World Health Organization

Malaria Policy Advisory Committee (MPAC) Draft Meeting Agenda

Dates: 10-12 September 2014. Location: Salle D, WHO HQ, Geneva

Wednesday, 10 September 2014

Time	Session	Purpose	Type
8.30 am	Session 1: Welcome from Chair, MPAC *(K Marsh)* Report from the Director, GMP *(J Reeder)*	For information	open
9.30 am	SME TEG: Updates from the May and August meetings, presentation of proposed programme of work *(D Schellenberg)*	For information	
10.30 am	**coffee**		
11.00 am	Session 2: Update on the development of the Vivax technical brief, Global Technical Strategy for Malaria, and Global Malaria Action Plan *(R Cibulskis, P Alonso, E Patouillard, D Brandling-Bennett)*	For information	open
1.00 pm	**lunch**		
2.00 pm	Session 3: Progress to date on implementation of the Global Plan for Insecticide Resistance Management (GPIRM) *(A Mnzava)*	For input	open
3.30 pm	**coffee**		
4.00 pm	Session 4: Vector Control TEG: Guidance on the control of residual malaria transmission by behaviourally resistant vectors *(G Kileen)*	**For decision**	open
5.00 pm	Chemotherapy TEG: Updated malaria treatment guidelines *(N White/ F Binka)*	**For decision**	
6.00 pm	**End of day/ cocktail reception** (WHO HQ restaurant)		

Update from WHO GMP Director a.i.:
Regional updates, GMP products and MPAC survey findings

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 10 September 2014

John Reeder
Reeder@who.int

World Health Organization

GLOBAL MALARIA PROGRAMME

Regional Updates - Americas

- 21 endemic countries with 430K cases and 82 deaths from malaria in 2013
- 64% reduction in cases and 79% reduction in deaths since 2000
- 14 countries malaria-free and Argentina has requested certification of elimination
- Malaria elimination targeted in Mesoamerica, Hispanola, Ecuador, Suriname, Argentina and Paraguay.
- Government financing remains stable in most countries with some decreases where cases decreasing; Global Fund and USAID provide majority of external funding. Need sustained financing for elimination.
- Key Priorities: national malaria plans reinforced, communicated, and prioritized; support equitable access to quality malaria diagnosis and effective treatment, including antimalarial efficacy surveillance strengthened; and strengthen surveillance, monitoring & evaluation

Regional Updates - African

- 80% of the estimated 207M cases and 90% of the estimated malaria deaths in 2012 were in Africa
- Significant reductions in both the malaria incidence (31%) and mortality rate (49%) between 2000-2012 in Africa
- Challenges include: ebola epidemic with similarity in clinical symptoms; weak health systems, gaps in programme management capacity; availability, access and quality of medicines and commodities; coordination among partners; and adequate funding
- Priorities for 2014-15: support coordinated planning, strengthen community based interventions and surveillance, strengthen capacity, and advocacy for resource mobilization
- Collaboration with DFID – Strengthen the use of data for malaria decision making and action in ten high burden countries; agreement in negotiation

Regional Updates – Eastern Mediterranean

- Estimated 13M cases and 18,000 deaths from malaria in 2012
- 7 malaria endemic countries remaining; 4 countries have become malaria free since 2000 (UAE, Morocco, Syria (?), and Iraq)
- Overall incidence is declining, particularly in Afghanistan and Iran, but outbreaks in Tunisia and Egypt threaten malaria-free status
- Imported cases are increasing; 97% from 4 countries (Sudan, Pakistan, Yemen and Afghanistan)
- 36% of malaria funding in 2012 was national resources
- Challenges in EMRO include: humanitarian crisis, increasing population movement and increase in imported malaria
- Poor health infrastructure, weak diagnostic systems, decentralization and ineffective surveillance systems are barriers to progress

Regional Updates - European

- Tashkent Declaration endorsed by all malaria-affected countries in the Region in 2006 calls for malaria elimination by 2015
- In 2013, there were 37 cases of local malaria transmission in EURO: 34 in Turkey and 3 in Tajikistan
- The outbreak of P. vivax in Greece beginning in 2009 was down to 3 locally acquired cases in 2013
- In 2012, there were 5759 imported cases and 24 deaths in 8 countries: Belgium, France, Germany, Netherlands, Russia, Spain, Switzerland and UK
- Turkmenistan (2010), Armenia (2011) and Kazakhstan (2012) have been certified as malaria-free
- Azerbaijan, Georgia, Kyrgyzstan and Uzbekistan are preventing re-introduction
- EURO is supporting the development of Tashkent 2 to maintain political commitment and funding for sustaining elimination after 2015

