNSE, USAID
- Summarizes key malaria targets & goals
- Documents trends in financing, intervention coverage and malaria cases and deaths
- Updates malaria burden estimates for decade: 2000-2010
- NEW: Profiles for 99 countries with ongoing transmission

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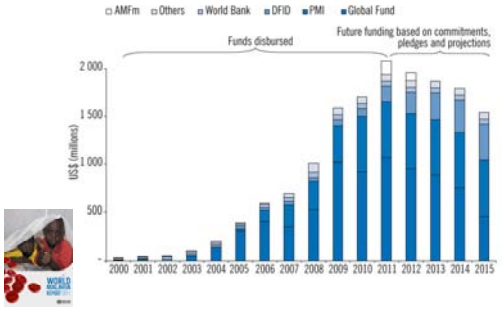
Past and projected international funding for malaria control



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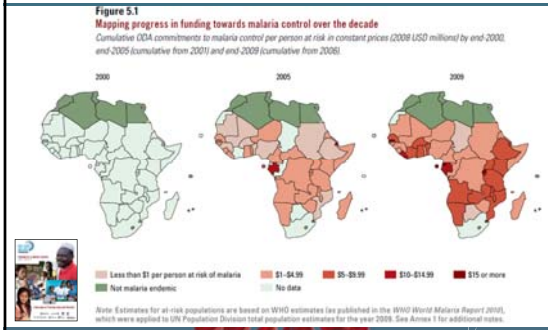
Malaria Funding 2000-2009, sub-Saharan Africa



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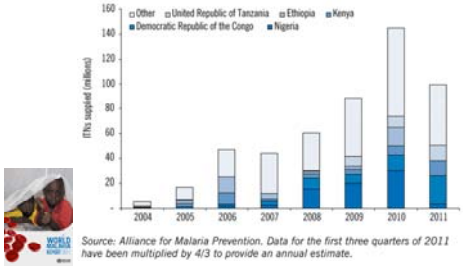
Number of LLINs delivered by manufacturers to countries in sub-Saharan Africa

294 million LLINs procured for distribution in Africa between 2008 and end 2010



Source: Alliance for Malaria Prevention. Data for the first three quarters of 2011 have been multiplied by 4/3 to provide an annual estimate.

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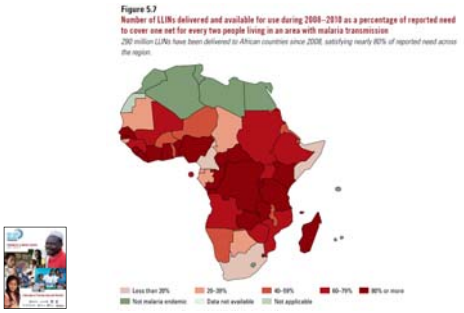
LLINs delivered 2008-2010, sub-Saharan Africa



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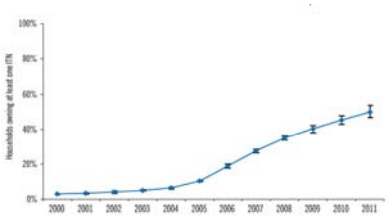
Trend in estimated proportion of households with at least one ITN in sub-Saharan Africa



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

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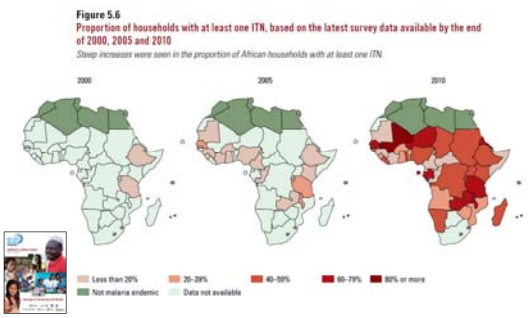
Proportion of HH with at least one ITN, Africa



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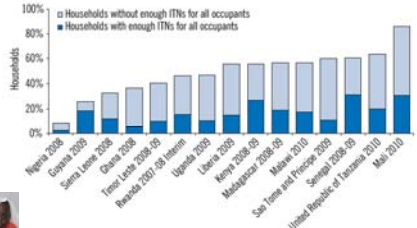
Household ownership of ITNs



Source: Demographic and Health Surveys (Timor Leste, Ghana, Guyana, Kenya, Madagascar, Malawi, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, United Republic of Tanzania); Malaria Indicator Surveys (Uganda, Liberia); and a Special Survey (Mali).

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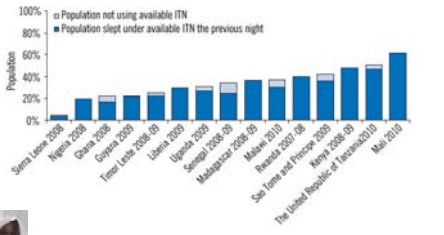
Use of ITNs available in households



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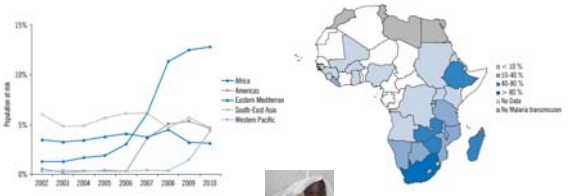
Proportion of population at malaria risk protected by IRS



Source: NMCP reports.

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Intermittent preventive treatment in pregnancy (IPTp): historical context

- IPTp with SP has been WHO policy for high transmission areas of Africa since 1998
- Uptake remains sub-optimal
- Recently hampered by concerns about SP resistance

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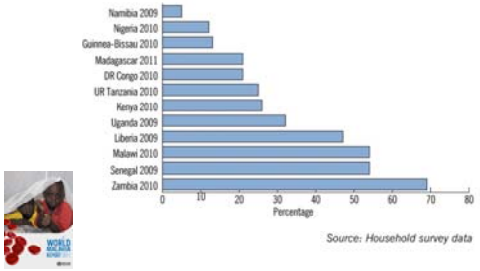
Proportion of all pregnant women receiving the second dose of IPTp, 2009-2011



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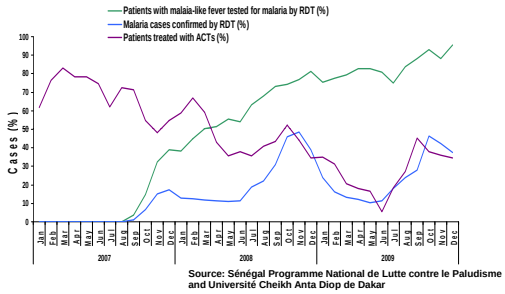
Universal diagnostic testing

- WHO recommends confirmation of malaria through parasite-based diagnosis in all patients prior to instituting treatment (Malaria Treatment Guidelines 2010)
- Rationale:
  - Malaria prevalence amongst fever cases decreasing in many areas: fever no longer equals malaria
  - Quality-assured RDTs are now available

  - Malaria diagnostic testing:
    - Improves differential diagnosis & fever management
    - Diminishes unnecessary use of ACTs
    - Provide accurate surveillance data to manage programmes

World Health Organization — Global Malaria Programme

Senegal: Rapid Diagnostic Tests (RDTs) are scaled up, and the need for antimalarial treatment drops



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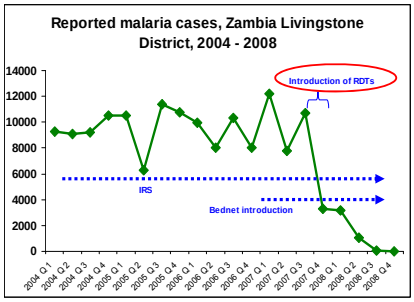
RDT Introduction, Zambia



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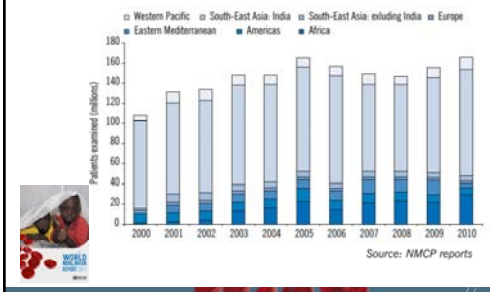
Number of patients examined by microscopy, by WHO Region



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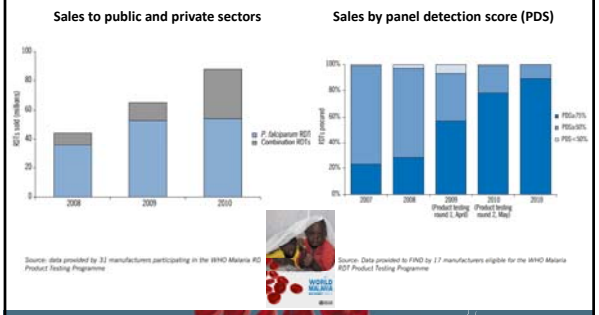
Malaria RDT sales



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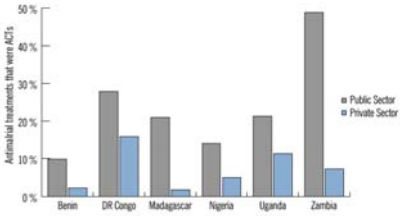
Proportion of African children under 5 with fever receiving a blood test for malaria



Source: adapted from Littrell, M., et al. Monitoring fever treatment behavior and equitable access to effective medicines in the context of initiatives to improve ACT access: baseline results and implications for programming in six African countries. Malaria Journal, 2011, 10:327.

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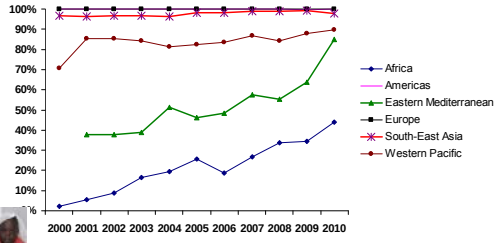
Proportion of suspected malaria cases at public health facilities receiving a parasitological test



Despite improvements, long way to go to reach universal access to diagnostic testing, especially in Africa

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Universal access to malaria diagnostic testing: an operational manual

UNIVERSAL ACCESS TO MALARIA DIAGNOSTIC TESTING

AN OPERATIONAL MANUAL 2011

- **Target Audience:** managers at national, regional or district levels
- **Content:** emphasis on HOW as opposed to WHAT
- **Technical inputs:** 15 agencies and 5 malaria control programmes
- **Released:** September 2011

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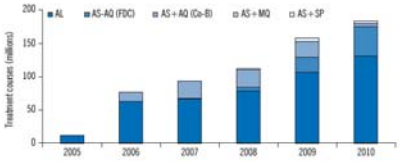
ACT sales to the public sector, 2005–2010



Source: data provided by 8 companies eligible for procurement by WHO/UNICEF

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Proportion of treated children receiving an ACT

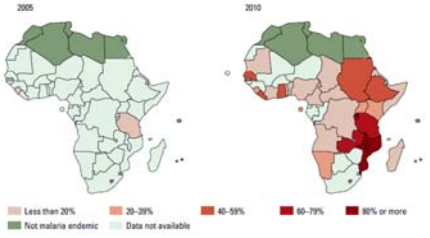

Figure 5.24
Proportion of febrile children younger than five years treated with any antimalarial drug who received ACT, based on the latest survey data available by the end of 2005 and 2010
While ACTs are the recommended first-line treatment in many countries, rates of administration to febrile children began increasing only late in the decade.

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Estimates of malaria cases and deaths by WHO Region, 2010

Region	Estimated cases ('000s) Estimate	Lower	Upper	% *P. falciparum*	Confirmed cases reported	Reported/estimated
Africa	174 000	113 000	239 000	98%	20 000	11%
Americas	1 000	1 000	1 000	34%	1 000	59%
Eastern Mediterranean	0.2	0.2	0.2	0%	0.2	10%
Europe	2	2	2	5%	2	85%
South-East Asia	28 000	23 000	35 000	54%	2 000	9%
Western Pacific	2 000	2 000	2 000	77%	257	13%
World	216 000	149 000	274 000	91%	24 000	11%

Region	Estimated deaths Estimate	Lower	Upper	% <5
Africa	596 000	468 000	837 000	91%
Americas	1 000	1 000	2 000	29%
Eastern Mediterranean	15 000	1 000	38 000	60%
Europe	0	0	0	4%
South-East Asia	38 000	28 000	50 000	31%
Western Pacific	5 000	3 000	6 000	41%
World	655 000	537 000	907 000	86%

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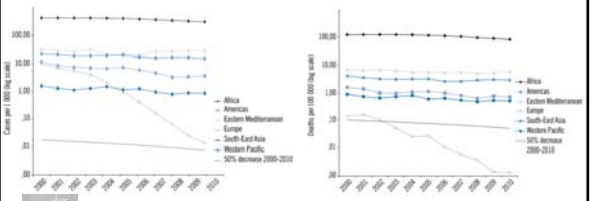
Estimated trends in malaria cases (per 1000) and deaths (per 100 000) persons at risk by WHO Region, 2000–2010



Source: WHO. Rates are plotted on a logarithmic scale. A line representing the slope required to achieve a 50% reduction between 2000 and 2010 is shown to aid interpretation.

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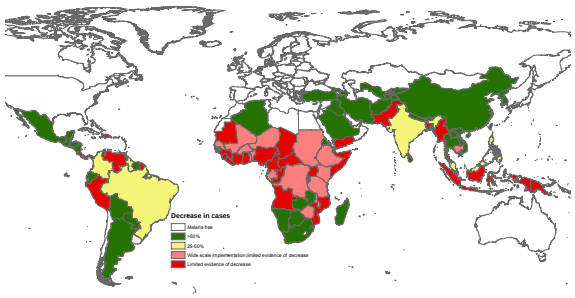
Reduction in malaria burden since 2000



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WHO committed to fulfill its mandate within a strong and diverse malaria community

A strong and diverse malaria community

The Roll Back Malaria partnership provides global advocacy as well as partner coordination mechanisms through the RBM Secretariat, Working Groups and the Global Malaria Action Plan (GMAP)

WHO committed to fulfill its 6 core functions

- Providing leadership on matters critical to health
- Shaping the research agenda
- Setting norms and standards, and promoting and monitoring their implementation
- Articulating ethical and evidence-based policy options
- Providing technical support, catalyzing change, and building sustainable institutional capacity
- Monitoring the health situation and assessing health trends

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Role of GMP within WHO

Malaria leadership at WHO HQ level	• GMP is WHO's disease-specific programme on malaria prevention, control, and elimination • GMP leads WHO efforts to support WHO Member States on all aspects of malaria control
Contact point for WHO regions and country offices	• GMP, together with the 6 WHO Regional Offices and 193 WHO Country Offices, provides a unique global footprint for malaria control efforts

GMP is responsible for coordination of WHO efforts on malaria prevention, control & elimination

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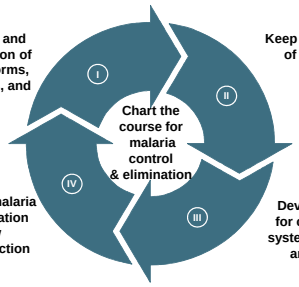
WHO Global Malaria Programme: four key roles

I. Set, communicate and promote the adoption of evidence-based norms, standards, policies, and guidelines

II. Keep independent score of global progress

III. Develop approaches for capacity-building, systems strengthening, and surveillance

IV. Identify threats to malaria control and elimination as well as new opportunities for action



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GMP deliverables
Role I: norms and standards

2011–2012

- Re-defined policy setting process (Malaria Policy Advisory Committee) (FIRST MEETING JAN 2012)
- Severe malaria practical handbook (Q2 2012)
- Severe malaria reference tool (Q2 2012)
- Global malaria surveillance guidelines (Q2 2012)
- Guidelines on implementing Intermittent Preventive Treatment in infants (IPTi) (LAUNCHED)
- Policy decision & guidance on Intermittent Preventive Treatment in children (IPTc) (Q1 2012)
- Updated tools to monitor drug efficacy and drug resistance (Q4 2011, and ongoing)
- Guidelines on implementing Community Case Management of malaria (Late 2012)
- Long Lasting Insecticidal Nets (LLIN) monitoring and procurement quality control methods
- Guidelines on methods for monitoring insecticide resistance (Q2 2012)

2013–2015

- Updated malaria treatment guidelines
- Updated guidelines on malaria diagnostics
- Guidance on parasite detection and surveillance in very low-transmission areas
- Guidance for universal vector control coverage (integrating a mix of delivery methods)
- Guidance for product stewardship and end-of-life management of LLINs
- Guidance on larval source control
- Updated field manual on malaria elimination for low and moderate endemic countries
- Guidance on malaria control in special populations and settings:
  - Migrants
  - Urban malaria
  - Cross-border transmission (Potentially 2012)

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GMP deliverables
Role II: keep independent score

2011–2012

2013–2015

- World Malaria Report (annually)
- Global Antimalarial Drug Resistance report (every 5 years)
- Annual malaria updates for international travelers
- Manage country malaria elimination certification

- Review of cost-effectiveness of malaria interventions (Q4 2011)
- On-line database to track progress in withdrawal of oral artemisinin monotherapies
- Topical reports on progress towards 2010 targets, e.g. elimination, malaria outside of Africa (Elimination Report LAUNCHED)
- Guidance on: (i) tracking malaria expenditures; (ii) cost analysis of malaria programs; and (iii) malaria country burden assessment (late 2012)
- Regional malaria reports
- Report on status of global supply of quality assured Artemisinin based Combination Therapies (ACTs) and artemisinin supply requirements (ongoing)
- Finalized guidance for Malaria Programme Review (potentially 2012)
- Special impact studies in highly endemic countries with poor health information systems to measure impact (ongoing)
- Comprehensive malaria program evaluations in selected countries combining surveys, routine data, and other sources

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GMP deliverables
Role III: develop approaches for capacity-building

2011–2012

- Good Procurement Practices for malaria Rapid Diagnostic Tests (RDTs) (LAUNCHED)
- Development of template, approach, and manual for District malaria program management (late 2012)
- Train the trainer manual on RDTs (mid 2012)
- Basic malaria microscopy training manual and image library (LAUNCHED)
- Malaria elimination training module (late 2012)
- Develop a template for producing regular National Malaria Bulletins (Q2 2011)

2013–2015

- Develop generic version of Indoor Residual Spraying (IRS) training manual
- Manuals for quality assurance of RDTs in peripheral health facilities and at community level
- Establish regional and national systems to accredit microscopy experts, develop reference slide banks and pool consultants on microscopy quality assurance (QA)
- Malaria stratification and integrated malaria control
- Analysis of human resource needs (by level and setting) for effective vector control

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GMP deliverables
Role IV: identify threats and opportunities

2011–2012

- Inter-agency operational manual on universal access to malaria diagnostics (LAUNCHED)
- Publish, launch and coordinate *Global Plan for Artemisinin Resistance Containment* (LAUNCHED)
- Launch Elimination Scenario Planning tool (Field Testing Q1 2012)
- Publish, launch and coordinate *Global Plan for Insecticide Resistance Management* (March 2012)
- Development of insecticide resistance database and production of Global report on insecticide resistance
- Publish 2nd edition of the *Handbook for Malaria Control in Complex Emergencies* (Q2 2012)

2013–2015

- Global Strategy for sustaining and advancing gains in malaria control, transmission reduction, and elimination from 2015-2025
- Update *Global Plan for Artemisinin Resistance Containment* (by 2015)
- Global strategy for *P. vivax* control and elimination
- Update existing technical guidance on prevention and control of malaria epidemics
- Policy recommendation on RTS,S malaria vaccine (with WHO-IVB)

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Recent GMP Products (1)

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Recent GMP Products (2)

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Recent GMP Products (3)

Malaria Policy Advisory Committee (MPAC) - background

- Setting policy, norms and guidance on malaria control is primary role of WHO/GMP
  - Malaria Expert Committee - 20th (last) meeting in 1998
  - Technical Expert Groups (TEGs) - since mid-2000s
  - Ad-hoc Technical Consultations as needed
- Scale up of malaria control + major investment in research = rapidly evolving policy environment for new tools and technology
- GMP strengthening policy setting process to be more:
  - Timely
  - Transparent
  - Accountable

MPAC: basic elements

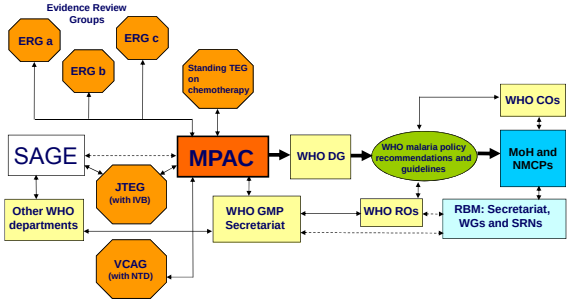
The Malaria Policy Advisory Committee (MPAC) will provide independent strategic advice and technical input to WHO for the development of policies related to malaria control and elimination

- 15 members, integrators, with **broad range** of
  - Expertise, professional affiliation, gender, geography
- To meet twice a year
- Open call for nominations
- Nominated by selection committee
- Appointed by WHO for three-year terms, renewable once
- Recommendations to be published within two months of meetings

MPAC: Chronology

- GMP Advisory Group on policy setting was convened in Geneva in March 2011
  - Review previous and existing WHO/GMP policy setting processes
  - Consider successful models from other WHO departments
  - Propose draft ToR for new policy setting body
- Selected model based on SAGE, to be called Malaria Policy Advisory Committee (MPAC)
- Draft ToR of MPAC sent to over 40 resource persons and stakeholders on 21 April; ~90% response rate
- Open call for nominations, September 2011: 100 applications received; 15 selected by independent nomination panel, and approved by WHO DG
- Inaugural meeting: 31 January – 2 February 2012

MPAC: organogram



Malaria control and elimination: GMP vision for 2011 – 2015

- The era of one-size-fits-all approach for malaria control is coming to an end as malaria transmission drops and new interventions are introduced
- Sustaining high intervention coverage may prove more difficult than initially achieving it
- Resistance to antimalarials and insecticides are major threats to continued success
- Malaria control paradigm is shifting, as countries move from lowering morbidity & mortality to reducing transmission
- Fundamental changes are happening (e.g. universal diagnostic testing) and are on the horizon (e.g. a malaria vaccine)
- Routine surveillance is critical to sustained control and eventual elimination
- *P. vivax* will become increasingly important as *P. falciparum* burden drops; *P. vivax* poses a more formidable elimination challenge

Major challenges ahead

- **Political commitment**
- **Financial resources**
- **Procurement and supply chain management**
- **Health system capacity**
- **Delivering quality case management in the private sector**
- **Human resource capacity**
- **Antimalarial drug resistance**
- **Insecticide resistance**
- **Inadequate surveillance and controversies over burden estimation**
- **Delivering results in highest burden countries**

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Challenge: Political commitment

- **Context**
  - Major shift towards non-communicable diseases
  - Sense that malaria has already made significant progress, so needs less support going forward
  - Fatigue (this is a long fight)
- **Potential solutions**
  - Consistent evidence-based policy setting (MPAC)
  - Careful and consistent documenting of impact
  - Link to wider health & development efforts
  - Resolutions from major organizations (e.g. UN, WHO)
  - Organizational support (e.g. ALMA)
- **Risks**
  - Advocacy sometimes out ahead of reality: a fine line

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Continued global political commitment

- Creation of African Leaders Malaria Alliance (ALMA), 2009
- United Nations General Assembly resolution on malaria: April 2011
- World Health Assembly (WHA) resolution on malaria: May 2011
  - Resolution text is in your packets
- Roll Back Malaria Partnership revised objectives, targets, and Priorities: June 2011

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Challenge: Financial

- **Context**
  - Despite increases in financing, well short of estimated 6 billion USD per year required
  - Concerning data to suggest that funds could decline by 2015
  - Global financial crisis and competing priorities with potential to worsen the situation
- **Potential solutions**
  - Increased efficiency and value for money
  - Increased domestic funding for malaria
  - Innovative financing mechanisms
  - See also: solutions for political commitment
- **Risks**
  - Worsening financial crisis; continued financial challenges at Global Fund

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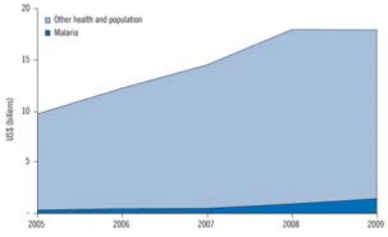
Official development assistance for malaria and other health and population activities



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

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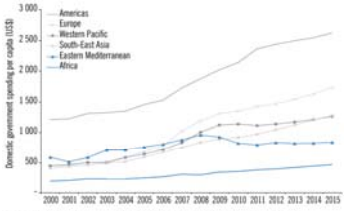
Median total domestic government spending in malaria-endemic countries by WHO Region



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

If 1% of total domestic spending were used for malaria control then would raise more than US$1.39 per capita in 75 out of 99 countries with ongoing malaria transmission – the cost to cover each person with ITN.