Regional Updates – South-East Asia

- Estimated population is 1.6 billion at risk in 10 countries
- Draft WMR reports from each country indicates progress in 2013
- 2014: outbreaks occurred in northeast India, Bangladesh and in northeast Thailand (bordering Lao PDR)
- Risk of outbreak in Nepal among around 300,000 populations displaced after flooding last August
- Zero indigenous case in Sri Lanka sustained since November 2012
- National elimination goals:
  - 2015 – Sri Lanka
  - 2016 – Bhutan
  - 2017 – India in pre-elimination
  - 2020 – Bangladesh, DPRK
  - 2024 – Thailand
  - 2026 – Nepal
  - 2030 – Indonesia, Myanmar
  - Timor Leste – not yet set

Regional Updates – Western Pacific

- 711M population at risk in 10 countries; 3 countries account for 79% of cases (PNG, Lao and Cambodia)
- The number of confirmed malaria cases reported declined from 390K to 299K and the deaths decreased from 2400 to 460 between 2000 and 2012.
- Eight countries (Cambodia, China, Malaysia, Philippines, Republic of Korea, Solomon Islands, Vanuatu and Viet Nam) achieved >75% decrease in incidence of confirmed cases in the same period.
- Challenges include: Multi-drug resistance including artemisinin resistance, maintaining domestic financing, addressing P. vivax and other species, resurgences (Lao), imported malaria (China) and reaching all populations at risk of malaria.
- WPRO will develop a 5-year regional action plan based on the GTS to submit to the Regional Committee in 2015.

GMP Products – March 2014 MPAC Report

- Published in the *Malaria Journal* in July 2014
- All meeting reports submitted within 3 months of every MPAC meeting
- Available on MPAC website and as part of WHO *GMP's Malaria Journal* series

http://www.malariajournal.com/content/13/1/253

WHO Malaria Policy Advisory Committee and Secretariat Malaria Journal 2014, **13**:253
http://www.malariajournal.com/content/13/1/253

MALARIA JOURNAL

MEETING REPORT **Open Access**

Malaria policy advisory committee to the WHO: conclusions and recommendations of fifth biannual meeting (March 2014)

WHO Malaria Policy Advisory Committee and Secretariat*

Abstract

The Malaria Policy Advisory Committee to the World Health Organization (WHO) held its fifth meeting in Geneva, Switzerland from 12 to 14 March 2014. This article provides a summary of the discussions, conclusions and recommendations from that meeting.

Meeting sessions covered: maintaining universal coverage of long-lasting insecticidal nets; combining indoor residual spraying with long-lasting insecticidal nets; the sound management of old long-lasting insecticidal nets; malaria diagnosis in low transmission settings; the Global Technical Strategy for Malaria (2016 -2025); and Technical Expert Group updates on vector control, the RTS,S vaccine, the Malaria Treatment Guidelines, anti-malarial drug resistance and containment, and surveillance, monitoring and evaluation.

Policy statements, position statements, and guidelines that arise from the Malaria Policy Advisory Committee meeting conclusions and recommendations will be formally issued and disseminated to WHO Member States by the WHO Global Malaria Programme.

Keywords: WHO, Malaria, Policy-making, Mosquito control, Drug resistance, Surveillance, Elimination, Plasmodium falciparum, Plasmodium vivax

Background

The Malaria Policy Advisory Committee (MPAC) to the World Health Organization (WHO) held its fifth meeting from 12 to 14 March 2014 in Geneva, Switzerland, following its meetings in February and September 2012, and March and September 2013 [1-4]. This article provides a summary of the discussions, conclusions and recommendations from that meeting as part of the *Malaria Journal* thematic series "WHO global malaria recommendations" [5].

The following sections of this article provide details and references for the background documents presented at the open sessions of the committee on: maintaining universal coverage of long-lasting insecticidal nets; combining indoor residual spraying with long-lasting insecticidal nets; the sound management of old long-lasting insecticidal nets; malaria diagnosis in low transmission settings; the Global Technical Strategy for Malaria (2016 -2025); and Technical Expert Group (TEG) updates on vector control, the RTS,S vaccine, the Malaria Treatment Guidelines, anti-malarial drug resistance and containment, and surveillance, monitoring and evaluation.

The MPAC discussion and recommendations related to these topics, which took place partially in closed session, are also included. MPAC decisions are reached by consensus [6]. The complete set of all MPAC meeting-related documents including background papers, presentations, and member declarations of interest can be found online on the MPAC website [7]. The next meeting of the MPAC will be 10 to 12 September 2014 [7].

Report from the WHO global malaria programme

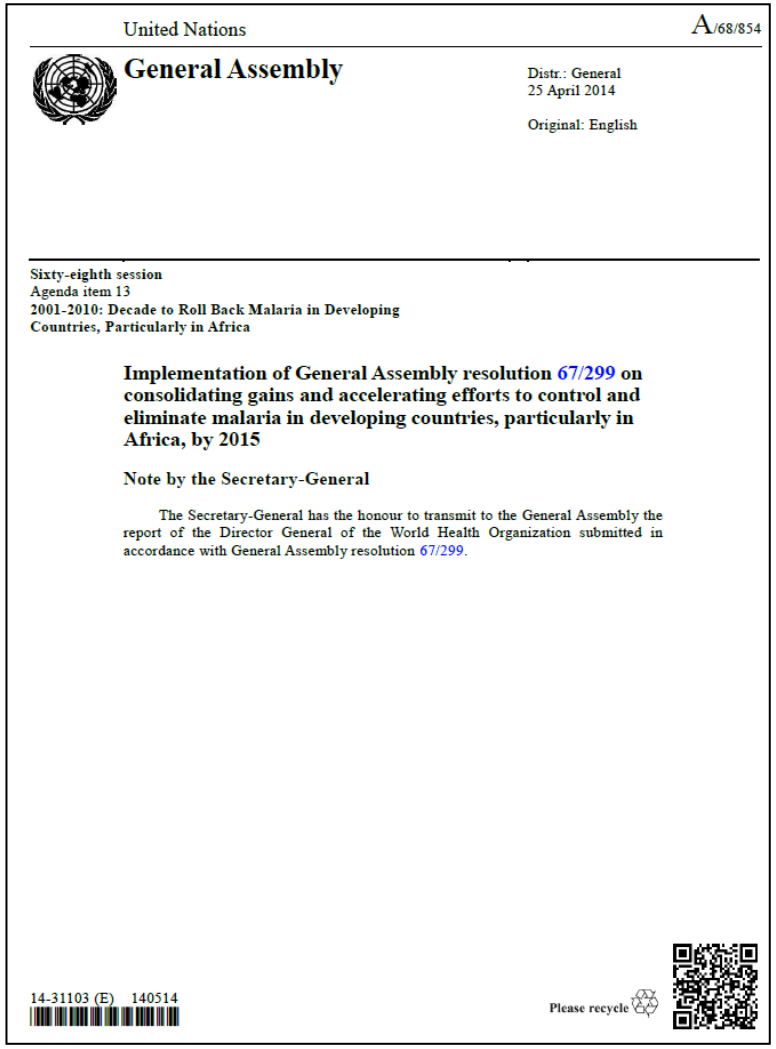
The acting Director of the WHO Global Malaria Programme (WHO-GMP) updated MPAC members on the major publications from WHO-GMP since its last meeting, including 'Eliminating malaria: The long road to malaria elimination in Turkey' [8], 'Malaria control in humanitarian emergencies: an inter-agency field handbook' [9], 'Epidemiological approach for malaria control training manuals' [10], and 'WHO informal consultation

* Correspondence: mpacgmp@who.int
Global Malaria Programme, World Health Organization, 20 Avenue Appia, CH-1211, Geneva 27, Switzerland

GMP Products – WHO Progress report (April 2014)

- WHO progress report on implementing UN General Assembly resolution 67/299
- Progress in the implementation of the resolution and scaling-up of interventions
- Assessment of progress toward the 2015 global malaria targets
- Elaborates on the challenges to fully achieving the targets and provides recommendations to accelerate progress to 2015

http://www.who.int/malaria/publications/atoz/report_un_general_assembly/en/



United Nations A/68/854

General Assembly

Distr.: General
25 April 2014

Original: English

Sixty-eighth session
Agenda item 13
2001-2010: Decade to Roll Back Malaria in Developing Countries, Particularly in Africa

Implementation of General Assembly resolution 67/299 on consolidating gains and accelerating efforts to control and eliminate malaria in developing countries, particularly in Africa, by 2015

Note by the Secretary-General

The Secretary-General has the honour to transmit to the General Assembly the report of the Director General of the World Health Organization submitted in accordance with General Assembly resolution 67/299.