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Innovative financing

- **Financial transactions taxes:**
  - UNITAID raised US$ 210 million in 2010
  - Currently operates in 9 countries: could be extended
- **Tax on bonds and derivatives transactions (0.0001% - 0.2% per transaction)**
  - Could generate €265 billion across G20 countries
  - But some opposition and other uses have been proposed
- **Schemes potentially useful on smaller scale**
  - Tourist tax, cigarette taxes
  - Malaria bonds

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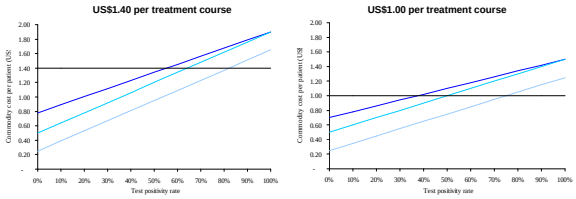
Savings on commodities: test and treat versus presumptive treatment



If ACTs cost US$1.40, commodity savings can be expected if test positivity rates are less than 60% (saving US$ 68 million in public sector per year)

If ACTs cost US$1.00, commodity savings can be expected if test positivity rates are less than 50%. (saving US$ 23 million in public sector per year)

RDT US$ 0.50 and 20% of negatives treated with ACT
RDT US$ 0.50 and 100% compliance with results
RDT US$ 0.25 and 100% compliance with results
Presumptive treatment

Source: WHO model

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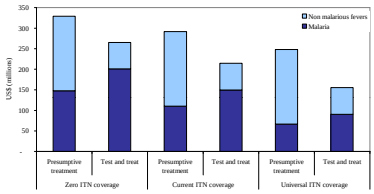
Impact of malaria control on treatment costs

Commodity cost of treating cases presumptively, or with a policy of test and treat, with different levels of ITN coverage



Source: WHO model with treatment cost US$ 1.40

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Challenge: Antimalarial drug resistance

- **Context**
  - Resistance to artemisinins has emerged in Mekong Region
  - Efforts at containment have reduced Pf burden, but not eliminated resistant parasites
  - Resistance to artemisinins now suspected in 4 countries
    - Unclear if spread or de novo emergence
- **Potential solutions**
  - Fully implement the *Global Plan for Artemisinin Resistance Containment*
- **Risks**
  - Loss of efficacy of partner drugs
  - Artemisinin resistance spreads to (or emerges in) Africa

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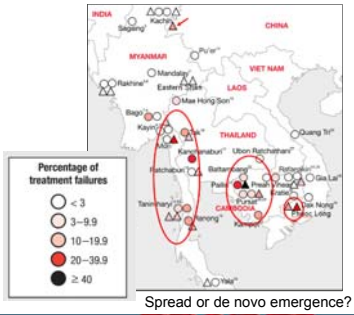
Percentage of positive cases on day 3 after ACT in Greater Mekong subregion



WHO 2010

from 2010 report
new data

Spread or de novo emergence? Sill not known…

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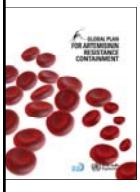
Global Plan for Artemisinin Resistance Containment (GPARC)



Contain or eliminate artemisinin resistance where it already exists
Prevent artemisinin resistance where it has not yet appeared

1. Stop the spread of resistant parasites
2. Increase monitoring & surveillance to evaluate the AR threat
3. Improve access to diagnostics & rational treatment with ACTs
4. Invest in artemisinin resistance-related research

5 Motivate action and mobilize resources

Development funded by Bill & Melinda Gates Foundation

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Challenge: Insecticide resistance

- **Context**
  - Current vector control efforts highly dependent on pyrethroids
  - Resistance to pyrethroids is widespread, particularly in Africa
  - Resistance to other insecticides also present in many settings
    - Not associated with widespread control failures to date
- **Potential solutions**
  - Fully implement the *Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM)*
    - Such a plan requested by World Health Assembly and the RBM Board
- **Risks**
  - Short term costs of IRM prevent timely action

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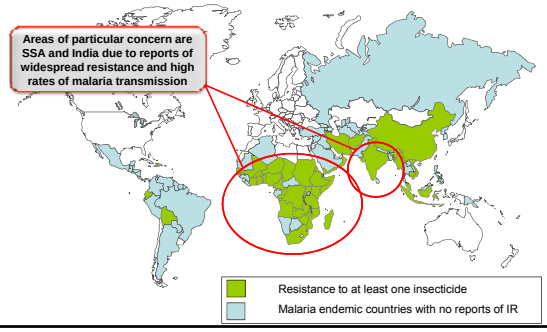
~40 endemic countries report insecticide resistance, most of them to at least pyrethroids

Countries reporting insecticide resistance in at least one of their main malaria vectors, as indicated by bioassays



Global Plan for Insecticide Resistance Management (GPIRM) in malaria vectors

- Global strategy to coordinate action against insecticide resistance and ensure continued effectiveness of current & future vector control tools on transmission, morbidity and mortality
- Currently being developed with input from >140 stakeholders
- Launch: March-April 2012
- End goal of GPIRM: Maintain effectiveness of malaria vector control in the long-term
- Near-term objective of GPIRM: Preserve susceptibility of major malaria vectors to pyrethroids and to other classes of insecticides at least until a range of new classes is made available for large-scale vector control

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GPIRM is being developed to coordinate action on the prevention and management of insecticide resistance

Objectives of GPIRM

1. **Define what is known, what is assumed and what remains unknown with regard to insecticide resistance among malaria vectors, its trajectory, its operational impact and options for managing the problem**
2. **Estimate the potential impact of insecticide resistance on malaria burden as well as the financial cost of monitoring and managing insecticide resistance**
3. **Using these elements as the foundation, define the plan for managing insecticide resistance and the way forward, including**
   - Short-term action plan with clear responsibilities
   - Ongoing research and development requirements

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GPIRM strategy: a window of opportunity to improve sustainability and impact of vector control

Short-term (~3 years) → **Medium-term (3-10 years)** → **Long-term (10+ years)**

Five pillars of strategy

I. Plan and implement IR management strategies in malaria endemic countries
II. Ensure proper & timely entomological and resistance monitoring and effective data management
III. Fill knowledge gaps on IR mechanisms and impact of current IRM approaches
IV. Develop new and innovative vector control tools
V. Ensure key enablers in place (advocacy, human and financial resources)

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Challenge: Delivering results in countries with highest malaria burden

- **Context**
  - Major progress in last decade, but progress lagging in highest burden countries
- **Potential solutions**
  - WHO-GMP and RBM Malaria Situation Room to track progress (intervention coverage and impact) in 10 countries in WHO African Region with highest burden
    - Proactively identify bottlenecks requiring resolution: political, financial, procurement and supply chain,
- **Risks**
  - Inadequate resources to fully scale up current interventions in countries with greatest burden

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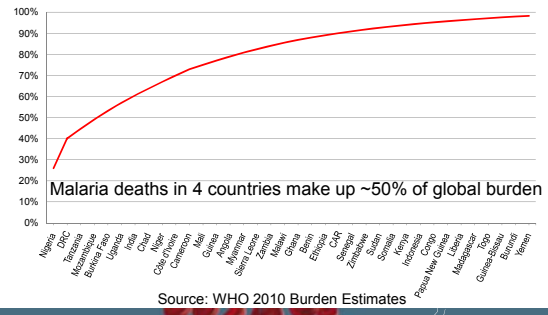
Need to increase our efforts in countries with the greatest malaria burden



Source: WHO 2010 Burden Estimates

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Major opportunities ahead

- **Malaria elimination**
- **New uses for existing tools. Example: Seasonal Malaria Chemoprevention**
- **New tools: malaria vaccine?**
- **Integrated community case management**
- **Improving efficiency and value for money. Example: a 5-year LLIN**
- **Stratification:**
  - Using data for decision making
  - Determining the optimal intervention mix for different epidemiological settings
- **Universal diagnostic testing, improved case management, and strengthened surveillance**

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Opportunity: Malaria Elimination

- **Context**
  - Many countries with strategic plans & en route to elimination
- **Actions needed**
  - Better document elimination successes through rigorous case studies (collaboration with Swiss TPH and Global Health Group at UCSF)
  - Develop more comprehensive guidance for accelerating progress from control to elimination
  - Provide realistic planning tools for countries
    - Elimination Scenario Planning (ESP) soon to be field-tested (collaboration with CHAI, GHG/UCSF, and Imperial College); launch in 2012
- **Risks**
  - Unrealistic expectations in some settings

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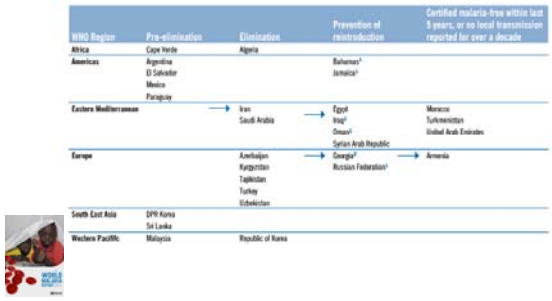
Elimination status of countries, 2011



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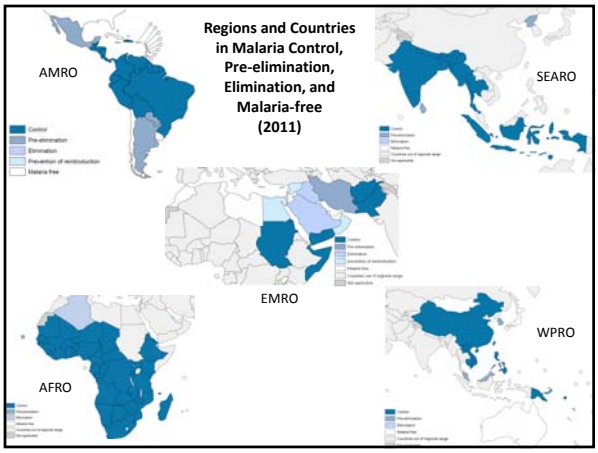

Opportunity: Malaria vaccine

- **One vaccine, RTS,S/AS01, in large Phase 3 trial**
- **11 sites in 7 sub-Saharan African countries; >15,000 children enrolled. Trial due to finish in Q4 2014.**
- **Target population: EPI co-administration in African infants**
- **First results published in NEJM October 2011: overall efficacy in 5-17 month group against clinical malaria was 55.8% again during 12 months of follow-up**

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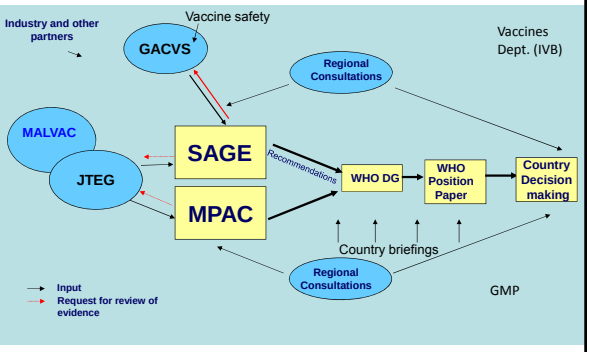
Joint Technical Expert Group (JTEG) on malaria vaccines

- Jointly convened by GMP and WHO Vaccine Department
- Terms of Reference: "Advise the secretariat of GMP and Vaccines Department on clinical trial data necessary and desirable for evaluation of public health impact of a malaria vaccine in malaria endemic countries"

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 (Biostatistician)
- Robert Johnson (Office Chief, NIAID Regulatory Affairs)
- Zulfiqar Bhutta (SAGE member, acts as liaison to SAGE)
- Graham Brown (MALVAC Chair)

Pathways for WHO Recommendations on Malaria Vaccine Use



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

Three JTEG meetings

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

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

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

Process for WHO policy recommendation regarding RTS,S

- MPAC will have key role on language related to other malaria control measures, and range of transmission settings for recommendation
- SAGE will have key role related to schedule for addition of RTS,S to routine EPI programmes, and ensuring satisfactory co-administration data
- Joint MPAC/SAGE session is foreseen at time of possible policy recommendation; ?early 2015

Opportunity: Value for money

- Context
  - Financial gap in malaria control unlikely to be closed through increased resources alone
- Actions needed
  - Thoroughly examine current malaria control efforts to identify opportunities for increased efficiency and better value-for-money
- Risks
  - Insufficient data to make well-informed decisions
  - Product development timeline may be too slow to produce near-term gains
  - Unintended consequences of new approaches

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

- **Multi-country analysis by A. Kilian et al found *average* 50% survivorship after 3 years**
- **Madagascar preliminary analysis of 3-year follow-up data:**
  - survivorship of 51% of polyester and 41% of polyethylene LLIN
  - residents report most holes caused by sparks from fire
- **Nigeria: AMP household surveys report high loss after 1 year**
- **Mentor Initiative: report high 3-year failure of 2 major current LLIN types in eastern Chad**

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Two 75 denier polyester nets, both 3 years old, in a durability study

(a) rate of physical deterioration is variable, and
(b) in such a study, some nets are kept which otherwise would have been discarded.
(Photos - Albert Kilian)

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Potential savings of a longer lasting ITN

	3 year net	5 year net	Saving
ITNs needed in Africa 2011-2020 (millions)	1,250	750	500
Financing required @ US$ 7.66 per ITN (US$ millions)	9,575	5,745	3,830

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Opportunity: Universal Diagnostic testing, improved case management and strengthened surveillance

- **Context**
  - In 20102, WHO recommended diagnostic testing in all suspected malaria cases prior to treatment
  - Uptake is happening, but treatment remains presumptive in many settings
  - Without diagnostic testing, malaria surveillance is weak: we are flying blind
- **Actions needed**
  - Launch of T3 Campaign: Test, Treat, Track
  - Launch of Malaria Surveillance Guidelines (April 2012)
  - Coordinated efforts to support endemic countries to implement T3
- **Risks**
  - Resistance to paradigm change
  - Weak health systems
  - Inadequate investments (especially in surveillance)

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T3 Test. Treat. Track.

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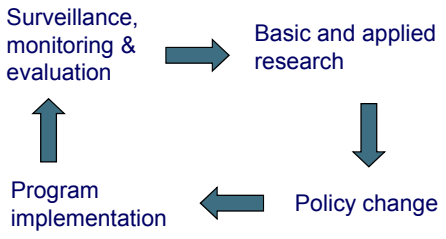
Fighting malaria - a continuous cycle requiring balanced investment



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Keep our eye on the prizes

- **First: near zero deaths from malaria**
  - In 2012, no one should die from malaria for lack of a 5 dollar bednet, a 50 cent diagnostic test, and a 1 dollar antimalarial treatment
- **Ultimately: a world free of malaria**

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Update on artemisinin resistance - September 2011

There is concern over the emergence and possible spread of *Plasmodium falciparum* resistance to artemisinins.[1] In January 2011, the *Global Plan for Artemisinin Resistance Containment* (GPARC) was released to outline the actions required to deal with the threat of artemisinin resistance. This note aims to: reiterate key points from the GPARC, provide background and updates on the current situation of artemisinin resistance in affected countries in the Mekong region, summarize current activities and recommend further action where needed.

Background

Routine monitoring

Routine monitoring of the therapeutic efficacy of artemisinin-based combination therapies (ACTs) is essential for timely changes to treatment policy and can help to detect early changes in *Plasmodium falciparum* sensitivity to artemisinins. WHO currently recommends a change in antimalarial treatment policy when the treatment **failure rate** of a 28- or 42-day follow-up study (depending on the medicine) exceeds 10%. The **proportion of patients who are parasitemic on day 3** is currently the best available indicator used in routine monitoring to measure *P. falciparum* sensitivity to artemisinins. If ≥10% of patients treated with an ACT are parasitemic on day 3, the area will be considered Tier I[2], and, consistent with recommendations in the GPARC, containment activities should begin immediately. Carefully controlled therapeutic efficacy studies using oral artesunate monotherapy should also be initiated to further confirm and investigate the presence artemisinin resistance in the area. Confirmation of artemisinin resistance should not delay containment activities.

Defining artemisinin resistance

The working definition of artemisinin resistance is based on clinical and parasitological outcomes observed during routine therapeutic efficacy studies of ACTs and clinical trials of artesunate monotherapy:

- an increase in parasite clearance time, as evidenced by ≥ 10% of cases with parasites detectable on day 3 after treatment with an ACT (suspected resistance)[3];

or

- treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for 7 days, or the presence of parasites at day 3 and recrudescence within 28/42 days (confirmed resistance).

[1] Artemisinin refers to artemisinin and its derivatives.
[2] WHO (2011). Global plan for artemisinin resistance containment. http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf
[3] Stepniewska K. et al. (2010). *Journal of Infectious Diseases*. 201(4):570-9.

The definition is likely to be adapted over time, for instance when molecular markers or better in vitro laboratory tests for artemisinin resistance become available. The current definition is also subject to potential confounding factors (i.e. splenectomy, haemoglobin abnormalities and reduced immunity), which can also delay parasite clearance.

The delayed response after a treatment with an ACT is of paramount concern to WHO. The unique ability of artemisinins to clear parasites rapidly is well known; it has been considered to be their 'pharmacodynamic hallmark'. Failure to rapidly clear parasites will compromise their use for the treatment of severe malaria and for treatment of uncomplicated falciparum malaria with ACTs. It causes more parasites to be exposed to the partner medicine alone, increasing the risk of resistance developing to the partner medicine. If resistance develops to the partner medicine, treatment failures are likely to increase. Most patients with delayed response are cured provided that the partner drug remains effective.

Global Plan for Artemisinin Resistance Containment (GPARC)[4]

The GPARC was established in response to confirmation of artemisinin-resistance in Cambodia and Thailand, and concerns that resistance could either spread or emerge spontaneously elsewhere. The primary objective of GPARC to protect ACTs as an effective treatment for *P. falciparum* malaria. The GPARC defined three areas of artemisinin resistance:

TIER I - areas for which there is credible evidence of artemisinin resistance, where an immediate, multifaceted response is recommended to contain or eliminate resistant parasites as quickly as possible;

TIER II - areas with significant inflows of mobile and migrant populations from tier I areas or shared borders with tier I areas, with intensified malaria control to reduce transmission and/or limit the risk of emergence or spread of resistant parasites;

TIER III - *P. falciparum* endemic areas which have no evidence of artemisinin resistance and have limited contact with tier I areas, where prevention and preparedness should focus on increasing coverage with parasitological diagnostic testing, quality-assured ACTs and vector control.

Countries should routinely monitor the therapeutic efficacy of their first- and second line-drugs in all the sentinel sites every two years, in order to promptly detect signs of emerging resistance and to keep their policy relevant. In addition to assessment of the 28- or 42-day cure rates, this should also include information on parasite clearance rate, measured as the proportion of patients still parasitemic 72 hours (3 days) after start of treatment. Based on the results countries should classify their region into one of the three tiers as listed above.

[4] WHO (2011). Global plan for artemisinin resistance containment.
http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf

Summary by country

Main source: Global report on antimalarial efficacy and drug resistance: 2000-2010

Cambodia

Background

- Between 2001 and 2007, the proportion of patients parasitemic on day 3 after treatment with either artemether-lumefantrine or artesunate-mefloquine exceeded 10% in western part of Cambodia, including Pailin, Battambang, and Kampot provinces;
- A research study conducted in 2006 in Tasanh (Battambang province) confirmed two cases of treatment failure after 7 days of artesunate treatment with delayed parasite clearance time and adequate plasma concentration of artesunate and dihydroartemisinin;
- These two findings led to additional studies with artesunate monotherapy (7 days) which were conducted in Pailin (Pailin province) and Tasanh (Battambang province) between 2007 and 2008 and which confirmed delayed parasite clearance in more than 40% of the patients and the emergence of artemisinin resistance;
- In response, a containment project was started in 2008 in zone 1 (tier I) including Pailin, Battambang, Pursat and Kampot provinces;
- First-line treatment was changed from co-blistered artesunate-mefloquine to fixed-dose dihydroartemisinin-piperaquine in tier I;
- The efficacy of artesunate-mefloquine, the first-line treatment in eastern Cambodia remained high (> 95%).

Update[5]

- After the implementation of the containment project, the number of falciparum malaria patients has been reduced significantly, but in the presence of continued artemisinin drug pressure, the proportion of patients parasitemic on day 3 after treatment with dihydroartemisinin-piperaquine increased from 26% to 45% between 2008 and 2010;
- An increasing trend of treatment failures with dihydroartemisinin-piperaquine was reported in Pailin during the same period (from 8.1 to 27.6%), although these numbers are based on a small number of treated patients in 2010;
- In addition, increased proportions of treatment failures (10.7%) with the same drug combination were reported in 2010 in Pursat province, south of Pailin province;
- Monitoring of dihydroartemisinin-piperaquine efficacy throughout Cambodia shows that this ACT remains highly effective in the other parts of the country and is also highly effective against vivax malaria nation wide.

[5] The information included in the Update paragraphs are data that are new and not included in the Global report on antimalarial efficacy and drug resistance: 2000-2010 (WHO, 2010).
http://www.who.int/malaria/publications/atoz/9789241500470/en/index.html

Interpretation of the data

- The increase in the proportion of patients parasitemic on day 3, may be a result of the containment efforts: as the number of falciparum malaria cases decreases, the more resistant parasites will have a higher likelihood of survival, resulting in selection of the resistant parasites;
- The high treatment failures observed with dihydroartemisinin-piperaquine in Pailin and Pursat are worrying and could be related to an emergence of piperaquine resistance, a drug which is related to chloroquine.

Way forward

- Because of the very limited alternative treatment options, *P. falciparum* resistance against piperaquine has far reaching consequences and needs urgent confirmation with inclusion of drug levels in vitro sensitivity testing and eventually molecular markers. If resistance to piperaquine is confirmed, this could seriously compromise the containment efforts. Alternative treatment options include:
    - Pyramax (artesunate-pyronaridine), which has been registered by the Korean FDA and has been submitted to the European Medicines Agency (EMA) for an opinion;
    - Quinine-doxycycline for 7 days. Disadvantage of this regimen is poor tolerability resulting in poor compliance and therefore difficult implementation;
    - Atovaquone-proguanil (which is prone to quick development of resistance);
- A consensus meeting is urgently needed to decide on optimal treatment scenarios for western Cambodia;
- Cambodia was successful in the application of its Global Funds for Aids, Tuberculosis and Malaria (GFATM) round 9 focusing on containment of artemisinin resistance. With this grant, activities started under the Bill & Melinda Gates Foundation (BMGF) funded project will be continued.

Laos

Background

- No cases of delayed parasite responses to artemether-lumefantrine (the first line treatment in Laos) were reported in Laos during routine monitoring between 2002-2007 and this ACT remained highly efficacious.

Update

- In 2011, a trial conducted in Savannakhet province confirmed that all patients were cleared of parasites within 48 hours after treatment with artesunate.

Myanmar

Background

- In 2009, preliminary data suggested delayed parasite clearance in Kawthaung Township (Tanintharyi Region in south-eastern Myanmar bordering Thailand) with 8%

of patients still parasitemic on day 3 following treatment with artesunate-lumefantrine and 18% following treatment with dihydroartemisinin-piperaquine;
- The overall 28-day treatment failure rates from all studies conducted between 2007-2010 were below 10%;

Update
- A 7-day artesunate monotherapy study has been conducted in Kawthaung in 2011 confirming a high rate of patients (27%) still parasitemic at day 3. Only one patient presented with a late treatment failure during the 28-day follow-up. Pharmacokinetics and molecular studies are on-going.
- During routine monitoring conducted in 2010 in sentinel sites, the study in Mon State (south-eastern Myanmar bordering Thailand) showed that 28% of patients still carried parasites at day 3 following treatment with dihydroartemisinin-piperaquine. These data are currently being validated;
- Other studies performed in 2011 in northern and western parts of Myanmar show that <3% of patients remain parasitemic on day 3 and all studies show low treatment failure rates <10% after 28-days of follow-up, including the above mentioned study in Mon State;
- The results showing delayed parasite clearance rates in several parts of the country led to the initiation of a Myanmar Artemisinin Resistance Containment (MARC) plan, based on the action points designed for tier I and tier II areas described in the GPARC. This containment project is planned to start in September 2011, funded by the donor consortium 'Three Diseases Fund'. Funding for the project has been granted till June 2012;
- Myanmar will apply for a GFATM Round 11 grant which could fund the containment project in south-eastern Myanmar.

Interpretation of the data
- Available data consistently show delayed parasite clearance times suggesting emergence of artemisinin resistance in south-eastern Myanmar;
- the three first-line ACTs used in the country (artesunate-mefloquine, artemether-lumefantrine and dihydroartemisinin-piperaquine) are still effective as treatment for uncomplicated falciparum malaria.

Way forward
- Funding for containment is currently only available until June 2012. If the application for GFATM round 11 is successful, there is still the threat of a funding gap of one year from July 2012-June 2013. Additional funding will be needed to bridge this gap.

Thailand

Background
- Until 2008, Thailand used a regimen of 2-day artesunate-mefloquine as first-line treatment. As a consequence, results of routine monitoring of the 2-day first-line ACT used in sentinel sites are difficult to compare with day 3 positivity rate from data compiled in neighbouring countries. Nevertheless it is noticeable that in Trat province bordering Cambodia, the mean parasite clearance time increased from 2 to 3.7 days between 2003-2007;

- Containment activities at the Thailand side of the border between Cambodia and Thailand were started simultaneously with Cambodia in 2008;
- The proportion of patients positive at day 3 in sentinel sites along the border between Thailand and Myanmar ranged between 0-20%, with foci in Ranong, Tak and Kanchanaburi showing proportions >10%. Therefore, the presence of parasites resistant to artemisinin is also highly suspected at the border between Thailand and Myanmar.

Update

- Despite the change to a 3-day regimen, treatment failures with artesunate-mefloquine increased in Tak and Ranong provinces. In Tak, the efficacy after 42-day follow-up decreased slightly from 96.8% in 2008 to 90.4% and 91.2% in 2009 and 2010, respectively. Similarly, the efficacy in Ranong decreased from 96.8% in 2008 to 87.5% and 90.9% in 2009 and 2010, respectively.

Interpretation of data

- Higher treatment failures observed in Thailand with artesunate-mefloquine could be explained by the presence of mefloquine resistance (which has been confirmed countrywide) on top of reduced artesunate susceptibility. Drug pressure with mefloquine has been considerable over the last decades, since Thailand has been using different regimens of mefloquine (15 to 25 mg/kg) as monotherapy or in combination with artesunate .

Way forward

- The first line treatment for Thailand is currently using a loose combination of artesunate and mefloquine. Consensus is urgently needed on optimal treatment scenarios for Thailand. Possibilities include dihydroartemisinin-piperaquine or fixed dose combination artesunate-mefloquine.
- Thailand was successful in the application of its GFATM round 10 focusing on containment of artemsinin resistance countrywide. With this grant, activities started under the BMGF project will be continued at the border between Thailand and Cambodia and will be started at the border between Thailand and Myanmar.

Viet Nam

Background

- In Bu Dang district of Binh Phuoc province, the proportion of patients still parasite positive at day 3 after artesunate monotherapy or dihydroartemisinin-piperaquine was reported to be 15% and 18% in 2009 and 2010 respectively (National Institute of Malaria, Parasitology and Entomology).
- Routine monitoring has not detected any other foci of reduced susceptibility to artemisinins in the rest of the country.

Update

- In 2011, another research team in Phuoc Long district located in the same province of Binh Phuoc reported similar high proportions (22-28%) of patients still parasite positive at day 3 after artesunate monotherapy or dihydroartemisinin-piperaquine.

- More detailed analysis of these studies performed in 2011, including studies on pharmacokinetics and molecular markers, is currently under way to obtain more accurate assessment of the presence of artemisinin resistance.

Way forward

- In mid 2011, Viet Nam begun containment activities based on the GPARC document with the support from WHO Western Pacific Regional Office and country office;
- A limited amount of funding has been provided by WHO HQ (200,000 $US over 2 years);
- Viet Nam is currently applying for a GFATM round 11 grant which could fund containment activities.

Research needed to refine the definition of artemisinin resistance

- Most research groups find that standard in vitro tests assessing artemisinin sensitivity do not correlate well to measures of parasite clearance in patients, including day 3 positivity rates. A modified test screening the activity of artemisinin on ring stage parasites is under development;
- The measurement of artemisinin concentrations in whole blood or within the parasitized erythrocyte (where the drug action takes place), might be more relevant than the assessment of plasma concentrations with respect to the observed differences in parasite clearance. New methodologies measuring the concentration in whole blood are being validated to allow a better analysis of the clinical results;
- In western Cambodia, it has been shown that prolonged parasite clearance time is to a large extent explained by a heritable trait of the parasite. However, the genes responsible for artemisinin resistance are still unknown. Molecular studies looking at mutations across the whole parasite genome are on-going and have thus far shown that the genetic basis of artemisinin resistance is likely multigenic, linked to clusters of significant SNPs on multiple chromosomes.
- An in vivo parasitological marker less prone to variation than the proportion of cases parasite positive at day 3 is the parasite clearance rate, which is the slope of the log-linear parasite clearance curve and is independent on the initial parasitaemia. An on-line version converting parasite clearance data into a clearance rate or ‘parasite half life’ is currently developed and provides a uniform method to describe the delayed clearance phenotype and its relation to resistance.

Conclusion

Despite the delayed response to artemisinin in some areas of the Greater Mekong subregion, ACTs remain the most effective treatment for uncomplicated falciparum malaria; most patients with delayed response are cured if the partner drug remains effective. Nevertheless, WHO is concerned with the growing evidence of resistance, as defined by delayed parasite clearance times, in south-eastern Myanmar and western Thailand and in Binh Phuoc province in Viet Nam. It is not known if these new foci represent spread or de novo emergence of artemisinin resistance. In response to the

new data, containment projects are planned in western Thailand, south-eastern Myanmar and Viet Nam that will draw lessons learned from the containment project in Cambodia and Thailand, as well as the GPARC. Additional funding will be needed to ensure that the containment projects initiated can be sustained. Furthermore, as artemisinin resistance is prevalent in border areas and migration is known to be a contributing factor in the spread of resistance, there is a need to increase cross-border coordination between national projects and programmes.

Routine monitoring must be continued to ensure that the recommended first line treatments are effective and that timely changes in treatment policies can be made, and to detect the emergence of artemsinin resistance. Many aspects of artemisinin resistance are still not well understood. Consequently, there is an urgent need for further research to refine our knowledge of artemisinin resistance, including the identification of molecular markers and better in vitro sensitivity tests .

For more information, please contact:
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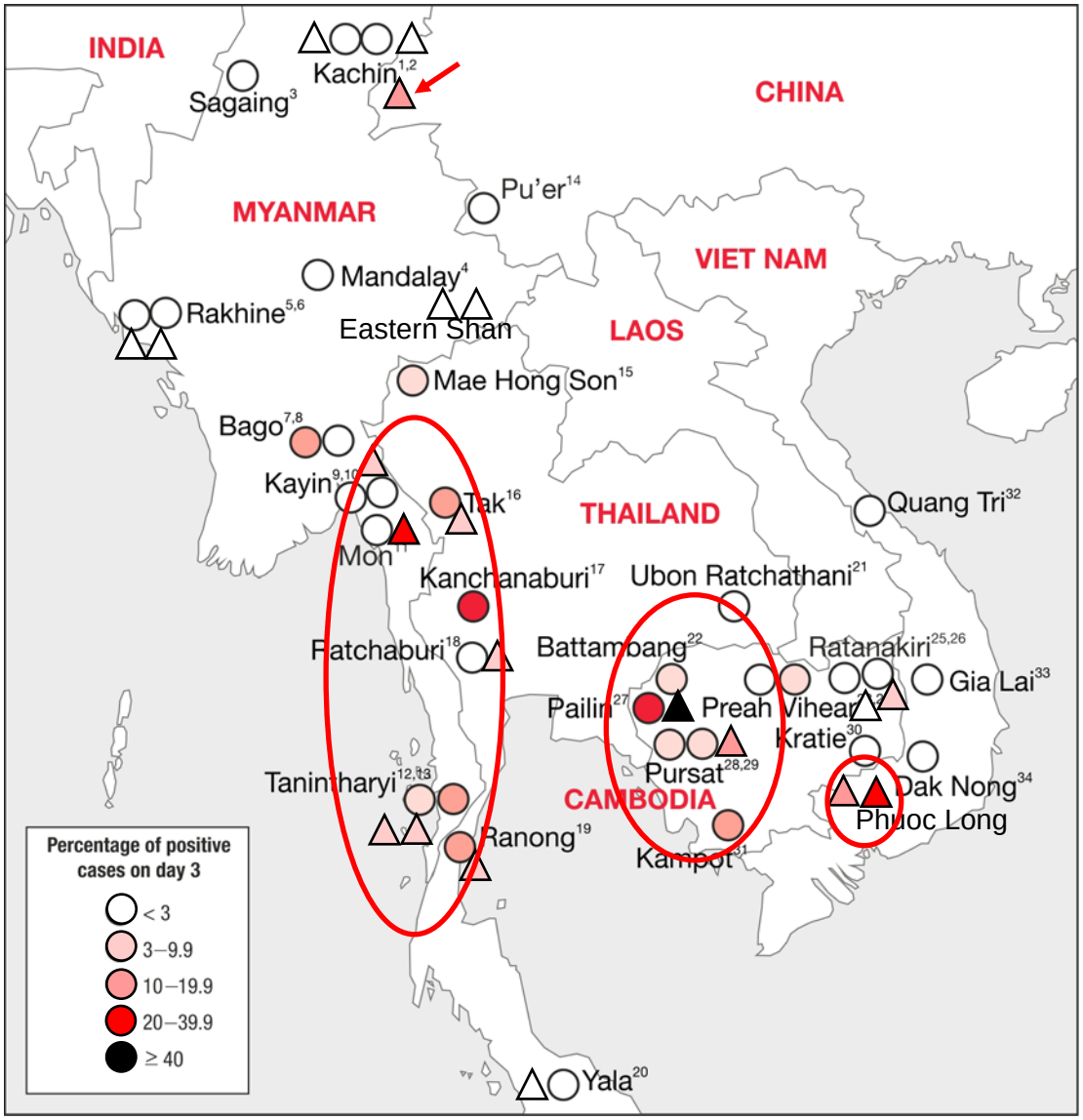
Figure. Percentage of positive cases on day 3 after ACT



Circles represent data before November 2010 and triangles data after November 2010.

Malaria Policy Advisory Committee

Technical Expert Group on Antimalarial Drug Resistance and Containment

Terms of Reference

I. Background and rationale

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

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

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

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

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

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

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

III. Membership and structure of the TEG

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

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

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

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

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

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

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

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

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

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

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

IV. Responsibilities of TEG members

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

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

V. Structure

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

VI. Working Procedures

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

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

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

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

VII. Dissolution of TEG

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

ANNEX 1

DECLARATION OF INTERESTS FOR WHO EXPERTS

WHO's work on global health issues requires the assistance of external experts who **may have interests related to their expertise.** To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a **potential conflict of interest** (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interest (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department).

Please complete this form and submit it to WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g, nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be **disclosed** to the other participants at the start of the activity and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage any declared interests will be **published** in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

Name: Institution: Email:

Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organizer of the activity):

_____

_____

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a Employment — Yes ☐ No ☐

1b Consulting, including service as a technical or other advisor — Yes ☐ No ☐

RESEARCH SUPPORT

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?

2a Research support, including grants, collaborations, sponsorships, and other funding — Yes ☐ No ☐

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) — Yes ☐ No ☐

Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work?

INVESTMENT INTERESTS

Do you have current investments (valued at more than US $10 000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

3a Stocks, bonds, stock options, other securities (e.g., short sales) — Yes ☐ No ☐

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) — Yes ☐ No ☐

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (including pending applications) — Yes ☐ No ☐

4b Proprietary know-how in a substance, technology or process — Yes ☐ No ☐

PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization? — Yes ☐ No ☐

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? — Yes ☐ No ☐

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? — Yes ☐ No ☐

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? — Yes ☐ No ☐

6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work? — Yes ☐ No ☐

6d Have your received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work? Yes ☐ No ☐

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes ☐ No ☐

7. **TOBACCO OR TOBACCO PRODUCTS** *(answer without regard to relevance to the subject of the meeting or work)*
Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity? Yes ☐ No ☐

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is **"yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.**

Nos. 1 - 4: Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) and basic descriptive details.	**Name of company, organization, or institution**	**Belongs to you, a family member, employer, research unit or other?**	**Amount of income or value of interest (if not disclosed, is assumed to be significant)**	**Current interest (or year ceased)**
Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details				

CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of WHO and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date: _____
Signature_____

ANNEX 2

CONFIDENTIALITY UNDERTAKING

1. The World Health Organization (WHO), acting through its Department of ……., has access to certain information relating to ……., which information WHO considers to be proprietary to itself or to other parties collaborating with it (hereinafter referred to as "the Information").

2. The Undersigned, as a member of the …….Committee ("the Committee"), may have access to the Information in the course of his/her participation in the Committee (whether at or in relation to Committee meetings, internet-based collaborative workspaces, telephone conferences or otherwise).

3. WHO is willing to provide the Undersigned the Information, or arrange for the provision of the Information to the Undersigned, for the purpose of performing his/her responsibilities in connection with the activities of the Committee ("the Purpose"), provided that the Undersigned undertakes to treat the Information as confidential and proprietary, and to disclose it only to persons who have a need to know for the purpose and are bound by like obligations of confidentiality and non-use as are contained in this Undertaking.

4. The Undersigned undertakes to regard the Information as confidential and proprietary to WHO or parties collaborating with WHO and agrees to take all reasonable measures to ensure that the Information is not used, disclosed or copied, in whole or in part, other than as provided in this Undertaking, except that the Undersigned shall not be bound by any such obligations if and to the extent he/she is clearly able to demonstrate that the Information:

   a) was known to him/her prior to any disclosure by or for WHO to the Undersigned; or
   b) was in the public domain at the time of disclosure by or for WHO to the Undersigned; or
   c) becomes part of the public domain through no fault of the Undersigned; or
   d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality.

5. The Undersigned also undertakes not to communicate the deliberations and decisions of the Committee to persons outside this Committee except as agreed by WHO.

6. If requested to do so, the Undersigned agrees to return to WHO any and all copies of the Information.

7. The Undersigned furthermore agrees that any and all rights in the work performed by him/her in connection with or as a result of his/her membership of the Committee shall be exclusively vested in WHO. The Undersigned hereby irrevocably and unconditionally assigns all such rights to WHO and waives any moral rights attached such work.
   The Undersigned understands and agrees that WHO reserves the right (a) to revise such work, (b) to use it in a different way from that originally envisaged, or (c) not use or publish it at all.

8. The obligations of the Undersigned shall survive the termination of his/her Membership of the Committee.

9. Any dispute relating to the interpretation or application of this Undertaking shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The parties shall accept the arbitral award as final.

Name:

Signature:
Date:

WHO selection criteria for procuring malaria RDTs

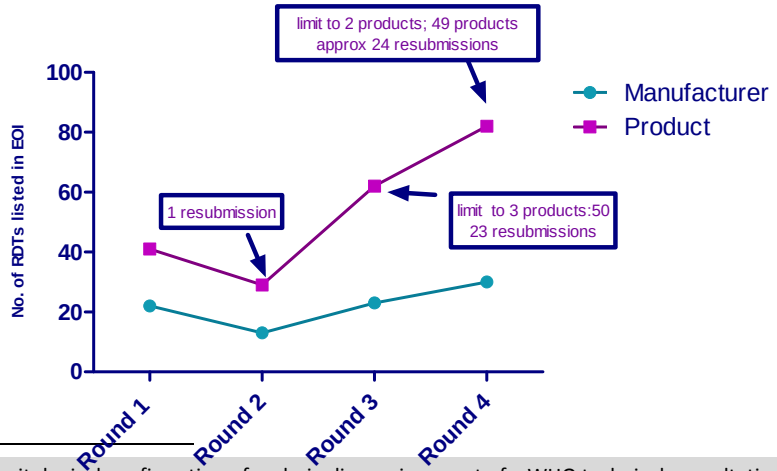
Working paper for discussion by the Malaria Policy Advisory Committee

WHO/GMP formulated the first recommendations on criteria for selection of malaria RDTs in 2010, based on the advice received by independent experts convened at a WHO Technical Consultation held in October ,2009[1]. The data on comparative rapid diagnostic test (RDT) performance is based on the results of WHO Malaria RDT Product Testing Programme, a joint project of TDR, Foundation for Innovative New Diagnostics (FIND), US Centers for Disease Control and Prevention and WHO/GMP, involving collaboration with a number of research institutions and control programmes in malaria endemic and non-endemic countries [2]. The WHO/GMP recommended selection criteria for procurement malaria RDTs form the basis for WHO RDT procurement practices, and are shared as an information note on the WHO/GMP website[3] for use by WHO Member States and interested agencies.

WHO malaria rapid diagnostic test (RDT) performance evaluation

WHO currently runs an evaluation programme for malaria RDTs on which current WHO procurement recommendations and those of other agencies are based. This programme includes (1) the largest WHO-coordinated product testing programme for a health commodity, which recently completed its third round of testing, having evaluated and published detailed comparative data on 120 products since 2009, and (2) a lot-testing programme that has evaluated over 700 lots of malaria RDTs since 2008 and provides batch testing to country programmes on request prior to deployment and use in the field.

Figure 1: Response to WHO Malaria RDT Product Testing Expression of Interest: Rounds 1-4



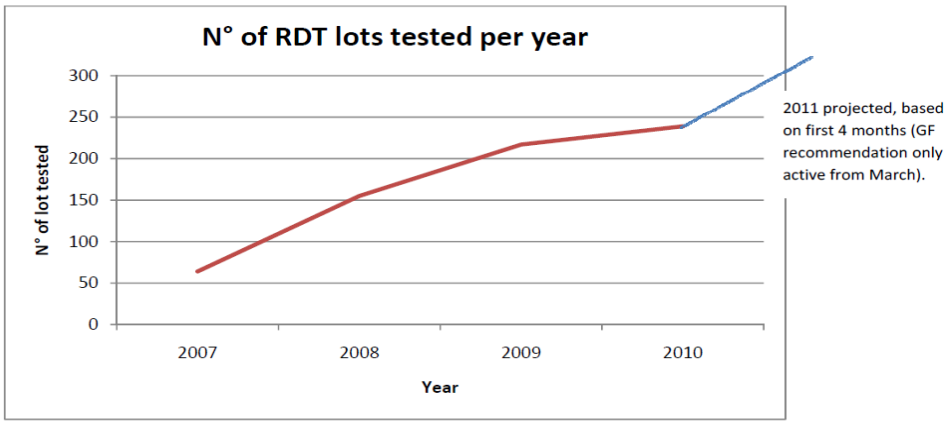
[1] WHO 2010 – Parasitological confirmation of malaria diagnosis: report of a WHO technical consultation, 6–8 October 2009 http://whqlibdoc.who.int/publications/2010/9789241599412_eng.pdf

[2] WHO product testing of malaria RDTs: Round 3 (2010-2011). http://apps.who.int/tdr/publications/tdr-research-publications/rdt_round3/pdf/rdt3.pdf

[3] WHO information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs) http://www.who.int/malaria/diagnosis_treatment/diagnosis/RDT_selection_criteria.pdf

Since 2010, lot-testing at a WHO-FIND quality assessed laboratory is mandatory for all procurement through the US President's Malaria Initiative (PMI), and is required by the Global Fund. In the first 3 quarters of 2011 300 lots were evaluated and capacity can easily be expanded. Currently WHO and FIND do not charge fees to manufacturers, programmes or Agencies submitting their product for evaluation through either of these programmes.

Figure 2: Lot testing trends 2007-2010



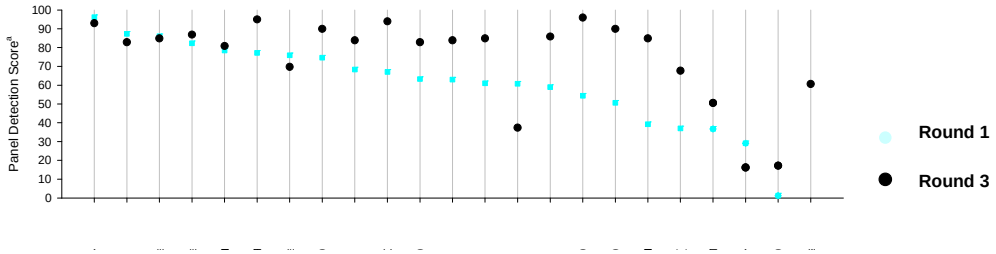
The same programme currently provides reference parasite panels for research and development to manufacturers, and is developing recombinant antigen-based panels to form the next generation of reference materials for malaria RDT evaluations that will allow for product testing at much lower costs as well as standardized country-based lot-testing.

Immuno-chromatographic tests are multi-component biological tests in which the performance may be significantly affected by a large number of variables, which can result in lot-to-lot variation. The current WHO product testing programme is producing detailed comparative performance data on a high number of products (120 have been assessed, including 23 products assessed in Round 3 that had been previously assessed in Round 1).

Figure 3: Improvement in RDT performance: Results of re-submitted products: Round 1 (2009) and Round 3 (2011)

Figure 1: Improvement in RDT Performance: Results of resubmitted RDTs: Round 1(2009) and Round 3 (2011)

Malaria RDT performance against wild-type (clinical) samples containing *P. falciparum* at low (200) and high (2000 or 5000) parasite densities (parasites/µl) and clean-negative samples - retested products



The lot-testing programme is conducting batch testing prior to release to the field, to ensure performance at release irrespective of manufacturing conditions. Both programs have a clear impact on the quality of RDTs being procured for public sector use: recent FIND market survey data indicates that in 2010, 78% (~78 million) of RDTs manufactured met the most stringent WHO procurement criteria[4], compared with just 23% (~ 6 million) in 2007. In parallel to these trends, the frequency of lot testing failures has progressively declined over the years. In 2010, batches had a 100% pass rate; only one failure was seen during the first half of 2011, indicating that manufacturers are maintaining quality, at least when they are aware the lots will be evaluated.

WHO recommended selection criteria for procurement [5]

In October 2009 WHO convened a technical consultation to review the evidence base for thresholds of diagnostic performance required by current malaria diagnostic tests and to make recommendations on their use. The consultation reviewed the clinical significance of parasite densities in patients with uncomplicated *P. falciparum* and *P. vivax* malaria, the risks of missing low parasite densities with routine field microscopy and most RDTs on the market, the implications of results of the product testing programme for malaria RDTs to provide advice to procurement agencies.

The Consultation reviewed factors affecting the frequency of low-density infections, including host immunity, parasite factors, stage of illness and effectiveness of treatment, and focussed on the frequency of parasite densities < 200/µL in patients seeking treatment in health facilities and its relation with transmission intensity and parasite species.

In high-transmission areas, only about 5% of patients with *P. falciparum* malaria have parasite densities < 200/µL. In low-to-moderate transmission areas, 5–10% of patients with *P. falciparum* malaria have parasite densities < 200/µL. Patients with *P. vivax* malaria present with parasite densities < 200 per microliter more commonly than those with *P. falciparum* malaria (~15%). The frequency of low parasite densities (< 200/µL) is higher in population and household surveys than among symptomatic patients who present to health facilities for treatment.

Based on these considerations and the review of results product testing and lot testing of tests on the market, the participants in the 2009 consultation recommended the following selection criteria for RDT procurement:

A. The *P. falciparum* panel detection score[6] for high transmission areas[7] should be at least 50% at 200 parasites/µL. Since the extent of high transmission areas is likely to decrease with effective malaria control, a panel detection score well above this level should become the basis for product selection in the future years.

[4] WHO Malaria RDT Product Testing: Panel detection score ≥75% for panels of *P. falciparum* and/or *P. vivax* at 200 parasites/µL

[5] See ANNEX 1 for a brief discussion on current status of WHO system for prequalification of malaria RDTs

[6] The term 'panel detection score' (PDS) is a composite index of test positivity as well as of inter-test and inter-lot consistency and is not a measure of clinical sensitivity.

[7] 'High transmission' areas are hyperendemic and holo-endemic areas in which the prevalence rate of malaria is over 50% during most time of the year among children from 2 to 9 years old. In these areas by late infancy or early childhood practically all individuals are infected.

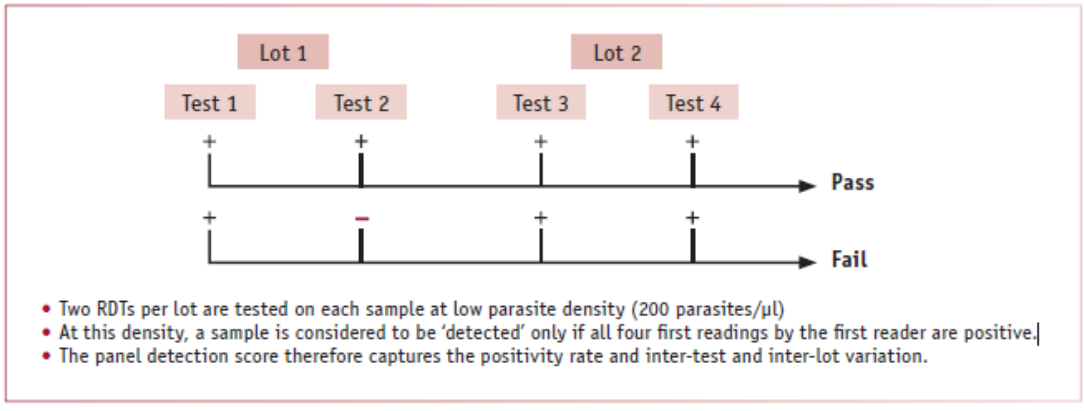
B. The *P. falciparum* panel detection score for low[8] and moderate[9] transmission areas should be well above 50% at 200 parasites/µL (e.g. ≥75%).
C. The *P. vivax* panel detection score for low and moderate transmission areas should be equivalent to those for *P. falciparum* - well above 50% at 200 parasites/µL (e.g. ≥ 75%).
D. In all areas false positive rate should be less than 10%.
E. In all areas invalid rate should be less than 5%.

Based on the above criteria out of the 95 unique[10] RDTs assessed in Rounds 1-3, a total of 24 Pf-only RDTs meet the above criteria for use in high transmission areas, and 21 Pf-only RDTs, 13 combination RDTs, 2 pan RDTs and 1 Pv-only RDT meet the criteria for areas with low or moderate transmission.

Calculation of the Panel Detection Score

The panel detection score ('detection rate' in the WHO/FIND round 1 evaluation) is a number between 0 and 100, calculated as the proportion of times a malaria RDT gives a 'pass' result in all tests on both lots tested in multiple samples of parasite panels of wild type parasites at a specific parasite density, i.e. four tests at 200 parasites/ µL and two at 2000 parasites/ µL. In each round, the panel detection score at low parasite densities was calculated against panels derived from 79-100 samples of *P. falciparum* and 20-40 samples of *P. vivax*. Invalid tests are excluded from the analysis. In the calculation of the score for low parasite densities, all four tests (two each from two different production lots) should be positive in order for the test to 'pass'. In the example shown in the figure, the test 'fails' to detect parasite in a given sample if three of four tests are positive.

Figure 4 **:** Determination of WHO Product Testing panel detection score at low parasite density (200 parasites/ µL)



[8] 'Low transmission' areas are hypo-endemic areas in which the prevalence rate of malaria is 10% or less during most time of the year among children from 2 to 9 years old. Here a person may attain adolescence before malaria infection is acquired and may escape acquiring a malaria infection altogether.
[9] 'Moderate transmission' areas are meso-endemic areas in which the prevalence rate of malaria is 11-50% during most time of the year among children from 2 to 9 years old. Here the maximum prevalence of malaria infection occurs in childhood and adolescence, though still not unusual for adult life to be attained before acquiring infection.
[10] This excludes 2 products that did not pass Phase 1 and 23 products resubmitted under the same product codes

The panel detection score is different from the sensitivity or positivity rate, as it includes a measurement of intra-lot consistency and inter-lot variation. Thus, a PDS of 80% at a parasite density of 200/µL is a good result and does not correspond to a sensitivity of 80% observed in the field. The largest difference in test performance that allows differentiation of RDTs that perform well and those that perform poorly is reflected in the panel detection score at the lower parasite density (200 parasites/µL).

Relation between Panel Detection Score and Sensitivity

The diagnostic performance of malaria RDTs, as measured from the panel detection score may not be directly related to the sensitivity of the test in clinical testing. More specifically, in product testing parasitized blood samples from patients are diluted to ensure they consistently have the same parasite density (and range of antigen concentrations); however in the field, samples of parasitized blood from patients are much more likely to have heterogeneous parasite densities -- generally with parasitaemias higher than 200 parasites/µL.

The performance of malaria RDTs can also be assessed from their diagnostic sensitivity and specificity in target populations, as reported in the scientific literature. However, the quality of studies is variable, and the reported parameters depend closely on samples selected for the study, RDT quality and storage conditions, the user's skill in preparing and interpreting test results and the quality of the microscopy used as reference standard. A Cochrane review of *P. falciparum* RDT field performance has recently been published[11].

The series of factors which may affect performance testing in a laboratory setting compared to field trials and may explain discrepancies in performance (panel detection score) in WHO RDT Product Testing and (populations based) sensitivity are listed in the table below.

[11] Abba K, Deeks JJ, Olliaro PL, Naing CM, Jackson SM, Takwoingi Y, Donegan S, Garner P. Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.:CD008122. DOI: 10.1002/14651858.CD008122.pub2.

Table 1 **:** Reasons for discrepancy between panel detection score and clinical sensitivity

Factor	Effect
Exposure to extreme temperatures	High temperatures accelerate degradation (deconjugation of the signal antibody–dye complex, detachment of capture antibody from the wick, and change the binding sites of antibodies and the nitrocellulose).
	Freeze-thawing may have similar effects.
Age and storage of blood sample	Stored blood may lose antigen activity; early lysis and protein coagulation can inhibit flow.
	The rate of loss of antigen activity varies among antigens.
	Lysis of cells can occur during mixing and storage.
Preparation of dilutions	Cell lysis and aggregation of parasitized cells can affect flow.
Visual acuity of technician	Can affect reading of faint test lines at low parasite density.
Patient and parasite	Parasite density affects sensitivity.
	Parasite density and parasite load (including sequestered parasites) determine antigen levels.
	Antigen production varies during the parasite life cycle and between parasite strains.
	Previous treatment and its effectiveness varies among patients.
	Factors that cause false-positive results can vary among patients.
	Antigen activity may be different in wild and cultured parasites.
Reference standard (microscopy or PCR)	Poor sensitivity reduces apparent RDT specificity.
	Poor specificity reduces apparent RDT sensitivity.

Small differences in panel detection scores among the better-performing RDTs in an evaluation are unlikely to result in noticeable differences in clinical sensitivity. On the other hand, the panel detection score at 200 parasites/µL provides an indication of which products are likely to be more sensitive in the field, particularly in populations with low-density infections.

Re-visiting WHO procurement criteria for malaria RDTs

The WHO recommendations set in 2009 on selection criteria for procurement of malaria RDTs have been considered by some stakeholders (e.g. procurement and funding agencies) as setting the bar too low, particularly the recommended threshold of *P. falciparum* panel detection score (PDS) for high transmission areas at 50% at 200 parasites/µL. However, other stakeholders (e.g. manufacturers and some end-users) have concerns that the current bars, particularly for combination tests, are too high and exclude tests that perform well in field settings .

It is almost certain that some of the concerns that the bar is too low stem from equating PDS with sensitivity, thereby implying that WHO condones detecting (and therefore treating) just 50% of patients with potentially fatal *P. falciparum* malaria. This however, is a very flawed conclusion. As previously mentioned, in reality, it is estimated that only 5% of the population in a high transmission zone would have parasite densities <200/µL and of these 50% could be missed, based on the current procurement criteria. It is on these grounds , plus the limited number of *P. vivax* samples included in the WHO Product Testing protocol and the Programme's rigorous requirements for inter-test and inter lot consistency, that some manufacturers think the current criteria may be too stringent.

With arguments on both sides, it is clear that a change in the current criteria must be accompanied by reasonable evidence of harm associated with the current criteria or conversely evidence/predicted public health benefits of raising the performance requirements.

Considerations in favour of an increase to a PDS of 75% as a threshold:

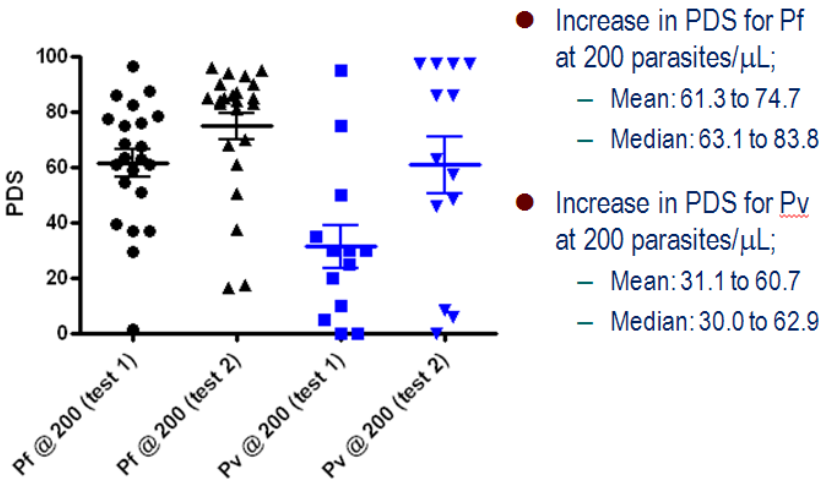
An increase in the PDS to 75% for Pf-tests in high-endemic areas will align the threshold used for this setting with that already used for the other settings (Pf-tests in low to moderate-endemic areas, and Pv-tests for any level of endemicity). This alignment will render RDT selection by countries much easier as they will not need to take into account local transmission which is changing in time and space.

An increase in the PDS to this new threshold of 75% will be met by 21 Pf-only RDTs , as opposed to 24 Pf-only RDTs if the threshold remains unchanged for areas of high transmission.

Many of the 23 tests which were re-submitted from Round 1 to Round 3 have been found to have increased panel detection scores, with the highest improvement in mean/median values for *P. vivax* scores (see figure below).

The shift of the threshold of panel detection score from 50% to 75% will be in line with conclusions of experts convened by WHO Technical Consultation held in 2009, which recommended that "As malaria control improves, there will be greater demand for RDTs that consistently have detection rates of at least 75% at low densities (200 parasites per microlitre) of *P. falciparum* and *P. vivax* parasites."

Figure 5: Improvement in Panel Detection Score in re-submitted RDTs products between Round 1 (2009) and Round 3 (2011)



Considerations against an increase to a PDS of 75% as a threshold:

The relationship between panel detection score and clinical sensitivity will vary depending on the local epidemiology, and small differences in PDS may not have relevance in terms of clinical impact. Indeed, several studies have shown that the use of RDT for clinical management is safe, even in moderate endemic areas when using RDTs with *P. falciparum* panel detection score (PDS) at 200 parasites/µL of much less than 75% (see Table 2).

The distribution of PDS results against panels of wild type panels of both *P. falciparum* and *P. vivax* diluted at low parasite densities (200 parasites/µL) is linear with small incremental differences making any threshold level arbitrary, possibly unfair and probably clinically irrelevant (no public health impact)

If a new threshold of 75% were adopted, 3 Pf-only RDTs will be no longer eligible for procurement for areas of intense transmission; the impact of this in terms of market share and use is unknown. However, since the Round 4 of WHO Product Testing is on-going, it is not yet know how many RDTs and manufacturer could be potentially affected by an increased in the recommended threshold for procurement of malaria RDTs.

Figure 6 **:** *P. falciparum* PDS at 200 parasites/ µL for RDTs tested during Rounds 1, 2 and 3. Red stars show 3 RDTs which will be not eligible for procurement for areas of high transmission if the recommended threshold were increased from 50% PDS (blue solid line) to 75% (blue dotted line).

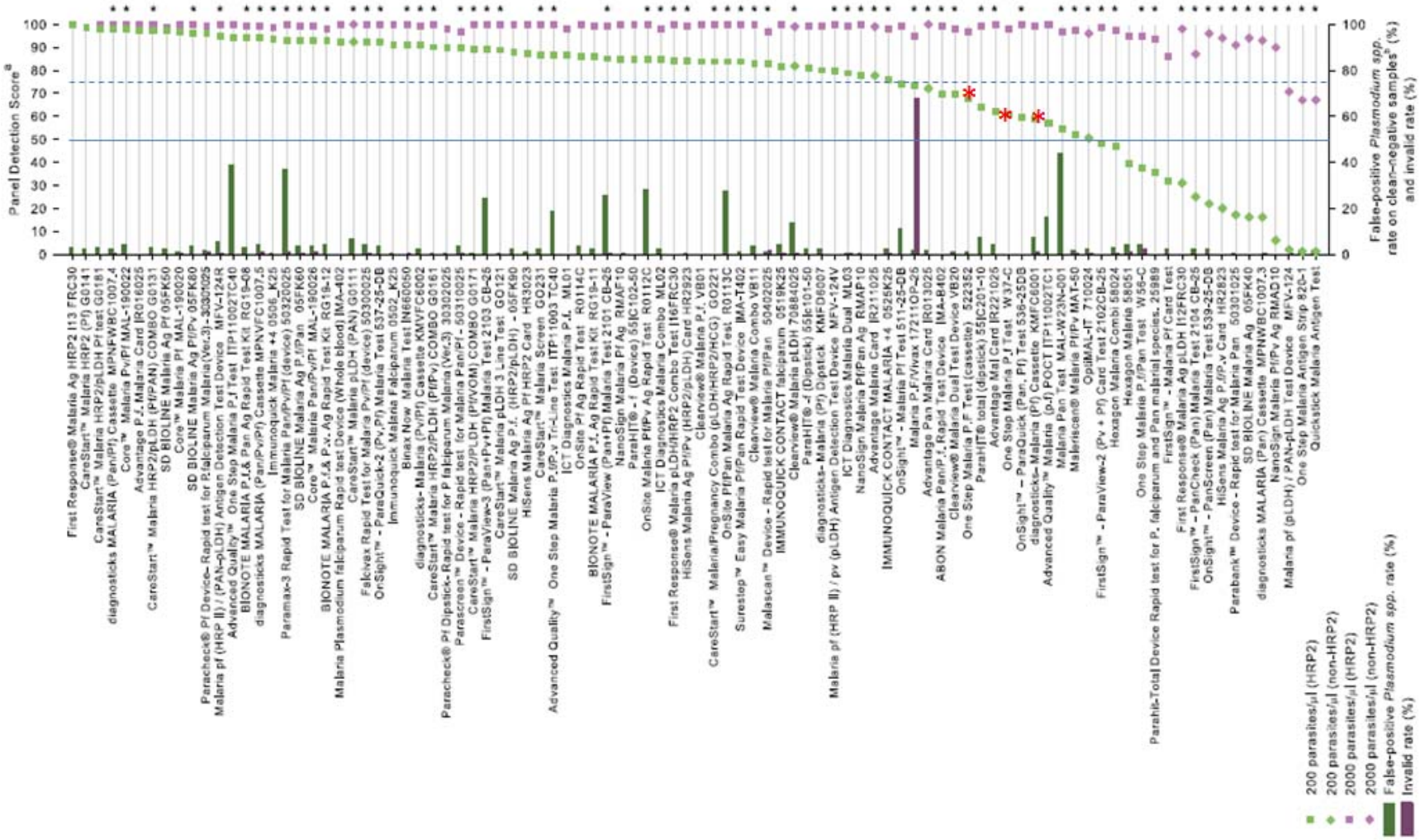


Table 2 - Review of studies providing the outcome of febrile patients managed on the basis of malaria negative RDT result (courtesy of Dr V. D'Acremont)

Reference	**- Country, year of patient inclusion** **- Positivity rate (PR) in patients** **- Main *Plasmodium* species** **- Geometric mean (GM) of parasite densities (range)**	**- Age group** **- Number of patients**	**Study design**	**RDT product used** **and Pf PDS at 200 parasites/µL (Round1)**	**Adherence to negative RDT result (no antimalarial given) in intervention arm**	**RESULTS** - ***Desired outcome:*** number of initially negative patients who developed severe malaria - ***Other valid outcomes:*** **- Complications:** hospitalizations; deaths **- Clinical outcome at follow-up:** clearance of fever (by history and/or elevated temperature); clearance of all symptoms; absence of reattendances
Msellem *et al,* *PLoS Medicine* 2009	Zanzibar, 2005 PR 29% *P falciparum* GM: 3,840 p/µl (range 16 - 457,326)	All ages (55% were children under five) Intervention arm: 1005 Control arm: 882	Cross-over randomized control trial of dispensaries using RDT (level of randomization: dispensary)	ParaCheck® Pf PDS = 54.4%	100%	**No initially negative case developed severe malaria** *Deaths:* None *No reattendance within 14 days:* 97% in intervention arm and 95% in control arm
D'Acremont *et al* *Clinical Infectious Diseases* 2010	Tanzania, 2007-2008 High prev. area: PR 51% Mod. Prev. area: PR 14% *P falciparum* GM: 22,473 p/µ (range 120- 490,800)	Children under five High prev. area: 700 Mod. prev. area: 300	Dispensaries using RDT No control arm	ParaHit® Pf PDS = 39.2%	100% (per protocol)	**No initially negative case developed severe malaria** *Deaths:* 2 (1 severe sepsis and 1 severe pneumonia[12#]) *Hospitalizations:* 0.5% *Clinical clearance at day 7:* 97%

[12] Both children were negative at inclusion. One developed severe sepsis and one severe pneumonia; they were both tested negative again by RDT and microscopy.

Reference	**- Country, year of patient inclusion** **- Positivity rate (PR) in patients** **- Main *Plasmodium* species** **- Geometric mean (GM) of parasite densities (range)**	**- Age group** **- Number of patients**	**Study design**	**RDT product used** **and Pf PDS at 200 parasites/µL (Round1)**	**Adherence to negative RDT result (no antimalarial given) in intervention arm**	**RESULTS** - ***Desired outcome:*** number of initially negative patients who developed severe malaria - ***Other valid outcomes:*** **- Complications:** hospitalizations; deaths **- Clinical outcome at follow-up:** clearance of fever (by history and/or elevated temperature); clearance of all symptoms; absence of reattendances
Yeboah *et al,* *Plos Medicine* 2010	Zambia, 2008 PR 28% *P falciparum*	Children under five Intervention arm: 1017 Control arm: 2108	Randomized control trial of CHW using RDT and respiratory rates (level of randomization: CHW)	ICT diagnostics® Pf PDS = 82.3%	99.6%	*Deaths:* 2 (1 severe pneumonia and 1 severe gastro-enteritis[13]) in intervention arm and 1 in control arm *Hospitalizations:* 0.4% in intervention arm and 0.7% in control arm *Fever and fast breathing clearance:* 93% in intervention arm and 92% in control arm
Tiono *et al,* *In preparation* 2011	Burkina faso, 2009 PR 74% *P falciparum*	Children under five Intervention arm: 525 Control arm: 576	Randomized control trial of CHW using RDT and respiratory rates (level of randomization: village)	First Sign® PDS = 31.6%	96.3%	**No initially negative case developed severe malaria** *Deaths:* none *Elevated temperature clearance:* 100% in intervention arm and 99 in control arm

[13] Both children were negative at inclusion. One developed severe pneumonia and was tested negative again by RDT; the other one developed severe gastro-enteritis but was not retested for malaria.

Reference	- Country, year of patient inclusion - Positivity rate (PR) in patients - Main *Plasmodium* species - Geometric mean (GM) of parasite densities (range)	- Age group - Number of patients	Study design	RDT product used and Pf PDS at 200 parasites/µL (Round1)	Adherence to negative RDT result (no antimalarial given) in intervention arm	RESULTS - ***Desired outcome:*** number of initially negative patients who developed severe malaria - ***Other valid outcomes:*** - **Complications:** hospitalizations; deaths - **Clinical outcome at follow-up:** clearance of fever (by history and/or elevated temperature); clearance of all symptoms; absence of reattendances
Anyorigiya *et al,* *In preparation 2011*	Ghana, 2009 PR 84% *P falciparum*	Children under five Intervention arm: 584 Control arm: 591	Randomized control trial of CHW using RDT and respiratory rates (level of randomization: village)	ParaCheck® Pf PDS = 54.4%	96.7%	**No initially negative case developed severe malaria** *Deaths:* none *Elevated temperature clearance:* 99% in intervention arm and 98% in control arm
Senn *et al,* *In preparation* 2011	Papua New Guinea, 2006-2010 PR 30% *P. falciparum (19%), mixte (37%), non-falciparum (44%)* GM Pf: 22,196 p/µl GM Pv: 4,792 p/µl (range 40 - 654960)	Children less than 2 years 5670	Dispensaries using RDT No control arm	ICT diagnostics® Combo PDS = 86.1%	100% (per protocol)	*Deaths:* 3 (1 severe malaria + pneumonia, 1 severe pneumonia, 1 meningitis[14]) *Hospitalization and/or severe illness:* 0.5% *No reattendance within 7 days:* 96%

[14] One child was positive at inclusion and developed severe pneumonia. Two children were negative at inclusion; one developed severe pneumonia and one got meningitis; they were both tested negative again by RDT and microscopy.

ANNEX 1

WHO Prequalification of malaria RDTs

WHO Essential Health Technologies (EHT) Department has started approximately 5 years ago a pre-qualification (PQ) programme diagnostic devices for a number of diseases including malaria. This programme has based its evaluation scheme on the model for prequalification of medicines, including assessment of a product dossier, and inspection of the manufacturing site of each product. Manufacturers have received communication informing them that they should participate in the PQ programme, and several have submitted dossiers to date, including 37 malaria RDTs (as of 28 November 2011). So far 2 RDTs have been prequalified by this programme (of which one in dipstick format, no longer in use by malaria programs). WHO EHT applies a non-refundable assessment fee of US $12,000 to manufacturers submitting their product dossier for evaluation by WHO PQP. Since September 2010 the WHO/EHT programme has included the results of the WHO Product Testing Programme as a third evaluation component required to achieve full prequalification, in addition to dossier review and inspection of the manufacturing facilities. In addition, recently applications have been closed due to product testing results that do not meet current WHO procurement criteria requirements[3].

There are currently over 60 manufacturers of malaria RDTs and approximately 200 malaria RDT products commercially available, with a high rate of entry of new and modified products. The proposed PQ model for malaria RDTs demands significant time investments as in the case for medicines, due to the requirements of product dossier compilation, acceptance/review, correspondence on observations, inspection and reporting, addressing observations, and review of corrective actions/re-inspection for possible approval. Often manufacturers of RDTs rely on multiple manufacturing production facilities, and each of these would require separate inspections and certification by the PQ team, to provide prequalification status. Furthermore, manufacturers often make minor changes to their products to improve performance and operational characteristics. WHO/EHT requires that they be informed and that a detailed description/report of any product variations be provided. A decision is taken, on a case-by-case basis as to whether or not the change constitutes a new product and would require re-submission to PQP. This approach proves challenging in being able to respond in a timely manner to the current rate of new product entry (and variations) on the market; by the time one product is processed, it is likely that new and improved products will be entering the market.

A meeting of experts, external stakeholders (UN agencies, global health initiatives, national regulatory authorities, and NGOs) and Regional Offices was held on 4-6 Oct 2011 to review WHO prequalification. They proposed a reorganization of prequalification in WHO to consolidate several of the different programmes, and strengthen the links between prequalification and capacity building. The immediate need is for a technical review of the mechanism for prequalification of diagnostics in WHO.

Background on the rationale and methods for developing the WHO Position Paper on Larviciding

There is renewed interest in attacks on the breeding sites of malaria vector mosquitoes ('larval source management', LSM) as a means of malaria control [1],[2],[3]. In particular, several African countries are currently planning a substantial expansion of larviciding activities [4]. However, effective larviciding for malaria control requires precise knowledge of the local breeding sites; whether or not these countries have the necessary specialised local expertise is therefore an important question.

For these reasons, WHO has been asked by a range of partners to clarify its recommendations concerning the role of larviciding as a means of malaria control. Since larviciding must compete for public resources with other interventions that are proven and life-saving, and since the decision to employ larviciding may sometimes be taken by non-experts, it is important that these decision-makers have access to independent and evidence-based guidance as to where such methods should and should not be used.

This position statement is the product of a review of existing evidence and programmatic practice by entomologists within the WHO-GMP Vector Control Unit. Because of the very meager volume of high quality data, it was felt that expert opinion needed to play a more prominent role in the development of the paper. Therefore, WHO-GMP undertook an extensive consultation exercise: in September 2011, a first draft was sent to a list of 100 experts drawn from the Vector Control Working Group and WHO contact lists, and chosen for regional balance as well as an interest in larval control of malaria vectors and/or practical knowledge of malaria vector control. Nearly 50 replies were received, and on the basis of this feedback, many changes were made, including two major ones: 1) the scope of the statement was restricted to larviciding, instead of larval control in general; and 2) more attention was paid to the potential advantages of larviciding (in certain environments).

Most vector control experts agree that there are some specific circumstances where larviciding programmes can be effective and useful for malaria control, and many other circumstances where such efforts unlikely to be cost-effective[5]. For malaria vector control, the key question is how national programme managers can distinguish between situations where larviciding is likely to be useful and cost-effective, and those where it is inappropriate.

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[1] Killeen GF, Fillinger U, Kiche I, Gouagna LC, and Knols BGJ (2002). Eradication of *Anopheles gambiae* from Brazil: lessons for malaria control in Africa. Lancet Infect Dis 2: 618–27.

[2] Worrall E, Fillinger U. (2011) Large-scale use of mosquito larval source management for malaria control in Africa: a cost analysis. Malar J. 8;10:338.

[3] Fillinger U, Lindsay SW. (2011) Larval source management for malaria control in Africa: myths and reality. Malar J. 10(1):353

[4] Notably, these programmes are mostly using national rather than donor resources.

[5] Walker K and Lynch M (2007). Contributions of *Anopheles* larval control to malaria suppression in tropical Africa: review of achievements and potential. Medical and Veterinary Entomology 21: 2–21.

World Health Organization

GLOBAL MALARIA PROGRAMME

Interim Position Statement

The role of larviciding for malaria control in sub-Saharan Africa

World Health Organization

Global Malaria Programme

Geneva, Switzerland

April 2012

World Health Organization

GLOBAL MALARIA PROGRAMME

Contents **page**

Executive Summary

A range of anti-larval methods is available for control of malaria vectors; this paper focuses on larviciding, which is the regular application of chemical and biological insecticides to breeding sites. This is an interim position statement which presents current recommendations about larviciding for the purposes of malaria vector control and within the context of integrated vector management (IVM) in sub-Saharan Africa. The statement does not address the use of larviciding to control vector species of other mosquito-borne diseases nor in other regions of the world where the context is different.

a) Larviciding has a specific and limited role in malaria vector control.

b) The number of unbiased studies on the efficacy or effectiveness of larviciding in Africa is very limited, and makes it difficult to draw generalized conclusions.

c) In order to be effective, larviciding must be specially adapted to each locality, and must be carried out thoroughly and selectively (not all water bodies are important vector breeding sites), often over a large area.

d) In general, larviciding should be considered for malaria control (with or without other interventions) only in areas where the breeding sites are **few, fixed and findable.**[1]

e) In all rural and most moderately urbanised areas with active malaria transmission, adult mosquito control with insecticide treated nets (ITNs) (including long-lasting insecticidal nets, LLINs) and indoor residual spraying (IRS) are currently considered the most cost-effective interventions, as long as WHO recommendations on insecticide resistance management[2] are followed.

f) Measures which reduce vector longevity, such as ITNs and IRS, have greater potential impact than measures which reduce only vector density, such as larviciding.

g) In most endemic settings, the appropriate way to use larviciding is as a supplement to ITNs or IRS; only in a very few specific circumstances with low transmission will it be appropriate to deploy larviciding alone and in the absence of measures against adult mosquitoes.

h) In sub-Saharan Africa, larviciding measures may be effective as the leading method of vector control in urban areas; however, more good quality evidence is needed to support this view.

[1] A fixed breeding site need not be permanent, but could be a pool of relatively long-standing duration that persists during or beyond the rainy season.

[2] WHO (2011). The technical basis for coordinated action against insecticide resistance: preserving the effectiveness of modern malaria vector control. Report of a meeting 4-6 May 2010. 46pp. Geneva: Global Malaria Programme, WHO.

i) The consensus among vector control specialists, based on currently available evidence, is that in most situations, larviciding with universal coverage across large areas and populations is unlikely to be feasible.

j) This information needs to be brought to the attention of policy decision makers in WHO member states to ensure that larviciding is only implemented where it is appropriate, and that vector control resources are used where they are expected to be cost-effective.

k) As with ITNs and IRS, sustained entomological monitoring is needed to guide decisions about vector control - including larviciding. Strengthening capacity in entomological skills is essential to ensure that control programmes at the national and local level are able to make decisions on where larval control is and is not appropriate.

l) Commercial larviciding products can be of variable quality, and quality control is an important issue. The website of the WHO Pesticide Evaluation Scheme (WHOPES) describes standard methods for testing larvicides and gives a list of recommended larviciding products[3], which have been found to be safe, of good quality, and reliably effective when properly applied. Only WHOPES recommended products should be used for larviciding**.**

Interim Recommendations

1) In general, anti-larval measures are likely to be cost-effective for malaria control ONLY in settings where the vector breeding sites are:
   a) **few**,
   b) **fixed** and
   c) **findable**.

2) In sub-Saharan Africa:-
   a) Larviciding measures should normally be used only as a supplement to the core interventions (ITNs or IRS); larviciding should never be seen as a substitute for ITNs or IRS in areas with significant malaria risk.
   b) Larviciding is most likely to be cost-effective in **urban** areas, because the conditions defined above are more likely to be present.
   c) In rural settings, larviciding is not recommended unless there are particular circumstances limiting the breeding sites, as well as evidence confirming that such measures can reduce the malaria incidence rate in the local setting.

3) Additional environmental factors that make larviciding more likely to be feasible and cost-effective include:

[3] http://www.who.int/whopes/Mosquito_Larvicides_sep_2011.pdf

a) a short transmission season;
b) cool temperatures extending the duration of the immature stages;
c) breeding sites that are man-made and homogeneous, so that numerous sites can be dealt with by a single preventive intervention.

4) Further evidence is needed of the value of larviciding as a routine and large-scale operation in both urban and rural areas; this evidence should examine not only questions of feasibility and effectiveness, but also issues of management, economics, environmental and health impacts and cost-effectiveness as a supplement.

1. Introduction

There is renewed interest in attacks on the breeding sites of malaria vector mosquitoes ('larval source management', LSM) as a means of malaria control[4,5,6]. There is a range of possible LSM interventions, ranging from permanent environmental engineering projects to larviciding. The latter involves the regular application of chemical or biological agents to kill mosquito larvae in their aquatic habitats. Thus the objective of LSM is to either kill the mosquito larvae or create a situation which is unfavourable for mosquito breeding.

Several African countries are currently planning to expand larviciding activities[7]. Effective larviciding for malaria control requires precise knowledge of the local breeding sites as well as intensive, widespread and sustained field operations. An important question is therefore whether or not malaria control programmes have the necessary specialised local expertise and operational resources. For these reasons, WHO has been asked by a range of partners to clarify its recommendations concerning the role of larviciding as a means of malaria control. Since larviciding must compete for public resources with other interventions that are proven and life-saving, it is important that the decision-makers have access to independent and evidence-based guidance as to where and when such methods should and should not be used. Where there are several potentially effective approaches there is a need to consider the level of priority of the alternatives.

Most vector control experts agree that there are some specific circumstances where larviciding programmes can be cost-effective and useful for malaria control, and many other circumstances where such efforts are unlikely to be cost-effective[8]. For malaria vector control, the key question is how national programmes can identify those specific situations where larviciding is likely to be useful and cost-effective.

This question is part of the broader task of deciding which vector control intervention (or combination of interventions) is likely to be most cost-effective in a given setting, and should therefore be deployed for malaria control purposes by a public health programme. The principles of Integrated Vector Management[9] were developed to provide rational and evidence-based guidance to this task.

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[4] Killeen GF, Fillinger U, Kiche I, Gouagna LC, and Knols BGJ (2002). Eradication of *Anopheles gambiae* from Brazil: lessons for malaria control in Africa. Lancet Infect Dis 2: 618–27.

[5] Worrall E, Fillinger U. (2011) Large-scale use of mosquito larval source management for malaria control in Africa: a cost analysis. Malar J. 8;10:338.

[6] Fillinger U, Lindsay SW. (2011) Larval source management for malaria control in Africa: myths and reality. Malar J. 10(1):353

[7] Notably, these programmes are mostly using national rather than donor resources.

[8] Walker K and Lynch M (2007). Contributions of *Anopheles* larval control to malaria suppression in tropical Africa: review of achievements and potential. Medical and Veterinary Entomology 21: 2–21.

[9] WHO position statement on integrated vector management 2008. whqlibdoc.who.int/hq/.../WHO_HTM_NTD_VEM_2008.2_eng.pdf

The relative cost-effectiveness of alternative interventions in a given setting depends not only on the local environment, but also on the specific biology of the local vector species. Each sub-region of the malarious world has its own range of vector *Anopheles* species, and each species has its own characteristic breeding site preferences. Thus, a universal set of rules covering every vector and every possible situation would be vast and complex.

Hence, this position statement does not explain the operational procedures of larviciding; instead it focuses on the general principles of where and when larviciding should be used for malaria control. It includes some observations about anti-larval measures in general, but the specific recommendations are focused on the role of larviciding, with special reference to Africa. Other forms of LSM, including the potential of community- based larval source reduction initiatives, as well as larviciding outside the context of sub-Saharan African will be considered in future WHO documents.

2. Key features of larviciding compared to other methods

2.1 The potential advantages of larviciding

In most settings, insecticide treated nets (ITNs) - which include long-lasting insecticidal nets (LLINs) - and indoor residual spraying (IRS) are the most powerful, reliable and practicable tools for malaria vector control; however these two interventions are not perfect, and they cannot serve all vector control purposes in all settings.

For example, it has often been observed in Africa that indoor transmission can be greatly reduced by careful indoor residual spraying (IRS)[10], but outdoor transmission may persist and prevent the complete interruption of transmission. However, it is important to note that major African malaria vectors prefer to rest indoors, where they are exposed to insecticides, even if they sometimes bite outdoors. Larviciding has the potential to overcome this problem, because it is expected to affect indoor and outdoor biting vectors equally.

Similarly, larviciding may sometimes have the potential to play a role in insecticide resistance management, although as of yet, there is no direct evidence that such a strategy will work. Of the larvicides that are recommended by the WHO Pesticide Evaluation Scheme (WHOPES), the majority have never been used to kill adult mosquitos and are unaffected by the resistance mechanisms currently spreading through malaria vector populations in Africa.

Consequently, larviciding can only potentially play important role in those settings where the procedure is feasible and cost-effective.

2.2. Limiting factors that constrain the use of larviciding

The feasibility and cost-effectiveness of anti-larval methods in general is constrained by two features of anopheline biology: the types of water-body in which such mosquitoes breed, and how far they fly.

[10] Kouznetsov RL (1977). Malaria control by application of indoor residual insecticides in tropical Africa and its impact on community health. Tropical Doctor 7, 81-91

For larval control to be effective, one must find and effectively prevent breeding in a very high proportion of the breeding sites located within the vector flight range of the community to be protected. It is normally not hard to kill the larvae in the breeding sites that one knows about: there is a variety of available methods, including environmental management, as well as the use of chemical and biological larvicides. The main challenge is finding an adequate proportion of the sites over a sufficiently large area to reduce adult mosquito densities (and hence transmission) in the target community, despite the constant inward movement of adult mosquitoes from breeding sites outside the intervention area.

2.2.1 Finding the Sites: To be effective, anti-larval measures must be targeted at the most productive breeding sites of the local vector species[11]. This normally requires local studies to identify those sites, since there is great variation not only among species, but also among locations for a given species[12].

Many important malaria vectors - notably *Anopheles gambiae s.l.* - breed in a wide range of aquatic habitats. These range from small temporary bodies of water to the margins of semi-permanent and permanent streams and ponds. Maintaining complete coverage of the small and temporary sites – including those scattered around the margins of larger water bodies – is important but difficult. This is because the smaller sites are often numerous, scattered and shifting, i.e. they can be new and slightly different locations every week, as old breeding sites dry out or are washed away, and new breeding sites are created elsewhere (see Figure 1).

Because new breeding sites are always appearing, and eggs laid in new sites may reach adulthood in just 7-10 days, it is normally necessary to repeat larviciding operations at weekly intervals, whatever the residual characteristics of the product used. This is not usually the case in places where the majority of the breeding sites are permanent i.e. cement lined pits or brick pits.

A few vector *Anopheles* species tend to exploit breeding sites that are relatively fixed – for example *An. funestus* in swamps and waterlogged grassland in Africa, and *An. sundaicus* in coastal brackish water in Southeast Asia. Some of the best examples of effective malaria control using larval source management have been targeted at such species[13, 14]. For example, environmental engineering interventions that replace

[11] Majambere S, Pinder M, Fillinger U, Ameh D, Conway DJ, Green C, Jeffries D, Jawara M, Milligan PJ, Hutchinson R and Lindsay SW (2010). Is Mosquito Larval Source Management Appropriate for Reducing Malaria in Areas of Extensive Flooding in The Gambia? A Cross-over Intervention Trial. Am J Trop Med Hyg 82: 176-184 doi: 10.4269/ajtmh.2010.09-0373.

12 Imbahale SS,Paaijmans KP, Mukabana WR, van Lammeren R, Githeko AK and Takken W (2011). A longitudinal study on *Anopheles* mosquito larval abundance in distinct geographical and environmental settings in western Kenya. Malaria Journal 2011, 10:81.

[13] United States Public Health Service and Tennessee Valley Authority (1947). Malaria Control on Impounded Waters. 422pp U. S. Government Printing Office, Washington, D.C.

[14] Keiser J, Singer BH, Utzinger J (2005). Reducing the burden of malaria in different eco-epidemiological settings with environmental management: a systematic review. Lancet Infect Dis 5: 695–708.

brackish water lagoons with 100% sea water can permanently prevent the breeding of brackish-water specialist species. Such opportunistic environmental interventions are normally expensive to install but inexpensive to maintain. They must be distinguished from larviciding operations, where a single operational round of treatment may be relatively inexpensive, but must be repeated every week for as long as transmission control is needed. Larviciding operations should therefore not be considered as a more fundamental, more permanent or more environmentally-friendly form of intervention than ITNs or IRS. In any case, each locality needs its own intervention plan, targeting the most productive local sites, and based on local entomological knowledge.

- This need for local adaptation and local entomological skills is a critical limitation on scaling-up of all kinds of larval source management measures, including larviciding.

2.2.2 Large Area *Anopheles* mosquitoes have a long flight range in open country; females are able to fly up to 1-1.5 km. For this reason, breeding must be prevented within a diameter of up to 3 km, or an area of potentially more than 9 km^2, in order to protect a small community inside that zone. In larger communities, the whole area of the settlement plus a buffer region between the community and breeding sites must be covered[15].

- It is a formidable challenge, during the rainy season, to find every potential breeding site throughout such a large area.

In addition, the fact that larval control can only be effective if carried out on a large scale has implications for three aspects of the evaluation of larval control methods:

- Indicators: It is not enough to show that larvae are killed or excluded from sites that are known and treated; rather the critical test is to show whether adult mosquito densities (and ideally, malaria incidence) have been reduced in the target community;
- Trial design: If larviciding is only effective when performed over a large area, then the minimum area of a replicate unit within a randomised controlled trial (RCT) must be similarly large. This means that larviciding trials must be conducted on a large scale, even by the standards of conventional vector trials[16];
- Limited Evidence: This requirement for scale makes trials expensive, and has been an important constraint on efforts to collect rigorous, unbiased, and conclusive evidence on the effectiveness of larviciding in a wide variety of settings.

[15] Macdonald G. Epidemiological basis of malaria control. *Bull. World Health Organ.* 1956;15:613–626.
[16] See Majambere et al (2010), above.

2.3 The advantages of anti-adult methods of malaria vector control (IRS and ITNs)

Methods of killing adult mosquitoes with residual insecticides have some critical advantages over anti-larval methods:

2.3.1 Exponential Effect on Transmission: With ITNs and IRS, female mosquitoes suffer a repeated risk of being killed every time they take a human blood meal. This reduces not just the size of the mosquito population, but also its mean lifespan. Transmission of malaria is extremely sensitive to the lifespan of the vector, because the parasite takes at least 10 days to develop inside the mosquito, and this is a long time relative to the life of a tropical mosquito.

Measures that target longevity of the adult vector would theoretically result in far greater reduction in potential transmission than measures that would reduce the number of vectors only[17]. Larviciding affects the rate of emergence and hence number of adult vectors, and has virtually no effect on adult longevity. ITN and IRS are generally more powerful methods of malaria vector control, mainly because both can reduce vector longevity and density and, in the case of ITNs (and with some IRS insecticides), human-vector contact as well. They also target mosquitoes associated with biting humans, and therefore most likely to become infective. They are capable of producing sustained reductions in potential transmission even when actual coverage is only moderately good. Transmission can be reduced to an extremely low level if a large proportion of the infected vectors are killed before the parasite attains an infective stage within the mosquito vector. By contrast, anti-larval methods can never produce more than a directly proportional effect on transmission. If density of adult mosquitoes is reduced by 50% by larviciding, the best that can be hoped for under ideal conditions is reduction of the transmission potential by 50%. However, reducing the life span of a normally long-living vector in tropical conditions by 50% can result in reduction of the transmission potential by 99% or more[18].

Vector longevity is a key factor underlying some major epidemiological patterns in malaria. For example, the fact that *Anopheles gambiae s.l.* and *An. funestus,* the main malaria vector species in Africa, are especially long-lived, compared to their equivalents in other continents, is an important reason why Africa suffers more than 80% of the world's malaria disease burden. Similarly, the fact that malaria in Southeast Asia is so closely associated with highland forests reflects the fact that one group of human-biting *Anopheles* species in the forest have a particularly long lifespan, while those outside the forest are all relatively short-lived.

[17] See Magesa et al. Acta Trop. **49**:97-108 (1991) for detailed evidence that community-wide use of IRS and ITNs can produce large reductions in vector longevity.

[18] Ferguson H, Nicholas M, Takken W, Lyimo I, Briet O, Lindsay S and T. Smith (2012). Selection of mosquito life histories: a hidden weapon against malaria? Malaria Journal 2012, 11: 107 (3 April 2012).

Although the importance of these effects has been recognised by malaria epidemiologists for more than fifty years, they are not well known outside this specialised world. As a result, non-specialist health professionals often assume, wrongly, that larviciding and anti-adult measures should, if carried out with equal care and completeness, have similar effectiveness. This is not true: in fact, coverage with larviciding needs to be much more complete than coverage with ITNs and IRS, in order to have the same effect on malaria transmission. Another claim is that anti-larval measures somehow deal with the root of the problem ("prevention is better than cure"), whereas ITNs and IRS are a short-term measure aimed at the symptoms not the cause. It is true that in some settings, it may be possible to achieve permanent source reduction through environmental interventions and landscape-engineering; history confirms that this kind of "building-out" of malaria can play an important long-term role in consolidating progress towards elimination. However, it is misleading to make such claims about larviciding, the effects of which are even more superficial, temporary and transient than those of ITNs and IRS.

Finally, it may be noted that *Anopheles* mosquitoes are especially vulnerable to ITNs and IRS because several important vector species tend to rest on indoor walls, and to bite exclusively at night. By contrast, the vectors of many other mosquito-borne diseases (e.g. dengue and other arboviruses) tend to rest on other (non-sprayed) indoor surfaces, and/or to be day-biting. As a result, these other mosquitoes tend to be less vulnerable to ITNs and IRS, and anti-larval methods are the primary means of vector control for these diseases. Similarly, it is worth noting that the main aim of mosquito control programmes in northern Europe and the USA is to control nuisance-biting, not disease transmission, and this is one important reason for their use of larviciding. Thus, the fact that larviciding is used for mosquito control in Europe and North America does not imply that it is the intervention of choice for malaria control in the tropics.

2.3.2. Long Duration of Residual Efficacy: ITNs and IRS are effective for months or years. By contrast, in most situations, larvicide treatments need to be re-applied every week. There are some larvicide formulations that have a much longer duration of residual activity in favourable conditions, but in practice, new breeding sites are always appearing, and the water in more permanent sites is constantly flushed out and replaced; for this reason the maximum interval between operational rounds is normally one week.

2.3.3 Standardised Methods: Both ITNs and IRS use standardised methods: they are executed in more or less the same way, and are more or less effective against vectors with a wide range of behaviours. It is this technological standardisation that has allowed them to be delivered in a very wide range of circumstances by teams with no entomological knowledge or skills, and still be effective. This in turn has allowed massive scaling-up. We now accept that programmes using these methods can routinely deliver effective protection against malaria to tens or even hundreds of millions

of people. This was unthinkable before the advent of IRS. There remains no evidence that larviciding can be delivered effectively at this scale in Africa, despite the fact that larviciding is useful in specific settings and at a local scale.

2.4 Larviciding as a supplementary measure

A further difference between larviciding and ITNs/IRS is that use of the core interventions of ITNs/IRS is supported by an extensive body of evidence particularly in Sub Saharan Africa. The evidence shows that ITNs and IRS produce substantial reductions in the burden of malaria, and do so consistently across a very wide range of epidemiological settings. With larviciding, the evidence is much less extensive. There is not sufficient evidence to support the use of larviciding as a stand-alone intervention, instead of the core interventions, in areas where there is a significant risk of malaria for a substantial fraction of the population. Therefore, in endemic areas, resources intended for core malaria control interventions should not be used instead for larviciding.

Larviciding may, however, be used as a supplement to these core interventions, depending on the objectives and resources of the programme. As always, larviciding should only be considered in areas where the breeding sites are particularly vulnerable (few, fixed, and findable), and where there is the opportunity to eliminate all or a large proportion of the breeding sites with little effort.

In considering the use of larviciding as a supplementary intervention, in addition to ITNs or IRS, it is important to note the following characteristics of the potential interaction between the interventions:

- The effect of larviciding on malaria transmission is expected to be independent of that of ITNs and IRS, i.e. the effect is expected to be additive, but neither synergistic or antagonistic.
- The cost-effectiveness of combination interventions may be affected by the fact that the incremental benefit of the second intervention is likely to be less than if it had been applied alone. Suppose two interventions act independently, are equally costly and each applied independently reduces transmission by 60%. Thus, the residual transmission is 40% of baseline in the presence of one intervention, and 16% of baseline with both. Thus, the second intervention prevents 60% fewer cases than the first, and in terms of dollars per case prevented, it is 2.5-times less cost-effective, assuming that the cost per person at risk is the same. In reality, there is likely to be overlap in effect between many interventions, so the benefit of the second intervention may be less than given in this example.
- If resources are limited, then the provision of both interventions to some people may be possible only if other people are left with no protection at all. In this

case, the additional risks for the latter must not be forgotten, and must be balanced against the benefits for the former. In general, therefore, a national strategy of "universal coverage with the locally-most-cost-effective single intervention" is normally to be preferred over a strategy of "double protection to some of the at-risk population, but no protection to others equally at-risk".

2.5 Larviciding as a stand-alone measure

At the geographical fringes of malaria, areas with and without local transmission may lie close together. In the locations where transmission is absent most of the time, infected people may arrive frequently from nearby endemic areas, resulting in a constant risk that transmission by local vectors could resume. Thus, some form of vector control may be needed, even though malaria risk is low. In such settings, general coverage with ITNs or IRS is not cost-effective and not justified. In these circumstances, larviciding may be used to consolidate elimination and reduce receptivity, and hence to prevent the re-appearance of malaria outbreaks. This is especially appropriate in settings where hotspots of high transmission risk are known to be associated with breeding sites – for example urban cultivation in the centres of large African cities or irrigated rice in otherwise arid areas. In such situations, larviciding (or other anti-larval measures) targeted at these hotspots may be used as a stand-alone intervention, in order to reduce the risk of resumption of transmission.

3. Lessons from Experience

Having considered the special features of larviciding, vis-à-vis other forms of malaria vector control, we may consider the lessons that may be drawn from experience in the past, including cases where larviciding and other larval control methods were deployed successfully.

As background, it is useful to note a passage from the 2004 meeting of the WHO Study Group on Malaria Vector Control and Personal Protection[19]:

"Before the discovery of DDT, the main approach to controlling anopheline vectors was directed towards the larval stage, which required a detailed knowledge of the bionomics of local vectors. In some cases, a high level of community participation (often enforced by legislation) and a continuity of effort for decades were needed to ensure slow, but often sustainable, progress. Only in projects of very high economical and political value was a highly disciplined organization rigorously enforcing the application of anti-larval measures able to achieve spectacular successes, even in relatively large areas, notably

[19] WHO (2006). Malaria vector control and personal protection. WHO Study Group. 62pp Tech Rep Ser. 936. WHO: Geneva.

the eradication of invading populations of *Anopheles gambiae s.l.* from Brazil and *An. arabiensis* from Egypt or the sanitation of the Pontine Marshes in the Roman Campagna. In other cases, detailed knowledge of species habitats led to methods of environmental manipulation and sustained, cost-effective control, as in parts of Malaysia and Indonesia. In each situation, the solution of a local malaria problem required an in-depth study by a multi-disciplinary team to design a multi-sectoral programme."

According to statements and reports from the late 1930s (just before the advent of DDT), by the Malaria Committee of the Health Organization of the League of Nations, effective control of malaria was considered to be a realistic and feasible objective only in a limited set of specific situations[20]. For most poor rural communities it was regarded as out of reach[21].

An example of what could be achieved in such a suitable situation can be seen in Watson's account of his work in Zambian copper mines[22]. This is best known as a showcase example of effective malaria control using larval control measures including larviciding, in a rural (or semi-urban) African setting in the 1930s. However, it is notable that in 1946, these same mines were among the first to try out the new method of indoor residual spraying (IRS) with DDT, and this innovation was associated with a considerable further reduction in malaria cases.

With the advent of DDT and IRS, effective malaria vector control became possible not only in areas of special economic importance, such as the mines, but also, and for the first time, in ordinary rural communities in remote rural areas. The spraying itself was technically and logistically demanding, but it had two great operational advantages. First, it needed to be repeated only once or twice a year -- whereas in most breeding sites, chemical larviciding needs to be repeated every week during the season. Second, it consisted of a standardised and uniform set of methods, and therefore could be scaled up rapidly to cover very large populations -- whereas anti-larval methods are effective only if carefully targeted to the most productive local breeding sites, a task that requires specialised entomological investigation in each new area.

The advent of IRS did not cause the complete disappearance of all forms of larval control everywhere, but it caused anti-larval interventions to become more restricted, i.e. there was a move towards (a) more permanent forms of environmental modification, and (b) use of larval source management in places where breeding sites are obviously restricted and therefore vulnerable to complete elimination.

[20] Hackett, LW, Russell, PF, Scharff, JW, and Senior White, R (1938). The present use of naturalistic measures in the control of malaria. *Bulletin of the Health Organisation of the League of Nations* **7**:1016-1064.
[21] Litsios S (2002). Malaria Control and the Future of International Public Health. Chapter 17 in *The Contextual Determinants of Malaria* (Casman E and Dowlatabadi H, eds) Washington DC: Resources for the Future.
[22] Watson M (1953). *African Highway: The Battle for Health in Central Africa*. John Murray, London.

Later, with the development of LLINs, malaria control gained an intervention that was even more standardised, and that was capable of being delivered at even longer intervals. This extended yet further the ability to deliver effective vector control to the most remote areas, without the need for local adaptation or entomological skills.

4. Which settings in Africa are suitable for larviciding?

4.1 Urban Areas Most vector control experts would agree that larviciding can be effective and useful for malaria control in some urban areas in Africa where malaria transmission exists. It is likely to be worth considering also in densely populated refugee camps and internally displaced person camps. If carefully executed and sustained, such methods may even be adequate as the main vector control intervention in the densely urbanised centres of major cities.

The reason for this urban-rural contrast is simple. The process of urbanisation creates a high density of humans, but reduces the density of African malaria vectors[23], which tend to avoid breeding in water that is enclosed in concrete, or in other man-made containers[24], or in water with rotting organic matter. The intensity of malaria transmission is therefore much lower in towns than in the surrounding countryside. For this reason, as one moves from the countryside into town, the relative effort needed to deliver either anti-larval or anti-adult interventions is reversed. This is illustrated in Table 1.

[23] Trape J-F, Lefebvre-Zante E, Legros F, Ndiaye G, Bouganali H, Druilhe P, and Salem G. (1992) Vector Density Gradients and the Epidemiology of Urban Malaria in Dakar, Senegal. Am. J. Trop. Med. Hyg., 47: 181-189.

[24] An exception to this rule can be seen in some arid parts of Sudan, Somalia and Yemen, where there is dry-season breeding of *An. arabiensis* in man-made water-storage tanks… and since these are typically few, fixed, uniform and easy to find, anti-larval interventions in these sites can be effective as a means of malaria control.

Table1: The urban – rural contrast

Houses/breeding sites	Urban	Rural
Houses (target for IRS, ITN)	Cover most of the landscape	Few, Fixed, Findable
Breeding Sites (target for LSM)	Few, Fixed, Findable	Cover most of the landscape

Delivering ITNs or IRS to all the houses in rural areas is likely to be easier than reaching all the breeding sites. By contrast, in urban areas, breeding sites are limited to a few fixed areas in the gaps between the buildings and it becomes easier and cheaper (in terms of cost per square kilometre or per capita) to reach all the breeding sites every week than to deliver nets or IRS to all the houses at much longer intervals. In other words, the relative cost of larviciding, as well as its feasibility, depends on the human population density relative to the density of aquatic habitats [25].

Although larviciding is conventionally regarded as appropriate for urban centres in Africa, and there have been some encouraging recent studies[26], the formal evidence for its general effectiveness is nevertheless very limited. In particular, it remains unclear how programme managers, outside of the context of research studies, can easily identify the urbanised conditions where larviciding is likely to work, and draw a clear line between these and the surrounding rural areas where it is inappropriate. In order to fill this evidence gap, further investigation of the effectiveness of larviciding in urban areas would be helpful, through operational research and implementation on a pilot scale that includes rigorous evaluation of the impact on malaria transmission.

25 Worrall E and Fillinger U (2011) Large-scale use of mosquito larval source management for malaria control in Africa: a cost analysis. Malaria Journal 10:338

[26] Geissbühler Y, Kannady K, Chaki PP, Emidi B, Govella NJ, et al. (2009) Microbial Larvicide Application by a Large-Scale, Community-Based Program Reduces Malaria Infection Prevalence in Urban Dar Es Salaam, Tanzania. PLoS ONE 4(3): e5107. doi:10.1371/journal.pone.0005107

Different *Anopheles* species are affected in different ways by urbanisation and other changes in land-use. This description of the African situation also applies broadly to many other settings, but not, it must be stressed, to India and Pakistan, where *Anopheles stephensi* transmits malaria in urban locations. This important malaria vector species has adapted to breeding in a variety of man-made containers, including water-storage tanks of all kinds. The Indian sub-continent is therefore the only region where malaria transmission is often more intense in towns than in the surrounding countryside.

4.2 Arid areas In deserts, there is hardly any surface water during the dry season; the remaining water bodies are few, fixed and well-known. They are therefore vulnerable to attack by a variety of methods. However, the two critical questions are: (a) is there public health value in attacking the few remaining breeding sites at a time of year when there is almost no transmission, and (b) are the same methods still effective in the rainy season, when for a brief period there may be numerous small breeding-sites all over the countryside? In the majority of cases, the answer to these questions is "probably not", and in these cases, anti-larval measures are not likely to be cost-effective. In a few cases, however, breeding sites may be few and fixed more or less throughout the year, or permanent enough to cause significant transmission even in the dry season, and in these cases, larval control may be worth trying. For example, in arid areas with persistent dry season transmission due to vector breeding in man-made water-storage tanks, there are a few cases where anti-larval measures have been shown to be useful in reducing adult mosquito densities and malaria incidence[27][28] In some parts of the world, there is a tradition of attacking dry season breeding sites in order to delay or slow down the expansion of the vector population when the next rainy season begins: although this is an attractive idea, it does not seem to be supported by sufficient evidence or consensus of expert opinion.

4.3 East African Highlands Most recently, a series of trials and pilot operations in Africa have brought renewed interest in the potential role of supplemental larviciding in settings where anti-larval measures have not previously been seen as having a role – for example in the East African highlands[29]. This evidence is encouraging, and justifies further operational research to confirm that these findings can be repeated in similar settings elsewhere. However, as already noted, the most critical questions are: whether it is possible to deliver larviciding, with the requisite quality and completeness of cover, on a much larger scale; whether it is cost-effective as an addition to IRS or LLINs; and whether this can be sustained for years. Pilot operations with careful assessment could help to answer these questions. It is not a straightforward task: it will

[27] Alio, Isaq, and Delfini (1985). Field trial of the impact of Oreochromis spilurus spilurus on malaria transmission in northern Somalia. WHO mimeographed document http://whqlibdoc.who.int/malaria/WHO_MAL_85.1017.pdf.
[28] Guido Sabatinelli (1991). The impact of the use of larvivorous fish *Poecilia reticulate* on the transmission of malaria in the federal Islamic Republic of Comoros. Annels de Parasitologie Humane et compare, 66: 84-88
[29] See Fillinger U and SW Lindsay (2011) above.

require operational routines that are (a) locally adapted to fit local variations in breeding sites, (b) carefully managed and supervised to sustain constant completeness. For now, and until such evidence becomes available, it is not yet possible to recommend adoption of supplemental larviciding measures in highland areas into routine public health programmes.

5. Priority Research Issues

There are many gaps in the evidence about larviciding, but some of the most important are:

- If anti-larval measures are mostly appropriate in urban centres but not in rural areas, where and how should the line be drawn between the two? What criteria can/should be used? Is it useful to think about the "house to breeding site ratio" or the "breeding sites to person ratio", and how such indices could be defined and potentially used?

- How can supplementary larviciding be scaled up to a generalised routine intervention with universal coverage across large areas and populations, while still providing for operational adaption to local variations in breeding sites, and maintaining the necessary completeness of coverage? How can the process of identifying and targeting the most important breeding sites in an area be streamlined and simplified so that it can be done by non-specialised staff?

- In some environments, many of the most productive breeding sites are man-made, and some forms of man-made breeding site are common in many locations, e.g. brick-making, and cultivation of rice, sweet potato, yam, and some salad vegetables. Are there standard methods by which brick makers and farmers can still work efficiently but avoid producing mosquitoes as an unintended and harmful side-product?

- Since there are already plans for large-scale larviciding in some African countries, can these plans be adapted to allow for more rigorous evaluation, for example using a "stepped wedge" design in comparison with other vector control interventions?

- Can larviciding with different classes of insecticide from those used in LLINs/IRS be used as an insecticide resistance management tool?

- What is the potential of treating dry season larval habitats to limit transmission seasons, in areas such as southern Africa?

World Health Organization

GLOBAL MALARIA PROGRAMME

Figure 1:

Photos: J Lines & V Robert

Caption:

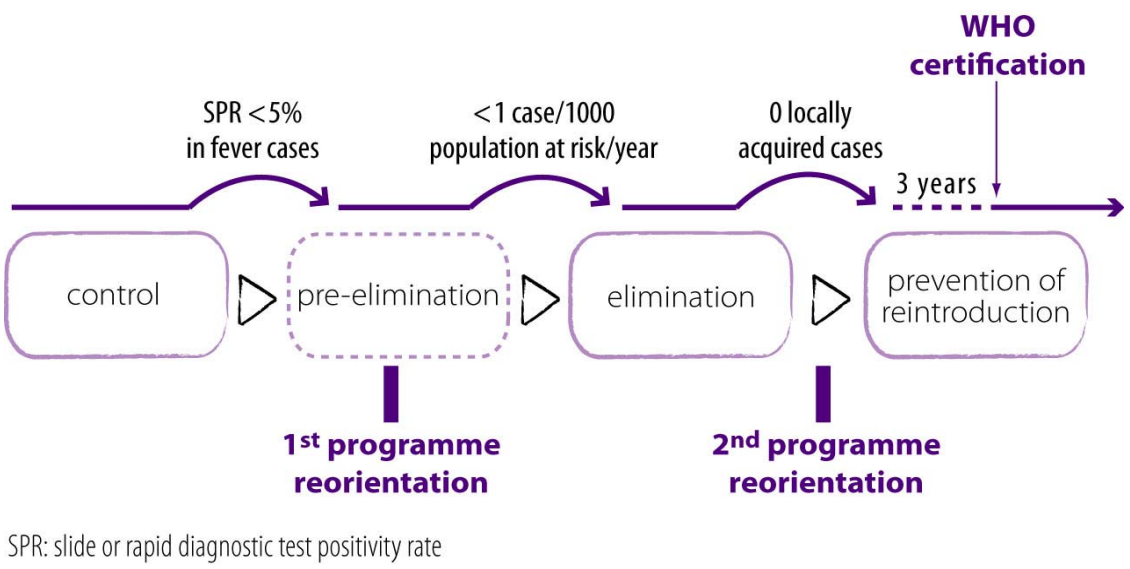
Muddy hoofprints in Muheza, Tanzania. The picture illustrates the shifting nature of typical breeding sites. This site contained at least some water for most of the year but its size and therefore the location of the water margins fluctuated from week to week. On the day this picture was taken, this was a very productive breeding site: each of these hoofprints contained >100 mature larvae and pupae of *Anopheles gambiae s.l.* (see inset). If the weather over the next few days is dry and sunny, then the wet hoofprints that we see now will dry out, but others will presumably appear in the parts of the stream that are now under deeper water. Conversely, if the there are several consecutive days of rain, the hoofprints that are now wet-mud will be submerged completely (and much less productive), but other wet hoofprints will appear further back, in the mud that is now dry. Either way, there will be no larvae here, but there will be wet muddy hoofprints somewhere else, newly colonised by a new set of larvae.

Country Classification by Elimination Phase

Background

GMP started to classify endemic countries by the phase of their elimination programme in 2007, after the development of the *Malaria Elimination Field manual for low and moderate endemic countries* with its "elimination continuum" flow diagram with indicative transition milestones.

Figure. Malaria programme phases and milestones on the path to malaria elimination[a]



[a]These milestones are indicative only: in practice, the transitions will depend on the malaria burden that a programme can realistically handle (including case notification, case investigation, etc.).

In consultation with the WHO Regional Malaria Advisers, GMP started to keep an unofficial list, classifying countries by the type of malaria programme that was implemented in the worst affected malaria-endemic part of the country. The Regions based their advice on evidence gathered from a combination of routine country reports, WHO staff country visits and reports, and country presentations and funding applications. The reason for choosing the worst affected area of a country for classification, as opposed to the most advanced, was that nearly all endemic countries have some areas where conditions for malaria transmission are marginal, seasonal or even completely absent (for instance due to altitude, desertification or affluence). On the other hand, malaria transmission is often most tenacious in peripheral areas with poor overall development, marginalized populations and weak health systems with inadequate coverage of control interventions.

Even though there are only 3 distinct programme phases (control, elimination, prevention of reintroduction), the GMP classification also included the transition phase of pre-elimination as well as a category of control-phase countries that are implementing projects aimed at achieving localized "malaria-free zones" (e.g., China - Hainan; Indonesia - Java, Bali; Philippines - province by province; Solomon Islands - Temotu; Sudan - Khartoum, Gezira; Vanuatu - Tafea; Yemen - Socotra).

Definitions:

Malaria elimination: the process of reducing to zero the incidence of infection caused by human malaria parasites in a defined geographical area, through deliberate efforts.

Pre-elimination consists of the period of reorientation of malaria control programmes between the sustained control and elimination stages, when coverage with good-quality laboratory and clinical services, reporting and surveillance are reinforced, followed by other programme adjustments to halt transmission nationwide.

Elimination programmes are characterized by four programme approaches, supported by large investments of local expertise and resources: (1) management of all malaria cases: detection, notification, investigation, classification and supervised treatment; (2) prevention of onward transmission from existing cases; (3) prevention and early detection of imported malaria infection; and (4) management of malaria foci: identification, investigation, classification, effective vector control in all foci of transmission, geographical mapping over time. The main indicator is the total number of locally acquired infections.

Prevention of reintroduction programmes are implemented in countries that have either recently achieved zero cases and aim to maintain the situation, or in countries that are generally considered non-endemic, having been malaria-free for well over a decade, that have experienced recent outbreaks of locally acquired malaria subsequent to importation of parasites. The main activity is vigilance (surveillance and response) by the general health services, which can be combined with vector control and other interventions to reduce receptivity in vulnerable areas.

Certification of malaria elimination: granted by WHO after proving beyond reasonable doubt that the chain of local human malaria transmission by *Anopheles* mosquitoes has been fully interrupted in an entire country for at least three consecutive years.

Re-establishment of transmission: renewed presence of a constant measurable incidence of cases and mosquito-borne transmission in an area over a succession of years. An indication of the possible re-establishment of transmission would be the occurrence of three or more introduced and/or indigenous malaria infections in the same geographical focus, for two consecutive years for *P. falciparum* and for three consecutive years for *P. vivax*.

Countries implementing projects in "malaria-free zones": Some malaria-endemic countries implement local projects aimed at achieving "malaria-free zones", while the remainder of the country is in the control phase. The term "malaria-free" is in this context not well-defined: while some countries are trying to eliminate the last locally acquired malaria infections in well-defined areas, for instance to encourage tourism (Socotra, Yemen), others in this group are trying to reduce mortality and morbidity due to malaria to a certain level (e.g. Khartoum, Sudan).

Sources: WHO 2007 and 2009

In 2008, WHO/GMP made its country classification public in the preparatory discussions around the development of the Global Malaria Action Plan (GMAP), providing the basis for the GMAP elimination objective that "by 2015, at least 8-10 countries currently in the elimination stage will have achieved zero incidence of locally transmitted infection". The following year (2009), the country classification was presented during the 4th meeting of the Malaria Elimination Group (convened by the UCSF Global Health Group, GHG), and was included as part of a full chapter on malaria elimination in the *World Malaria Report* (chapter 5, WMR 2009). WHO has published annually updated classifications of countries into (pre-elimination, elimination, and prevention of reintroduction in the WMR ever since.

As of 1 December 2011, 8 countries were considered to be in pre-elimination stage, 9 in elimination stage, and another 8 in prevention of reintroduction stage. This list of classifications as published in the *WMR 2011* is included below table.

TABLE 7.1
Classification of countries in the Pre-elimination, Elimination, Prevention of Reintroduction and Malaria-free stages, as of 1 December 2011

WHO Region	Pre-elimination	Elimination	Prevention of reintroduction	Certified malaria-free within last 5 years, or no local transmission reported for over a decade
Africa	Cape Verde	Algeria		
Americas	Argentina El Salvador Mexico Paraguay		Bahamas[1] Jamaica[1]	
Eastern Mediterranean	→	Iran Saudi Arabia	→ Egypt Iraq[2] Oman[1] Syrian Arab Republic	Morocco Turkmenistan United Arab Emirates
Europe		Azerbaijan Kyrgyzstan Tajikistan Turkey Uzbekistan	→ Georgia[2] Russian Federation[1] →	Armenia
South East Asia	DPR Korea Sri Lanka			
Western Pacific	Malaysia	Republic of Korea		
Typical additional programme activities and considerations in different phases of elimination (Footnote)				
Malaria situation	SPR < 5%[3] among suspected malaria patients throughout the year; a "manageable number" of cases	1 per 1000 population at risk[3]	Zero (or only very sporadic cases of) local transmission in recent years	
Programme goal	Programme reorientation from control towards elimination approach	Halt local transmission nation-wide	Prevent re-establishment of local transmission	
Case management	All malaria cases are microscopically confirmed, covering public and private sector Microscopy quality-assurance systems are put in place	Radical treatment of *P. vivax*; ACT plus gametocytocidal treatment for *P.falciparum* Routine QA/QC expert microscopic diagnosis	Case management of imported malaria	
Vector control and malaria prevention	Total IRS coverage in foci; IVM and LLIN as complementary measures in specific situations	Vector control to reduce receptivity in recent foci	Cluster response; and prevention in travelers	
Surveillance, monitoring and evaluation	All malaria cases are immediately notified GIS-based database for cases, vectors and foci Elimination database initiated	Active case detection cases and foci investigation and classification Collect documentation for eventual certification	Vigilance by the general health services Case investigation of imported cases; and response to introduced cases Certification process	
Health systems and financing	Mobilization of domestic resources	Largely reliant on domestic resources	Integration of malaria programme into other health and vector control programmes; maintance of a central nucleus of malaria expertise	

Arrows indicate movement of countries between categories in the interval 2010 to 2011. For further details of categores please refer to WHO 2007 Elimination Field manual.

1 Recently achieved zero locally acquired cases
2 Recent outbreaks after imported cases
3 These thresholds are indicative: in practice they will depend on the number of malaria cases that a programme can manage (including case notification, case investigations, etc.)

Issues

Experience over the last 4 years shows that the pre-elimination category is the hardest to define and most hotly debated. For instance, if a country is starting island-by-island elimination while continuing a control approach elsewhere, why would that not count as pre-elimination (e.g., Solomon Islands)? If a country has already adopted a national plan of action on elimination, why is it still classified as being in the control phase (e.g., China)? If a country shows an increase in cases over time, should we continue to call it pre-elimination (e.g., Republic of Korea)? Is establishment of a drug regulatory authority and/or the cessation of all over-the-counter sales of antimalarial medications a valid prerequisite for classification as pre-elimination (e.g., Swaziland)? A milder confusion arises at the end stage of elimination: once a country has reported zero cases, does it automatically classify as prevention of reintroduction, or should it wait three years, or perhaps even wait for certification?

Some confusion also arises from the diverging list of "eliminating countries" that is published by GHG, which includes countries that *have formally declared a national, evidence-based elimination goal, have assessed the feasibility of such a goal, and have embarked on a malaria-elimination strategy. Other countries are strongly considering an evidence-based national elimination goal, and have already made substantial progress in spatially-progressive elimination, for example, by eliminating malaria from specific islands, provinces, or geographical areas* (2011). In some cases the GHG list is more inclusive than the WHO classification, in other cases more restricted. Apart from the countries in the stage of prevention of reintroduction, which are not included among the GHG eliminating countries, the current discrepancies can be summarized as:

1. Included in GHG "eliminating country" list, while classified by WHO as control phase: Belize, Bhutan, Botswana, Costa Rica, Dominican Republic, Namibia, Nicaragua, Panama, São Tomé and Príncipe, South Africa, Swaziland, Thailand, Vietnam.
2. Excluded from GHG eliminating country list, while classified by WHO as having projects to achieve localized "malaria-free zones": Indonesia, Sudan, Yemen.

Questions for the MPAC

- Should GMP continue to categorize countries by the type of malaria programme that is implemented in the worst affected malaria-endemic part of the country?
- Are the current qualitative classification criteria adequate; if not, how should they be improved upon?

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Methodological Approaches in Estimating the Number of Malaria Cases and Deaths

Background

Systems for tracking malaria cases and deaths are weakest in areas that malaria is most prevalent. Consequently, precise information on the number of malaria cases and deaths is rarely available and various procedures have been used to estimate them.

For estimating the number of cases the approaches include:

(C1) Using data on reported deaths, adjusting them for incomplete reporting, and dividing by an estimated case fatality rate (Mendis *et al*, 2001)

(C2) Mapping climatic suitability for malaria, linking it to malaria incidence rates and adjusting over time and space to account for differences in intervention coverage (Snow *et al* 2003, Korenromp 2005, Cibulskis *et al* 2011, World Malaria Report 2011)

(C3) Mapping parasite prevalence and linking it to malaria incidence rates (Snow *et al* 2005, Hay *et al* 2010).

(C4) Using data from routine information systems and adjusting them for incomplete reporting, diagnostic testing and use of public sector facilities (Cibulskis *et al* 2011, World Malaria Report 2011).

For estimating the number of deaths the approaches include:

(D1) Using data on reported deaths and adjusting them for incomplete reporting and use of public sector facilities (Mendis *et al*, 2001)

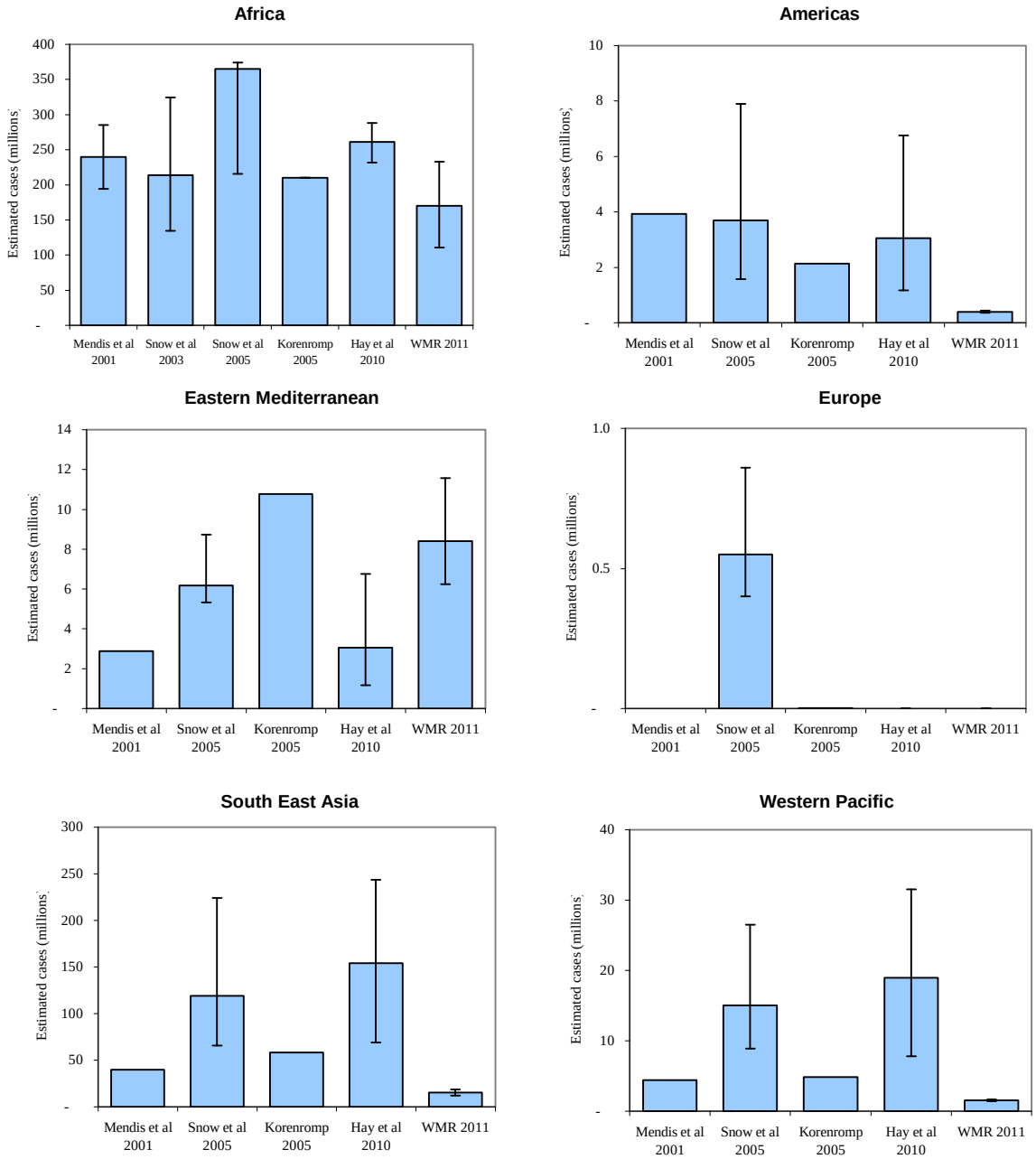
(D2) Using results of verbal autopsies and adjusting over time and space to account for progress in intervention coverage (Rowe *et al* 2005, Black *et al* 2008, IHME unpublished)

(D3) Using an estimated number of cases and multiplying by an estimated case fatality rate (World Malaria Report 2011).

WHO uses a combination of approaches. Outside of Africa - and for a small number of countries in Africa where data from routine health information systems is considered sufficiently reliable - WHO uses method C4 for cases and method D3 for deaths. For countries where data from routine health information systems is not sufficiently complete WHO uses C2 for cases and D2 for deaths; in practice methods C2 and D2 are limited to countries in sub-Saharan Africa. In the estimation of deaths in sub-Saharan Africa, the number of malaria deaths under age 5 is estimated by the Child Health Epidemiology Reference Group (CHERG), while adult deaths are inferred from an empirical relationship between endemicity and the proportion of deaths that occur in children.

The different approaches have resulted in disparate sets of estimates globally, regionally and at country level particularly outside of Africa (see Figure 1).

Figure 1. Estimated number of *P. falciparum* malaria cases according to different sources



For malaria-related deaths, a particular issue concerns the proportion occurring in adults. In 2007 WHO noted that a high proportion of deaths recorded in the Medical Certification of Cause of Death (MCCD) system in India were in adults. This seemed unusual given the current understanding of malaria epidemiology. Accordingly, WHO commissioned a small study to determine if the malaria deaths recorded in 6 Indian hospitals were truly due to malaria. The study was undertaken by Prabhat Jha and colleagues of the Centre for Global Health Research, University of Toronto, Canada and found that of 30 malaria deaths that had received a parasitological test, only 15 were test positive, raising doubts about the accuracy of medical certification. When the validation study was extended to look at the results of verbal autopsy, it found that of 48 deaths classified as malaria by verbal autopsy that had also attended hospital only 4 had a medical diagnosis of malaria. The majority of deaths classified as malaria by verbal autopsy were recorded as septicaemia in medical records. Despite these results, verbal autopsy results were considered to be reliable and a paper was published in the Lancet claiming there are approximately 200,000 deaths in India (Dhingra et al 2010);WHO's estimate for the same period is approximately 24,000.

In the near future, a paper will be published by IHME in the Lancet claiming that there were 1.4 million deaths from malaria globally in 2010 -- compared to 655,000 estimated by WHO. The numbers of deaths estimated by IHME for under 5's in Africa (700,000) is similar to WHO (560,000) but IHME has estimated many more deaths in adults in Africa (450,000 versus 55,000) and many more deaths outside of Africa (280,000 versus 58,000 of which 223,000 are in adults). In support of their work, IHME undertook a "Gold Standard" validation study to assess the sensitivity and specificity of verbal autopsy in four countries. In most sites, however, there was little or no malaria[1] and in the one site where malaria deaths might be expected, Dar es Salaam, the quality of diagnostic testing has been questioned (Kahama-Maro J et al).

IHME's estimates for the numbers of cases (223 million globally in 2010) are similar to WHO's (216 million), implying that case fatality rates are higher than those assumed by WHO, particularly in adults.

MPAC Decision Point

Given the current lack of consensus on estimates of cases and deaths WHO proposes to establish an Expert Review Group (ERG) to examine approaches to burden estimation with a view to identifying procedures that:

- Provide robust burden estimates around which there is consensus
- Are open/ transparent
- Can be readily updated to reflect latest situations e.g. changes in program coverage
- Can be applied by endemic countries

[1] Mexico (no malaria deaths), Philippines (an island with no malaria), India (areas with very little malaria), Tanzania - Pemba (few if any malaria deaths) and Dar es Salaam (relatively light malaria burden).

Advice is sought on how this group should operate and on what particular studies may be required to resolve issues of contention. If endorsed, the ERG would report back to the MPAC at its second meeting in 2012.

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WHO/GMP TECHNICAL EXPERT GROUP ON PREVENTIVE CHEMOTHERAPY, *Geneva 4-6 May 2011*

Report of the Technical consultation on Seasonal Malaria Chemoprevention (SMC) /

Chimio-prévention saisonnière du paludisme (CSP)

Background

Across the Sahel region falciparum malaria is a major cause of childhood death. Most of the malaria mortality and morbidity occurs in short rainy season. Giving effective malaria chemoprevention during this period has been shown to prevent illness and death from malaria in children.

Seasonal malaria chemoprevention (SMC) previously referred to as Intermittent preventive treatment in children (IPTc) is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk.

A group of researchers who have worked on IPTc established a task force (IPTc Working Group) to collate and summarize data on the efficacy, safety, tolerability, acceptability and affordability of IPTc.

As a first step in the policy making process of the Global Malaria Programme (GMP), the Technical Expert Group (TEG) on Preventive Chemotherapy was convened to review the evidence compiled by the IPTc Working Group. The objective was to formulate recommendations which will be presented to the newly established Policy Advisory Committee of the Department in order to formulate a WHO policy on the role of SMC as a potential in malaria control strategy for children.

The specific objectives of the consultation were:

- To review the current evidence on efficacy, safety and large-scale implementability of SMC, and assess the risks and potential benefits of SMC for use as an additional malaria control strategy in different malaria epidemiological settings.
- Based on this assessment, to advise WHO on the potential role of SMC as a malaria control strategy.
- To identify the critical gaps in knowledge and priority research agendas for the implementation of SMC as a WHO malaria control strategy if recommended.

Eight randomized controlled trials (7 published and 1 unpublished, (Table 1)) in children aged between 3 and 59 months during the rainy season comparing treatment doses of amodiaquine-sulfadoxine-pyrimethamine (AQ-SP) at monthly or two monthly intervals versus no treatment conducted in several

countries in west Africa were included in the analysis for protective efficacy. The end points for the analysis were

1. Uncomplicated clinical malaria (defined as fever or a history of fever plus any level of *P.falciparum* parasitaemia) during the period of drug administration and one month following the last SMC course.

2. Severe malaria (defined as per the WHO definition[1] during the period of drug administration and one month following the last SMC course) (WHO, 2000).

3. Moderate anaemia (Hb < 8g/dL) at the cross-sectional survey at the end of the intervention period (approximately one month following the last SMC course).

4. All-cause mortality during the period of drug administration and one month following the last SMC course.

Table 1 – List of studies included in the analysis of protective efficacy

Study	**Site**	**Drug Regimen**
Cisse *et al*, 2006[2]	Niakhar, Senegal	AS+SP monthly
Dicko *et al*, 2008[3]	Kambila, Mali	SP bimonthly
Kweku *et al*,2008[4]	Hohoe, Ghana	AS+AQ monthly
Bojang *et al*, 2010[5]	Basse, The Gambia	SP+AQ monthly SP+PQ monthly DHA+PQ monthly
Dicko *et al*, 2011[6]	Kati Region, Mali	SP+AQ monthly
Konate *et al*, 2011[7]	Bousse District, Burkina Faso	SP+AQ monthly
Sesay *et al*, 2011[8]	Farafenni, The Gambia	SP+AQ monthly
Zongo *et al*, unpub.	Bobo Dioulasso, Burkina Faso	SP+AQ monthly DHA+PQ monthly

SP: sulphadoxine-pyrimethamine, AS: artesunate, AQ: amodiaquine, PQ: piperaquine, DHA: dihydroartemisinin

Conclusions

The summary of the conclusions of the evidence review by the TEG are as follows:

1. Monthly or bimonthly administered SMC regimens (irrespective of the drug used) showed a protective effect of SMC against clinical malaria of 78% [95%CI: 69% to 84%, p<0.001]. A slightly higher protective effect against clinical malaria was found when the analysis was restricted to monthly administered SMC (all drugs) [PE=83%, 95%CI: 78% to 87%, p<0.001] or monthly administered SP+AQ only [PE=83%, 95%CI: 72% to 89%, p<0.001]. The benefit was observed also in areas with good ITN coverage.

2. Monthly administered SMC using any drug regimen had a protective efficacy (PE) of 61% (95% CI: 15% to 82%, p=0.02) against severe malaria, defined as an episode of malaria which met the WHO definition of severe malaria or which resulted in hospital admission. A higher PE against severe malaria was demonstrated using monthly administered SP+AQ alone [PE=77%, 95% CI: 45% to 90%, p<0.001].

3. Monthly administered SMC (all regimens) and monthly administered SP+AQ gave a PE against moderate anaemia (Hb <8g/dl) of 20% [95% CI: -5% to 38%, p=0.11] and 29% [95% CI: -11% to 54%, p=0.14] respectively.

4. There were no serious adverse events reported attributed to SMC in over 900,000 treatment courses. Only a small number of deaths were observed in the eight controlled studies during the intervention period limiting possible evaluation of the effect of SMC against all-cause mortality, although the results are consistent with a protective effect and do not exclude a substantial benefit. Monthly administered SMC and monthly administered SMC using SP+AQ gave a pooled protective efficacy against all cause mortality of 18% (95% CI: -69% to 61%, p=0.58) and 34%, (95% CI: -73% to 75%, p=0.40) respectively.

5. A high level of protection against uncomplicated clinical malaria (defined as fever or a history of fever with parasitaemia at any density) was maintained for 4 weeks after the administration of each treatment with SP+AQ; thereafter protection decayed rapidly. The cumulative efficacy over 21 days was 91% and over 28 days it was 86%. This duration of protection was also demonstrated for severe malaria (mainly cerebral malaria and severe anaemia)

6. Age based dosing schemes used either a half or whole tablet. There was no association between efficacy and the dose of SP given, however there was an association between AQ dose and malaria incidence, the effect being most marked in children under 2 years of age. There is evidence of a moderate increase in the incidence of vomiting when the

dose of AQ given exceeds the maximum recommended value (>15mg/kg daily). To ensure maximum efficacy balanced with tolerability, and for effective wide-scale deployment, a dosing scheme using either a half or a whole tablet is ideal. For AQ, a regimen of ½ of a 153mg tablet should be used in infants <12 months old, and a full tablet in those aged 12-59 months. Use of a similar age regimen for SP tablets ensures that the majority of children receive the recommended minimum SP dose of 25/1.25mg/kg.

7. Analysis of the costs of delivering SMC suggest that in areas where the incidence of malaria in children in the target age group is above 0.2 attacks of malaria per transmission season, SMC will be a highly cost-effective intervention as assessed by both the cost of a case and a DALY prevented. In areas where the incidence of clinical attacks of malaria in children is between 0.1 and 0.2 attacks per transmission season, SMC may still be an attractive option although relatively more expensive. At an incidence rate of less than 0.1 clinical attacks per transmission season, SMC is unlikely to be a cost effective intervention.

Recommendations

The committee made the following recommendations -

- A complete treatment course of AQ+SP at monthly intervals to a maximum of four doses during the malaria transmission season should be given to children aged between 3 and 59 months as Seasonal Malaria Chemoprevention in areas of highly seasonal malaria transmission across the West Africa Sahel Sub-Region (where both drugs retain sufficient antimalarial efficacy).

- Target areas for implementation are areas where

    - more than 60% of clinical malaria cases occur within a maximum of 4 months,

    - the clinical attack rate of malaria is greater than 0.1 attack per transmission season in the target age group, and

    - AQ+SP remains efficacious (>90% efficacy[*])

*(*Note in some countries, the eligibility for SMC deployment might apply only to part of their malaria endemic area).*

- A complete treatment course of AQ+SP should be dosed at monthly intervals to a maximum of 4 doses a year (transmission season). The recommended dosing schedule is AQ - ½ of a 153mg tablet for infants <12 months old, and a full tablet in those aged 12-59 months given once daily for three days; and a single dose of SP - ½ of a 500/25mg tablet for infants and a full tablet for children aged between 12 and 59 months. Administration of at least the first dose of AQ and the SP dose must be directly observed, and efforts to ensure adherence to the full three day course of AQ strengthened.

- For maximum protection and to minimize selection for drug resistance, children should receive preventive treatments each month during the transmission period, and should comply to the complete 3-days treatment course each month.

- Treatment of breakthrough malaria infection during the course of SMC should not include either AQ or SP.

[*] Based on therapeutic efficacy assessment in children under 5 years of aged using the WHO therapeutic efficacy testing protocol

- Intermittent Preventive Treatment with SP in infancy and SMC should not be administered concomitantly. Therefore in target areas for SMC, IPTi should not be deployed.

- SMC Contraindications:

    - HIV positive children receiving co-trimoxazole.

    - Subject has received a dose of either AQ or SP drug during the past month.

    - Allergy to either drug (AQ or SP).

- Other considerations

    - While there are several potential approaches to implement this strategy, there is presently insufficient evidence to recommend a standard deployment strategy. However, the committee strongly recommends integration into existing programmes, such as the integrated Community Case Management and other Community Health Workers schemes.

    - In areas where SMC is deployed,

        - pharmacovigilance should be strengthened or instituted,

        - drug resistance monitoring and system evaluation should be supported or instituted, including systems to assess the number of breakthrough infections and their intervals from the last dose of SMC,

        - the health system needs to record and monitor AQ+SP doses administered in order to evaluate the impact of the intervention. Existing systems to document severe malaria, malaria deaths, and record confirmed cases of malaria should be strengthened.

Research gaps

Although there is evidence to support the initiation of SMC, there are still practical questions concerning the roll out of this additional malaria intervention. The committee did not feel that these questions should limit the imminent roll out and deployment of SMC, but can be incorporated into the implementation of the program. These include:

- Drug related

    - Are there alternative dosing regimens for SMC?

- Pharmacology studies are required to inform optimum dosing, assess the prophylactic responses, evaluate adverse effects, and characterize relevant drug interactions
- Toxicity studies are needed to determine the risks of AQ related neutropenia and hepatotoxicity from repeat dosing of AQ for SMC
- Studies of other age groups are needed to inform policies in other regions.

- Health and socioeconomic Impact
  - Implementation research on acceptability, implementation strategies and impact assessment
    - Is there an impact on malaria transmission?

- Monitoring and evaluation
  - How should SMC be evaluated and how can effectiveness thresholds be defined and set to guide starting, stopping, or changing the strategy?

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Annex 1

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***** Declaration of Interest.***

The members of the Technical Expert Group (a standing committee of GMP,) along with other invited participants attending the technical consultation on Seasonal Malaria Chemoprevention reported relevant interests, in accordance with the WHO procedures. All declared interest was discussed before the start of the meeting. All members of the TEG (core and co-opted members) reported no interest relevant to the meeting.

However, of note are the members of the IPTc taskforce (a group of researchers who have undertaken the studies on IPTc) who were invited to the meeting solely to present the results of the studies and clarifications as required to the committee, and where not a part of the review panel. The members of the Task force were thus excluded from the discussions and formulation of recommendations. Sections of the meeting with discussions related to recommendations was conducted exclusively as a closed door section of the TEG and excluded the members of the IPTc Task Force and observers.

Seasonal Malaria Chemoprevention (formally known as Intermittent Preventive Treatment in children) for preventing malaria morbidity in children aged less than 5 years living in areas of marked seasonal transmission

GRADE tables to assist guideline development and recommendations

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Plain Language Summary of Results

Seasonal chemoprevention given to children aged < 5 years in areas of marked seasonal malaria transmission:

- Prevents approximately 75% of all malaria episodes *(high quality evidence)*
- Prevents approximately 75% of severe malaria episodes *(high quality evidence)*
- Probably produces a small decrease in child mortality of around 1 in 1000 *(moderate quality evidence).*
- Probably reduces the incidence of moderately severe anaemia *(moderate quality evidence)*
- Does not result in an increase in clinical malaria in the following malaria transmission season *(high quality evidence)*
- Does not result in an increase in moderately severe anaemia in the following transmission season *(moderate quality evidence)*
- Probably does not result in rebound increase in mortality in the following malaria transmission season *(moderate quality evidence)*

In addition:

Serious adverse events have not been reported and are probably rare *(moderate quality evidence)*

There is increased vomiting with amodiaquine plus sulfadoxine-pyrimethamine *(high quality evidence)*

These effects are still present even when ITN use is high *(high quality evidence)*

Date: 26 October 2011

Definitions

Seasonal malaria chemoprevention (formally known as 'Intermittent Preventive Treatment of Malaria* (IPT)') is currently defined as 'the administration of a full curative dose of an antimalarial or antimalarial combination to a selected, target population at specified times without determining whether or not the subject is infected'.[1]

'Marked seasonality' is defined by the World Health Organization for the purposes of SCM, as an area where 60% of clinical malaria cases occur within 4 months of the year or less.[2]

GRADE approach

In July 2011, we updated the Cochrane systematic review of randomized controlled trials comparing seasonal chemoprevention with placebo, or no seasonal chemoprevention. The results of this review and an assessment of the quality of evidence they provide is presented in five GRADE tables, addressing the following questions:

In malaria endemic areas with marked seasonality:

- Does seasonal chemoprevention reduce all-cause mortality and malaria morbidity in children aged less than 5 years? Table 1
- After stopping seasonal chemoprevention is there a rebound increase in all-cause mortality and malaria morbidity during the following malaria transmission season? Table 2
- Is seasonal chemoprevention still effective in settings where ITN coverage is high? Table 3
- Is seasonal chemoprevention still effective where home-based management of malaria is practiced? Table 4
- Is amodiaquine plus sulphadoxine-pyrimethamine (AQ+SP) an effective and safe option for seasonal chemoprevention Table 5

The GRADE system considers 'quality' to be a judgment of the extent to which we can be confident that the estimates of effect are correct. The level of 'quality' is judged on a 4-point scale. Evidence from randomized controlled studies is initially graded as HIGH and downgraded by one, two or three levels after full consideration of : any limitations in the design of the studies, the directness (or applicability) of the evidence, and the consistency and precision of the results.

High:	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low:	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low:	We are very uncertain about the estimate.

In moving from evidence to formulating recommendations the panel should consider the following factors:

- The quality of the evidence
- The balance of benefits and harms
- Values and preferences
- The resource implications

There are two strengths of recommendation:[3]

- A STRONG recommendation: Implies that the recommendation can be applied in most settings (with marked seasonal transmission)
- A WEAK or CONDITIONAL recommendation: Implies that local policy will require further debate and stakeholder involvement

[1] Greenwood B. Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas. Malaria Journal 2010;9(Suppl 3):S2.
[2] WHO, Report of the Technical Expert Group Consultation on Seasonal Malaria Chemoprevention; Geneva, 4-6 May 2010.
[3] Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. GRADE Working Group. Rating quality of evidence and strength of recommendations: Going from evidence to recommendations. BMJ. 2008 May 10;336(7652):1049-51

Question 1. Does seasonal chemoprevention reduce all-cause mortality and malaria morbidity in children aged < 5 years?

Setting: Areas with marked seasonal malaria transmission

Reference: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							No of events/patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seasonal chemoprevention	Control	Relative (95% CI)	Absolute		
Clinical malaria												
6	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	none	0.7 episodes per child per year	2.5 episodes per child per year[5]	Rate Ratio 0.26 (0.17 to 0.38)	1.8 fewer episodes per child per year (from 1.6 fewer to 2.1 fewer)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria												
2	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness[7]	no serious imprecision[4]	none	9 episodes per 1000 children per year	35 episodes per 1000 children per year[8]	Rate Ratio 0.25 (0.1 to 0.68)	26 fewer episodes per 1000 children per year (from 11 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	Critical
Death from any cause												
6	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[3]	serious[9]	none	10/4751 (0.21%)	16/4782 (0.33%)[10]	RR 0.66 (0.31 to 1.39)	1 fewer per 1000 (from 2 fewer to 1 more)	⊕⊕⊕O MODERATE	Important
Moderately severe anaemia												
5	randomised trials	no serious risk of bias	serious[11]	no serious indirectness	no serious imprecision	none	203/4373 (4.6%)	296/4432 (6.7%)[10]	RR 0.71 (0.52 to 0.98)	19 fewer per 1000 (from 1 fewer to 32 fewer)	⊕⊕⊕O MODERATE	Important
Serious drug-related adverse event												
6	randomised trials	no serious risk of bias[1]	no serious inconsistency[12]	no serious indirectness[3]	serious[13]	none	4751	4782	-	-	⊕⊕⊕O MODERATE	Important
Non-serious adverse event												
6	randomised trials	serious[14]	no serious inconsistency	no serious indirectness[3]	no serious imprecision	none	4751	4782	-	-	⊕⊕⊕O MODERATE	important

[1] The studies were well conducted with allocation concealment at low risk of bias in all studies, and 5 out of 6 studies were blinded and used placebos.

[2] There was substantial heterogeneity between these 6 trials. All 6 trials showed a statistically significant benefit but the magnitude of this benefit was variable. Not downgraded.

[3] The included trials were conducted in Ghana, Mali (2), The Gambia, Senegal and Burkina Faso, in areas described as 'seasonal malaria transmission'. Most studies were limited to pre-school aged children. Three studies administered monthly AQ+SP, two studies used bimonthly SP, and one study used monthly SP + AS.

[4] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

[5] The incidence of malaria in the control groups was 2.25 episodes per child per year in Senegal, 2.4 in Mali, and 2.88 in Burkina Faso.

[6] These two trials were well conducted and at low risk of bias.

[7] These trials were conducted in areas of seasonal transmission in Mali and Burkina Faso. Both trials compared SP+AQ with placebo in pre-school age children. Of note, LLITN use was high in both the intervention and control groups in both studies.

[8] The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso

[9] Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect an effect on mortality. Larger trials are necessary to have confidence in this effect. However, a reduction in death would be consistent with the high quality evidence of a reduction in severe malaria.

[10] These control group risks are taken from the sum of events and participants in the included trials.

[11] There was substantial heterogeneity between these 5 trials and the trials from Ghana and the Gambia did not show an effect. Downgraded by 1 for Inconsistency. There was no reason to downgrade for study limitations, directness or precision.

[12] All six trials reported that there was no case of drug-related serious adverse event. One trial reported that four participants were withdrawn from the treatment arm: two cases for non-severe skin rash, one for itching and another for acute respiratory infection. One trial reported skin eruptions with macular hyper-pigmentation which was neither Stevens Johnson syndrome nor any other form of severe skin lesions.

[13] Downgraded by 1 under precision. Trials of this size are underpowered to fully detect or exclude rare serious adverse events. Observation should continue once implemented.

[14] Downgraded by 1 under study limitations. All seven trials commented on observed adverse events. However, the thoroughness of the methods used to collect these data are incomplete in some of these trials. The only adverse event found to be statistically more common with seasonal chemoprevention was vomiting after AQ+SP (see GRADE table 5).

Question 2: After stopping seasonal chemoprevention is there a rebound increase in all-cause mortality or malaria morbidity during the following malaria transmission season?

Setting: Areas with marked seasonal transmission

Reference: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seasonal chemoprevention	Control	Relative (95% CI)	Absolute		
Clinical malaria												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[3]	none	2.5 episodes per child per year	2.5 episodes per child per year[4]	Rate Ratio 0.98 (0.82 to 1.17)	0 fewer episodes per child per year (from 0.5 fewer to 0.4 more)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria - not reported												
0	-	-	-	-	-	-	-	-	-	-		Critical
Death from any cause												
1	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness[6]	serious[7]	none	8/594 (1.3%)	8/613 (1.3%)[8]	RR 1.03 (0.39 to 2.73)	0 more per 1000 (from 8 fewer to 23 more)	⊕⊕⊕O MODERATE	Important
Moderately severe anaemia												
1	randomised trials	no serious risk of bias[5]	no serious inconsistency	serious indirectness[9]	no serious imprecision	none	36/376 (9.6%)	47/392 (12%)[8]	RR 0.8 (0.53 to 1.2)	24 fewer per 1000 (from 56 fewer to 24 more)	⊕⊕⊕O MODERATE	Important

[1] These trials were well conducted and considered at low risk of bias.

[2] Three trials report clinical malaria during the following malaria season when seasonal chemoprevention was not given. These were conducted in Senegal, Mali, and Ghana.

[3] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

[4] The incidence of malaria in the control groups was 2.25 episodes per child per year in Senegal, 2.4 in Mali, and 2.88 in Burkina Faso.

[5] This trial was well conducted and considered at low risk of bias.

[6] This trial was conducted in Ghana. A large reduction in clinical malaria was seen during the intervention period, following seasonal chemoprevention with either bimonthly sulfadoxine-pyrimethamine or amodiaquine plus artesunate.

[7] Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect or exclude an effect on mortality. Larger trials are necessary to have confidence that there is no increase.

[8] These control group risks are taken from the sum of events and participants in the included trials.

[9] Downgraded by 1 for indirectness: Only one trial reports the incidence of moderately severe anaemia during the following transmission season. This trial found no statistically significant benefit on anaemia during the administration of seasonal chemoprevention.

Question 3: Is seasonal chemoprevention still effective where ITN coverage is high?

Setting: Areas with marked seasonal transmission

Reference: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seasonal chemoprevention	Control	Relative (95% CI)	Absolute		
Clinical malaria - (where bed-nets are also used)												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[3]	none	0.6 episodes per child per year	2.5 episodes per child per year[4]	Rate Ratio 0.22 (0.13 to 0.38)	1.9 fewer per child per year (from 1.6 fewer to 2.2 fewer)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[3]	none	9 episodes per 1000 children per year	35 episodes per 1000 children per year[5]	Rate Ratio 0.25 (0.1 to 0.68)	26 fewer episodes per 1000 children per year (from 11 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	Critical

[1] These trials were well conducted and considered at low risk of bias.

[2] Two trials compared seasonal chemoprevention with placebo where both groups were also given insecticide treated bed-nets. These trials were conducted in Mali and Burkina Faso. ITN usage was over 99% in both groups in Mali, and 92% in both groups in Burkina Faso.

[3] There was no reason to downgrade for study limitations, insistency, directness or precision.

[4] The incidence of malaria in the control groups was 2.4 in Mali, and 2.88 in Burkina Faso.

[5] The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso

Question 4: Is seasonal chemoprevention still effective where home-based management of malaria is practiced?

Setting: Areas with marked seasonal transmission

Reference: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Seasonal chemoprevention**	**Control**	**Relative (95% CI)**	**Absolute**		
Clinical malaria - (where home-based management of malaria is used)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	0.2 episodes per child per year	0.5 episodes per child per year[4]	Rate Ratio 0.34 (0.04 to 3.05)	0.3 fewer episodes per child per year (0.5 fewer to 1.0 more)	⊕⊕OO LOW	Critical
Severe malaria- Not reported												
0	-	-	-	-	-	-	-	-	-	-	–	Critical

[1] Downgraded by 1 for risk of bias: This trial did not adequately describe the methodology to make judgements about the risk of bias.

[2] One trail conducted in Ghana compared seasonal chemoprevention with no seasonal chemoprevention in the context of an on-going programme of home-based management of malaria.

[3] Downgraded by 1 for imprecision: The result is not statistically significant.

[4] The incidence of febrile episodes (treated presumptively as malaria) in the control group was lower in this trial than seen elsewhere.

Question 5: Is amodiaquine plus sulfadoxine-pyrimethamine an effective and safe option for seasonal chemoprevention?

Setting: Areas with marked seasonal transmission

Bibliography: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amodiaquine plus sulfadoxine-pyrimethamine**	**Control**	**Relative (95% CI)**	**Absolute**		
Clinical malaria												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	none	0.6 episodes per child per year	2.5 episodes per child per year[5]	Rate Ratio 0.23 (0.14 to 0.37)	1.9 episodes fewer per child per year (from 1.6 fewer to 2.2 fewer)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[6]	no serious imprecision[7]	none	9 episodes per 1000 children per year	35 episodes per 1000 children per year[8]	Rate Ratio 0.25 (0.1 to 0.68)	26 fewer episodes per 1000 children per year (from 11 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	Critical
Death from any cause												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[3]	serious[9]	none	6/3498 (0.17%)	10/3512 (0.28%)[10]	RR 0.62 (0.23 to 1.65)	1 fewer per 1000 (from 2 fewer to 2 more)	⊕⊕⊕O MODERATE	Important
Moderately severe anaemia												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[6]	no serious imprecision[7]	none	66/2866 (2.3%)	139/2874 (4.8%)[10]	RR 0.48 (0.36 to 0.63)	25 fewer per 1000 (from 18 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	Important
Serious drug-related adverse event												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency[11]	no serious indirectness[3]	serious[12]	none	-	-	-	-	⊕⊕⊕O MODERATE	
Non-serious adverse events- vomiting												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[6]	no serious imprecision[7]	none	387/1814 (21.3%)	131/1730 (7.6%)[10]	RR 2.78 (2.31 to 3.35)	135 more per 1000 (from 99 more to 178 more)	⊕⊕⊕⊕ HIGH	

[1] The studies were well conducted with allocation concealment at low risk of bias in all studies, and all studies were blinded and used placebos.

[2] There was substantial heterogeneity between these 3 trials. All 3 trials showed a trend to favour chemoprevention but the magnitude of this benefit was variable. Not downgraded.

[3] Two trials compared seasonal chemoprevention with placebo where both groups were also given insecticide treated bed-nets. These trials were conducted in Mali and Burkina Faso. ITN usage was over 99% in both groups in Mali, and 92% in both groups in Burkina Faso. The third trial was conducted in the Gambia. All were in pre-school age children, and administered monthly SP+AQ.

[4] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

[5] The incidence of malaria in the control groups was 2.4 in Mali, and 2.88 in Burkina Faso.

[6] These trials were conducted in areas of seasonal transmission in Mali and Burkina Faso.
[7] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
[8] The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso
[9] Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect an effect on mortality. Larger trials are necessary to have confidence in this effect. However, a reduction in death would be consistent with the high quality evidence of a reduction in severe malaria.
[10] These control group risks are taken from the sum of events and participants in the included trials.
[11] All three trials reported that there was no case of drug-related serious adverse event. One trial reported that four participants were withdrawn from the treatment arm: two cases for non-severe skin rash, one for itching and another for acute respiratory infection. One trial reported skin eruptions with macular hyper-pigmentation which was neither Stevens Johnson syndrome nor any other form of severe skin lesions.
[12] Downgraded by 1 under precision. Trials of this size are underpowered to detect or exclude rare serious adverse events.

IPTc BIBLIOGRAPHY

PUBLICATIONS ON IPTc IN CHILDREN IN THE COMMUNITY UNDER FIVE YEARS OF AGE

Published

2006

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1. Cissé B, Sokhna C,Boulanger D, Milet J, Ba el H, Richardson K, Hallett R, Sutherland C, Simondon K, Simondon F, Alexander N, Gaye O, Targett G, Lines J, Greenwood B, Trape JF. Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial. Lancet 2006; 67: 659-67.

This randomised, controlled, double-blind study assessed the impact of IPTc using artesunate + sulphadoxine-pyrimethamine (SP) on the incidence of clinical malaria in over 1000 children aged 2-59 months in Senegal. IPTc led to an 86% reduction in the incidence of clinical malaria during the 13 weeks of follow up. No significant difference in the prevalence of anaemia was observed between the two study arms at the end of the intervention. The prevalence of SP resistance mutations was higher in the IPTc arm than in the placebo arm but the prevalence of drug resistant parasitaemia was lower in the IPTc arm due to a lower parasitaemia prevalence in these children. Children who received IPTc were more likely to vomit than children who received placebo but generally the intervention was well tolerated.

2. Greenwood, B. Review: Intermittent preventive treatment - a new approach to the prevention of malaria in children in areas with seasonal malaria transmission. Trop Med Int Health 2006; 11: 983-91.

This review discusses the definitions of IPT, chemoprophylaxis and mass drug administration and the potential for overlap between these forms of chemoprevention. The paper also summarises experience with IPTc and highlights future challenges and research priorities.

2007

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3. Ntab B, Cisse B, Boulanger D, Sokhna C, Targett G, Lines J, Alexander N, Trape JF, Simondon F, Greenwood BM, Simondon KB . Impact of intermittent preventive anti-malarial treatment on the growth and nutritional status of preschool children in rural Senegal (west Africa). Am J Trop Med Hyg 2007; 77: 411-17.

This study assesses the impact of IPTc on growth and nutritional status in children aged 2–59 months who participated in a randomised, double-blind, placebo-controlled trial of IPTc conducted in Senegal (Cisse at al, Lancet, 2006) Children who received IPTc gained three times as much weight as children in the placebo arm. Triceps and subcapsular skinfold thickness fell in both arms but the loss was greater in the placebo rather than the IPTc arm. IPTc did not have any effect on wasting or stunting. The study indicated that malaria prevention using IPTc in areas of seasonal transmission has the potential to improve nutritional status in children.

2008

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4. Dicko A, Sagara I, Sissoko MS, Guindo O, Diallo AL, Kone M, Toure OB, Sacko M, Doumbo OK . Impact of intermittent preventive treatment with sulphadoxine-pyrimethamine targeting the transmission season on the incidence of clinical malaria in children in Mali. Malar J 2008; 7: e123.

This study assessed the effect of IPT using sulphadoxine-pyrimethamine (SP) on the incidence of clinical malaria and anaemia in children aged 6 months – 10 years in Mali. 262 children were individually randomised to receive either IPT with two doses of SP 8 weeks apart or no IPT during the peak malaria transmission season. Children

were followed up until the end of the subsequent transmission season. IPTc with SP bimonthly had an age adjusted protective efficacy against clinical malaria of 67.5% during the 16 week intervention period, which fell to 42.5% during the 12 month follow up period. The incidence of clinical malaria during the subsequent malaria transmission season was similar among both groups of children.

5. Kweku M, Liu D, Adjuik M, Binka F, Seidu M, Greenwood B, Chandramohan D. Seasonal intermittent preventive treatment for the prevention of anaemia and malaria in Ghanaian children: a randomized, placebo controlled trial. PLoS ONE 2008; 3: e4000.

2451 children aged 3-59 months were enrolled in this study conducted in an area of perennial transmission with seasonal peaks in Ghana. Children were individually randomised to receive artesunate + amodiaquine (AS + AQ) either monthly or bimonthly, sulphadoxine-pyrimethamine (SP) bimonthly or placebo delivered by community volunteers over a period of 6 months of intense transmission. All regimens significantly reduced the incidence of malaria and anaemia compared to placebo. Monthly AS + AQ was found to be the most effective regimen, reducing the incidence of malaria by 69% and anaemia by 45%. Monthly administration of AS+AQ was more effective than bimonthly administration. No significant reductions in all-cause or malaria related hospital admissions were observed among children who received IPTc compared to those who received placebo.

6. Sokhna C, Cisse B, Bâ EH, Milligan P, Hallett R, Sutherland O, Gaye D, Boulanger K, Simondon F, Simondon G, Targett G, Lines J, Greenwood B, Trape J-F. A trial of the efficacy, safety and impact on drug resistance of four drug regimens for seasonal intermittent preventive treatment in Senegalese children. PLoS ONE 2008; 3: e1471.

This study compared the safety and efficacy of four different IPTc regimens [sulphadoxine-pyrimethamine (SP) +1 dose of artesunate (AS), SP + 3 doses of AS, SP + 3 doses of amodiaquine (AQ) or 3 doses of AQ + 3 doses of AS]. IPTc was delivered once a month on 3 occasions during the peak transmission period to a total of 2020 children. All children showed an improvement in haemoglobin concentrations and a reduction in parasite prevalence at the end of the intervention period. Children who received SP + 3 doses of AQ had the lowest incidence of clinical malaria and a lowerparasite prevalence at the end of the intervention period than children who received the other regimens. Adverse events were more common among children who received AQ-containing regimens than AS-containing regimens. Markers of resistance to SP were found in virtually all samples tested at the end of the intervention, although the parasite prevalence was low.

2009

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7. Aguas R, Lourenco JM, Gomes MG, White LJ The impact of IPTi and IPTc interventions on malaria clinical burden - *in silico* perspectives. PLoS ONE 2009; 4, e6627.

This modelling study assessed the impact of IPT in infants (IPTi), children (IPTc) and school children (IPTsc) on clinical malaria. Models were used to simulate the effects of IPTi, IPTc and IPTsc under different transmission settings, while varying the assumptions for acquisition of immunity. Data from the study conducted by Cisse et al in Senegal (Lancet, 2006) was used to parameterise one of the models. The study suggests that IPTc has a significant potential to reduce transmission, particularly in areas of low to moderate transmission, as evidenced by the reduction in clinical cases and asymptomatic infections.

8. Ahorlu CK, Koram KA, Seakey AK, Weiss MG. Effectiveness of combined intermittent preventive treatment for children and timely home treatment for malaria control. Malar J 2009; 8:e292.

This study was conducted in Ghana in an area with perennial malaria transmission with a seasonal peak during the rainy season. Community assistants delivered IPTc using artesunate (AS) + amodiaquine (AQ) every 4 months during a 12 month period to children aged 6-60 months and presumptively treated all episodes of febrile illness also using AS + AQ. All children received both interventions and a pre-post design was used with baseline and follow-up surveys for parasite prevalence and haemoglobin concentration. These surveys demonstrated a significant, beneficial effect of combining IPTc and community case management (CCMm) on both outcome

measures. The study demonstrated the feasibility of training community assistants to deliver both IPTc and CCMm.

9. Cisse B, Cairns M, Faye E, NDiaye O, Faye B, Cames Y, Cheng M, Ndiaye A, Thiaw A, Simondon K, Trape JF, Faye JL, Ndiaye JL, Gaye O, Greenwood BM, Milligan PJM. Randomized trial of piperaquine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children. PLoS ONE 2009; 4: e7164.

This study, conducted in Senegal, compared the tolerability and efficacy of three different IPTc regimens: sulphadoxine-pyrimethamine (SP) + amodiaquine (AQ), dihydroartemisinin (DHA) + piperaquine (PQ) or SP+PQ. IPTc drug regimens were given by community health workers three times during the high transmission period. A total of 1893 children were enrolled. PQ combinations were found to be better tolerated than SP + AQ with a significantly lower risk of common, mild adverse events. The risk of clinical malaria in children who received each regimen was very similar and PQ combinations were found to be non-inferior to SP + AQ. The proportion of children who carried parasites with markers of resistance to SP was low in all groups at the end of the transmission season.

10. Kweku M, Webster J, Adjuik M, Abudey S, Greenwood B, Chandramohan D. Options for the delivery of intermittent preventive treatment for malaria to children; a community randomised trial. PLoS ONE 2009; 4:e7256.

This cluster randomised study compared coverage with IPTc using sulphadoxine-pyrimethamine (SP) + amodiaquine (AQ) that could be achieved through either community based delivery using community volunteers or facility based delivery (static health facility or expanded programme on immunisation outreach teams) in Ghana. High levels of coverage were achieved with both delivery mechanisms, although the proportion of children that received at least the first dose of at least 3 courses of IPTc was slightly higher in the community delivery arm than in the facility based arm. Doses of AQ on days 2 and 3 were given to caregivers to administer at home and surveys found that over 90% of children in both arms received these doses.

2010

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11. Bojang K, Akor F, Bittaye O, Conway D, Bottomley C, Milligan P, Greenwood B. A randomised trial to compare the safety, tolerability and efficacy of three drug combinations for intermittent preventive treatment in children. PLoS ONE 2010; 5:e11225.

This study, which was conducted in The Gambia, compared the safety, tolerability and efficacy of alternative drug regimens for IPTc: sulphadoxine-pyrimethamine (SP) + amodiaquine (AQ), SP + piperaquine (PQ) and dihydroartemisinin (DHA) + PQ. A total of 1008 children were individually randomised to receive IPTc delivered by nurses in the local health centre. No drug related severe adverse events were observed and the total percentage of children who reported any adverse event was higher among a group of control children who received no medication than among study children. Comparison of the incidence of clinical malaria in an age matched group of control children from nearby villages allowed estimation of the protective efficacy of each of the drug regimens. The protective efficacy against clinical malaria was 87% for DHA+PQ and 93% for both SP + AQ and SP + PQ.

12. Boulanger D, Sarr JB, Fillol F, Sokhna C, Cisse B, Schacht AM, Trape JF, Riveau G, Simondon F, Greenwood B, Remoué F. Immunological consequences of intermittent preventive treatment against malaria in Senegalese preschool children. Malar J 2010; 9: e363.

This study assessed whether IPTc increases children's susceptibility to subsequent malaria infection by altering their anti-Plasmodium acquired immunity. IgG antibody responses to P. falciparum schizont extract were measured in Senegalese children who had received IPTc using artesunate + sulphadoxine-pyrimethamine or placebo eight months earlier. Anti-schizont antibody responses were slightly lower among children who had received IPTc. In a multivariate model, parasitaemia, past malaria morbidity and increasing age were strongly associated with a higher specific IgG response. Carriage of Plasmodium appeared to be the key factor

influencing anti-schizont IgG responses, irrespective of the preventive treatment received, although the possibility of some contributory effect from the anti-malarial drugs used for IPT could not be completely excluded.

13. Gosling RD, Cairns ME, Chico RM, Chandramohan D. Intermittent preventive treatment against malaria: an update. Expert Rev Anti Infect Ther 2010; 8:589-606.

This paper reviews three IPT strategies, namely IPT in pregnancy (IPTp), IPT in infants (IPTi) and IPT in children (IPTc), focusing on the mechanism of action, choice of drugs available, controversies and future research.

14. Cairns M, Cisse B, Sokhna C, Cames C, Simondon K, Ba EH, Trape J-F, Gaye O, Greenwood BM, Milligan PJM. Amodiaquine dosage and tolerability for intermittent preventive treatment to prevent malaria in children. Antimicrob Agents and Chemother 2010; 54: 1265-1274.

This study determined the association between amodiaquine (AQ) dosage by body weight and the incidence of mild adverse events using data from two trials of IPTc using sulphadoxine-pyrimethamine (SP) + AQ in Senegal. In one of these trials the dose of AQ was determined by age and in the other the dose was determined by body weight. Both dosage strategies resulted in some children receiving AQ doses above the recommended therapeutic range. The odds of vomiting increased with increasing AQ dosage and, in one study, the incidence of fever also increased with increasing dosage. Simple amendments to the age based dosing schedule could increase the tolerability of IPTc using SP +AQ in situations where weighing the child is impractical.

15. Conteh L, Patouillard E, Kweku M, Legood R, Greenwood B, Chandramohan D. Cost effectiveness of seasonal intermittent preventive treatment using amodiaquine and artesunate or sulphadoxine-pyrimethamine in Ghanaian children. PLoS ONE 2010; 5:e12223.

This study assessed the cost effectiveness of IPTc using either artesunate (AS) + amodiaquine (AQ) administered monthly or bimonthly, sulphadoxine-pyrimethamine (SP) administered bimonthly or placebo delivered by community volunteers in Hohoe, Ghana (Kweku et al, PLoS ONE, 2008). Economic costs per child who received at least the first dose of each course were lowest for SP bimonthly, followed by AS + AQ bimonthly and then AS + AQ monthly. In this study, AS + AQ administered monthly was the most cost effective regimen due to its substantially higher protective efficacy against clinical malaria. The cost per child enrolled fell substantially when scale up to district level was modelled.

16. Liljander A, Chandramohan D, Kweku M, Olsson D, Montgomery SM, Greenwood B, Färnert A. Influences of intermittent preventive treatment and persistent multiclonal *Plasmodium falciparum* infections on clinical malaria risk. PLoS ONE 2010; 5:e13649.

This study f used samples collected during an IPTc trial conducted in Hohoe, Ghana (Kweku et al, PLoS ONE, 2008) to assess how IPTc affects the genetic diversity of P. falciparum infections and the risk of clinical malaria in the 12 months following the intervention. Effective seasonal IPT temporarily reduced the prevalence and genetic diversity of P. falciparum infections as measured by genotyping of the merozoite surface protein 2 gene. The reduced risk of malaria in children with multiclonal infections seen only in untreated children suggests that persistence of antigenically diverse P. falciparum infections is important for the maintenance of protective malaria immunity in high transmission settings.

17. Tagbor H, Cairns M, Nakwa E, Browne E, Sarkodie B, Counihan H, Meek S, Chandramohan D. The clinical impact of combining intermittent preventive treatment with home management of malaria in children aged below 5 years: cluster randomised trial. Trop Med Int Health 2010; 16: 280-289

This study, conducted in the middle belt of Ghana, randomised 13 communities to receive home management of malaria with artesunate (AS) + amodiaquine (AQ) with our without the addition of three courses of IPTc with AS + AQ delivered at two monthly intervals during the peak transmission period. Malaria experience in approximately 700 children in each group was compared during the six month period peak transmission period.

IPTc resulted in a 62% reduction in presumptive cases of malaria but had no effect on anaemia. Malaria diagnosis was presumptive and not confirmed by malaria microscopy or a rapid diagnostic test.

2011

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18. Beeson JG, Rogerson SJ, Mueller I, Richards JS, Fowkes FJ. Intermittent preventive treatment to reduce the burden of malaria in children: new evidence on integration and delivery. PLoS Med 2011; 8: e1000410.

A commentary which discusses new evidence published in PLoS Medicine on potential delivery mechanisms for IPTc (Bojang et al), as well and on integration of IPTc with other malaria control interventions such as ITNs (Dicko et al and Konaté et al).

19. Bojang KA, Akor F, Conteh L, Webb E, Bittaye O, Conway DJ, Jasseh M, Wiseman V, Milligan PJ, Greenwood B. Two strategies for the delivery of IPTc in an area of seasonal malaria transmission in The Gambia: a randomised controlled trial. PLoS Med 2011;8:e1000409.

This cluster-randomised study assessed the effectiveness of IPTc using sulphadoxine-pyrimethamine + amodiaquine in children aged up to five years when delivered by village health workers (VHWs) or reproductive and child health trekking teams in The Gambia. Delivery by village health workers showed a substantially higher level of coverage with three courses of IPTc than delivery by the trekking team (74% versus 48%) primarily because the VHWs could more easily follow up children who missed doses due to their presence in the community. Delivery of IPTc by VHWs was less costly in both economic and financial terms compared to delivery by the trekking team. A nested case control study indicated a substantial protective efficacy of IPTc against clinical malaria of 87%.

20. Dicko A, Diallo AI, Tembine I, Dicko Y, Dara N, Sidibe Y, Santara G, Diawara H, Conaré T, Djimde A, Chandramohan D, Cousens S, Milligan PJ, Diallo DA, Doumbo OK, Greenwood B. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Mali: a randomised, double-blind, placebo-controlled trial. PLoS Med 2011; 8:e1000407.

This study, conducted in over 3000 children aged up to five years in Mali, assessed whether IPTc provides additional protection to children sleeping under an ITN. Children were individually randomised to receive an ITN plus either three rounds of IPTc using sulphadoxine-pyrimethamine + amodiaquine or placebo during the high transmission season. A highly significant protective efficacy of 82% against clinical episodes of malaria was observed in the IPTc + ITN arm compared to ITN alone group. Beneficial effects on severe malaria, as well as parasitaemia and moderately severe anaemia at the end of the transmission season were also observed. No serious adverse events were observed and adverse events were similar between arms.

21. Konaté AT, Yaro JB, Ouédraogo AZ, Diarra A, Gansané A, Soulama I, Kangoyé DT, Kaboré Y, Ouédraogo E, Ouédraogo A, Tiono AB, Ouédraogo IN, Chandramohan D, Cousens S, Milligan PJ, Sirima SB, Greenwood B, Diallo DA. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Burkina Faso: a randomised, double-blind, placebo-controlled trial. PLoS Med 2011; 8: e1000408.

This individually randomised, placebo controlled study assessed the additive benefit of providing IPTc with sulphadoxine-pyrimethamine + amodiaquine to children aged up to five years sleeping under an ITN in Burkina Faso. A total of over 3000 children were enrolled in the study. IPTc had a protective efficacy of 70% against clinical malaria, a protective efficacy of 69% against severe malaria and reduced all-cause hospital admissions by 46% compared to the ITN + placebo arm. Beneficial effects on the prevalence of parasitaemia and moderately severe anaemia at the end of the transmission season were also observed.

22. Sesay S, Milligan P, Touray E, Sowe M, Webb EL, Greenwood BM, Bojang KA. A trial of intermittent preventive treatment and home-based management of malaria in a rural area of The Gambia. Malar J 2011; 10:e2.

This study assessed whether there is an additive effect of administering IPTc with sulphadoxine-pyrimethamine + amodiaquine to children aged under five years on top of an existing home management programme using arthemeter-lumefantrine treatment for clinical episodes of malaria delivered by village health workers in The Gambia. A protective efficacy against clinical malaria of IPTc of 66% was observed, but this result was not significant as a result of the extremely low incidence of clinical malaria in the study area. The study found that village health workers were able to deliver both interventions successfully with 94% of study children receiving at least the first dose of all three IPTc courses.

23. Wilson AL. A systematic review and meta-analysis of the efficacy and safety of intermittent preventive treatment in children (IPTc). PLoS ONE; 6:e16976.

This paper describes a systematic review and meta-analysis of IPTc studies. Twelve relevant studies were identified. Meta-analysis showed an overall protective efficacy of monthly administered IPTc against clinical malaria of 82% during the transmission season. IPTc reduced all-cause mortality during the transmission season by over a half, although the number of deaths was relatively small. No serious adverse events attributable to IPTc were observed in any of the twelve studies. Meta-analysis of data from three studies indicated a slight increase in the incidence of clinical malaria in the transmission season in the year following IPTc administration.

24. Ross A, Maire N, Sicuri E, Smith T, Conteh L (2011) Determinants of the Cost-Effectiveness of Intermittent Preventive Treatment for Malaria in Infants and Children. PLoS ONE 6(4): e18391.

A comprehensive individual-based model fitted to data from sites across sub-Saharan Africa was used to simulate the epidemiological impact and cost-effectiveness of IPTi and IPTc varying characteristics of the setting, drug or implementation. Cost components were taken from economic evaluations of published trials. The numbers of DALYs averted by IPTc were driven mainly by the predicted effect on deaths. IPTc was cost-effective, defined using the threshold suggested by the World Bank of US2009$223 per DALY, in most of the simulated scenarios. Cost-effectiveness was predicted to decrease with low transmission, badly timed seasonal delivery in a seasonal setting, shorter-acting and more expensive drugs, higher frequencies of drug resistance and high levels of treatment of malaria fevers. The number of DALYs averted was predicted to decrease if the five-year age band for IPTc was shifted from children under five into older children, except in settings with very low transmission intensities.

In Press

Under Review

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25. Cairns M, Ghani A, Okell L, Gosling R, Carneiro I, Anto F, Asoala V, Owusu-Agyei S, Greenwood BM, Chandramohan D, Milligan PJM. Modelling the protective efficacy of alternative delivery schedules for intermittent preventive treatment of malaria in infants and children. PLoS One

This paper describes a modelling study in which the protective efficacy of IPT in infants (IPTi) and children (IPTc) using alternative delivery strategies was estimated for a range of epidemiological scenarios. The model was parameterised with data from Navrongo, Ghana where, although transmission is seasonal, there is some transmission all year round. In Navrongo, the predicted protective efficacy against clinical attacks of malaria at 24 months of age was 26.1% with 4 courses of seasonal IPTc compared to 15.6% with 4 courses of IPTi linked to EPI. Post treatment prophylaxis following the use of long acting artemisinin combination therapies (ACT) for case management may provide a similar level of protection to IPTi. Both IPT strategies will be more protective if combined with long acting ACTs.

26. Greenwood B, Bojang, K, Tagbor H, Pagnoni F. Community case management (home management) and intermittent preventive treatment of malaria in children. Trends Parasitol.

This paper reviews the current evidence on community case management of malaria (CCMm) and IPTc and discusses the potential for combining these two interventions. Evidence from three studies which combined IPTc and CCMm are reviewed. In areas of seasonal transmission where IPT is an appropriate intervention, community health workers could deliver IPTc during the peak transmission season and also provide CCMm during this period and throughout the year when occasional cases of malaria may occur.

27. NDiaye JL, Cisse B, Ba EH, Gomis JF, Molez JF, Fall FB, Sokhna C, Faye B, Kouevijdin E, Niane FK, Cairns M, Trape JF, Gaye O, Greenwood BM, Milligan PJM. Safety of seasonal intermittent preventive treatment against malaria with sulfadoxine pyrimethamine and amodiaquine when delivered to children under 10 years of age by district health staff in Senegal. PLoS Med.

The study aimed to evaluate the safety and effectiveness of IPTc using sulphadoxine-pyrimethamine (SP) + amodiaquine (AQ) in children aged below ten years when delivered by district health staff on a large scale in three rural districts in Senegal. A surveillance system was set up in order to record all deaths, malaria cases diagnosed in health facilities and adverse events. No severe adverse events attributable to IPTc have been observed during a two-year period in which 313,000 courses of IPTc have been administered. The study demonstrates that IPTc using SP + AQ is safe and well tolerated when delivered on a large scale.

28. Pitt C; Conteh L; Diawara H; Ouédraogo D J; Diarra S; Kaboré H; KouélaK; Traoré A; Dicko A; Konaté A; Chandramohan D; Diallo D; Greenwood B. Intermittent preventive treatment of malaria in children (IPTc): a qualitative study of Community Perceptions and Recommendations in Burkina Faso and Mali. PLoS ONE.

This paper presents the results of a qualitative study of community perceptions of IPTc in the context of two clinical trials conducted in Mali and Burkina Faso assessing the added benefit of IPTc to children sleeping under an ITN. In-depth interviews and focus group discussions were held with caregivers and community health workers. Participants observed significant reductions in malaria in children, which they attributed to IPTc. Participants did not express any concerns about the specific drug combination used or about the concept of providing tablets to children without clinical symptoms of malaria. There was no evidence that IPTc was perceived as a substitute for bed net usage, nor did it inhibit care seeking. In these two clinical trials, IPTc (including doses of AQ on days 2 and 3) was delivered by the research team at the local health centre. However, many caregivers stated that they would prefer delivery from a fixed point in the village.

29. Dicko A *et al*. Morbidity from malaria in children in Mali in the year after receiving intermittent preventive treatment of malaria with sulphadoxine pyrimethamine plus amodiaquine. PloS ONE

This study determined whether administration of IPTc was associated with a subsequent increase in incidence of malaria by continuing surveillance for clinical malaria during the post- intervention malaria transmission season. In the intervention year, study children were randomised to receive and ITN and ITPc with either active drugs or placebo (Dicko et al, Plos Med, 2011). There was a small increase in risk of clinical malaria during the post intervention malaria transmission season (Relative Risk 1.09) which was more marked in younger children but the benefit of IPTc was maintained over the 24 month period of follow-up.

30. Konaté AT *et al*. Morbidity from malaria in children in Burkina Faso in the year after receiving intermittent preventive treatment of malaria with sulphadoxine pyrimethamine plus amodiaquine.

This study determined whether administration of IPTc was associated with a subsequent increase in incidence of malaria by continuing surveillance for clinical malaria during the post- intervention malaria transmission season. In the intervention year, study children were randomised to receive and ITN and ITPc with either active drugs or placebo (Konate et al, Plos Med, 2011). Ninety-four percent of children enrolled were followed for a second year. A slight increase in clinical malaria was observed in the post intervention period (Relative Risk 1.12) but this did not offset the beneficial effect of IPTc during the intervention period. Over the whole 16 month period following administration of the first IPTc dose there was still a significant protective effect of IPTc, which was

more marked in the younger children. At the end of the year 2 transmission season, there was no increase in the risk of moderately severe anaemia, wasting, stunting or underweight among children who had received IPTc.

31. Patouillard E, Conteh L, Webster J, Kweku M, Greenwood BM, Chandramohan D. Economic costs of IPTc coverage and adherence under 2 different delivery systems. PLoS One

This costing study is a component of a community randomized trial designed to assess the effectiveness of IPTc in terms of adherence obtained through 2 different delivery system: a facility-based system, including health facility or EPI outreach team and a community-based system by volunteers (Kweku et al, PLoS ONE, 2009). For each of the delivery systems, economic and financial total costs were calculated from the perspective of the health care provider (Ministry of Health). Under the facility-based delivery system, the main economic cost categories were personnel cost for dispensing IPTc to children, supervision cost and cost for delivering IPTc to the distribution points; under the community-based delivery system, the main cost categories were supervision cost, transport cost for delivering IPTc drugs to the distribution points and personnel cost for dispensing IPTc to children. The following economic unit costs are presented and compared across delivery systems: the cost per child "fully" covered; the cost per child "acceptably" covered; the cost per "fully" adherent child; and finally the cost per "acceptably" adherent child.

In Preparation

Cisse B, Dial Y, Faye S, Conteh L, Coggle S, NDiaye M, Faye O, Gaye O, Greenwood BM, Milligan PJM Pilot Study of the Implementation of Seasonal Intermittent Preventive Treatment in Children (IPTc) with Community Participation in Senegal.

The aim of this pilot study was to investigate the feasibility of delivering IPT to children in rural areas through the routine health service, and the acceptability of the intervention to communities, prior to a large-scale implementation study. Consultations with health staff at regional and local level were held to identify an appropriate method of delivery, which was then piloted during one transmission season. Costs of delivery, coverage, compliance, the incidence of adverse events, and the acceptability of IPTc by the community and health care providers, were assessed. The study showed that high coverage of the intervention, with good adherence to supervised doses and the doses administered unsupervised by the mother, could be achieved through monthly rounds delivered at home by local community health workers. 81% of eligible children received all 3 scheduled courses of treatment; the most common reason for not receiving IPT doses was being away from the village at the time of the treatment round. The main cost driver was the daily incentives paid to community health workers.

WHO Global Malaria Programme

WHO Policy Recommendation: Seasonal Malaria Chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa

March 2012

Background

Malaria remains a leading cause of ill health, causing an estimated 216 million cases of clinical malaria and 655 thousand deaths in 2010[a]. More than 85% of malaria cases and 90% of malaria deaths occur in Africa south of the Sahara, here the vast majority of cases and deaths occur in young children.

Across the Sahel sub-region most childhood malaria mortality and morbidity occurs during the rainy season, which is generally short. Giving effective malaria treatment at intervals during this period has been shown to prevent illness and death from malaria in children.

Key interventions currently recommended by WHO for the control of malaria are the use of insecticide treated nets (ITNs) and/or indoor residual spraying (IRS) for vector control, and prompt access to diagnostic testing of suspected malaria and treatment of confirmed cases. Additional interventions which are recommended in areas of high transmission for specific high risk groups include Intermittent Preventive Treatment in pregnancy (IPTp), and Intermittent Preventive Treatment in infancy (IPTi).

With the changing epidemiology of malaria, there is a progressive paradigm shift from a "one size fits all" approach, to the targeting of malaria control strategies to specific populations and/or locations for maximal effectiveness. In keeping with this approach, WHO is now recommending a new intervention against *Plasmodium falciparum* malaria: Seasonal Malaria Chemoprevention (SMC). This intervention has been shown to be effective, cost-effective, safe, and feasible for the prevention of malaria among children less than 5 years of age in areas with highly seasonal malaria transmission.

Seasonal malaria chemoprevention[b] (SMC), previously referred to as Intermittent Preventive Treatment in children (IPTc), is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk.

[a] World Malaria Report 2011. Geneva, World Health Organization, 2011 (ISBN 978 92 4 156440 1) http://www.who.int/malaria/world_malaria_report_2011/9789241564403_eng.pdf

[b] The word chemoprevention is used in SMC because the intervention comprises the administration of full curative treatment courses as opposed to chemoprophylaxis, which usually involves administration of sub-therapeutic doses.

The recommendation for SMC [c]

WHO recommends

- Seasonal Malaria Chemoprevention (SMC) is recommended in areas of highly seasonal malaria transmission across the Sahel sub-region[1]. A complete treatment course of amodiaquine plus sulfadoxine-pyrimethamine (AQ+SP) should be given to children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season (provided both drugs retain sufficient antimalarial efficacy).
- The age-based recommended dosing schedule is:

  Infants < 12 months old: AQ – half (½) of a 153mg tablet given once daily for three days and a single dose of SP - half of a 500/25mg tablet.

  Children 12 – 59 months: AQ – a full tablet of 153 mg given once daily for three days and a single dose of SP - a full tablet of 500/25mg.

  The single dose of SP is given only on the first day together with the 1st dose of AQ.
- Target areas[2] for implementation are areas where:
  - Malaria transmission and the majority of clinical malaria cases occur during a short period of about four months[3].
  - the clinical attack rate of malaria is greater than 0.1 attack per transmission season in the target age group, and
  - AQ+SP remains efficacious (>90% efficacy)[4].
- SMC Contraindications:

SMC should not be given to -

- A child with severe acute illness or unable to take oral medication
- An HIV-positive child receiving co-trimoxazole.
- A child who has received a dose of either AQ or SP drug during the past month.
- A child who is allergic to either drug (AQ or SP).

1. SMC with AQ plus SP is not currently recommended for countries in southern and eastern Africa, even though there are some locations where the transmission pattern would suggest suitability, because of the high level of *P. falciparum* resistance to AQ and/or SP, and the absence of adequate efficacy and safety data for other potential anti-malarial regimens for use in SMC.
2. Note that in some countries, the eligibility for SMC deployment might apply only to part of their malaria endemic area.
3. Areas where on average more than 60% of clinical malaria cases occur within a maximum of 4 months; these areas are characterized by more than 60% of the average annual rainfall falling within 3 months.
4. Based originally on therapeutic efficacy assessments of AQ+SP in children under 5 years of age using the WHO therapeutic efficacy testing protocol. Methods to assess continued SMC efficacy will be developed.

[c] The recommendation was made at the consultative meeting of the Technical Expert Group (TEG) of Preventive Chemotherapy, GMP, WHO, May 2011
http://www.who.int/malaria/publications/atoz/smc_report_teg_meetingmay2011.pdf
and was subsequently reviewed and endorsed by WHO's Malaria Policy Committee (MPAC), in January 2012
http://www.who.int/malaria/mpac/feb2012/mpac_article_03_2012.pdf

Other Considerations for deployment of SMC

- While there are several potential approaches to implementing SMC, there is presently insufficient evidence to recommend a standard deployment strategy and individual approaches best suited to local conditions should be used. However, if possible, its delivery should be integrated into existing programmes, such as Community Case Management and other Community Health Workers schemes.

- For maximum protection, and to minimize selection of drug resistance, children should receive preventive treatments each month during the transmission period, and should comply with the complete 3-day treatment course each month.

- In areas where SMC is deployed:

    1. Pharmacovigilance should be strengthened where it exists, and where it does not, it should be instituted.
    2. Drug resistance monitoring and system evaluation should be supported or instituted, including systems to assess the number of breakthrough infections and their intervals from the last dose of SMC.
    3. The health system needs to record and monitor AQ+SP doses administered in order to evaluate the impact of the intervention. Existing systems to document severe malaria, malaria deaths, and record confirmed cases of malaria should be strengthened.

- Treatment of breakthrough *Plasmodium falciparum* infections during the period of SMC should not include either AQ or SP or combination drugs containing either of these medicines, such as AS+AQ. In areas where SMC is implemented, alternative antimalarial combinations containing neither AQ nor SP must be made available for the treatment of clinical malaria in the target age group.

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- Intermittent Preventive Treatment with SP in infancy (IPTi) and SMC should not be administered concomitantly. Therefore in target areas for SMC, IPTi should not be deployed.

Based on clinical trial data, a high level of protection against uncomplicated clinical malaria is likely to be maintained for four weeks after the administration of each treatment course with AQ+SP; thereafter protection appears to decay rapidly.

Expected benefits

The recommendation is based on results from 7 studies on SMC (IPTc) conducted in areas of highly seasonal transmission of malaria. The evidence suggests that SMC using AQ+SP monthly for up to 4 months during the transmission season in children less than 5 years of age:

- Prevents approximately 75% of all malaria episodes
- Prevents approximately 75% of severe malaria episodes
- May result in a decrease in child mortality of around 1 in 1000
- Probably reduces the incidence of moderately severe anaemia
- Does not result in an increase in clinical malaria in the following malaria transmission season after one year of administration but the consequences of giving SMC for several years have not yet been evaluated.
- Serious adverse events have not been reported and are probably rare