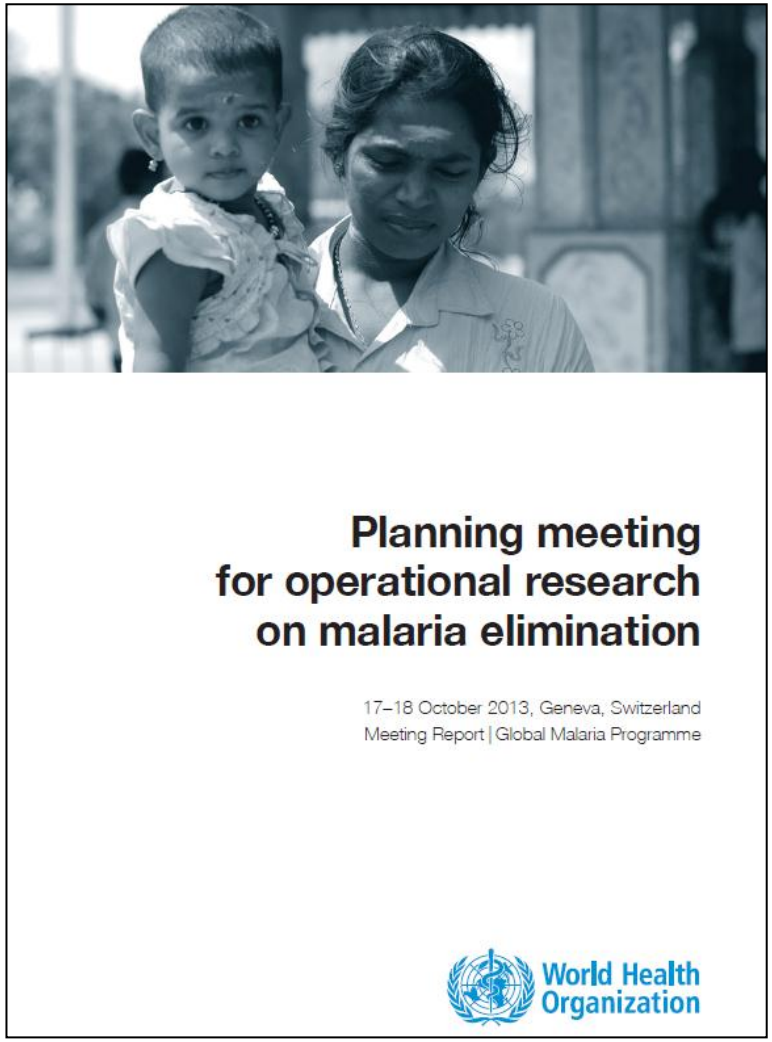
14-31103 (E) 140514

Please recycle

GMP Products – Operational research for malaria elimination (May 2014)

- Planning meeting for operational research on malaria elimination – meeting report
- Summarized the landscape of operational research
- Discussed the operational challenges for malaria elimination
- Identified priority OR questions
- Provided recommendations to WHO

http://www.who.int/malaria/publications/atoz/operational-research-malaria-elimination/en/



GMP Products – Intensified efforts required to withdraw oral artemisinin-based monotherapies

- Emergence and spread of artemisinin resistance calls for intensified efforts to withdraw oral artemisinin-based monotherapy from the market (May 2014)
- Update provides an overview of recommended regulatory actions and progress to date

http://www.who.int/malaria/publications/atoz/policy-brief-withdrawal-of-oral-artemisinin-based-monotherapies/en/

GLOBAL MALARIA PROGRAMME

World Heal Organizati

Emergence and spread of artemisinin resistance calls for intensified efforts to withdraw oral artemisinin-based monotherapy from the market

1 May 2014

Key messages

In January 2014, the WHO Global Malaria Programme published the latest status report on artemisinin resistance: foci of artemisinin resistance have been identified in five countries in the Greater Mekong subregion, and resistance is suspected in two countries and one territory in South America.

Continued use of oral artemisinin-based monotherapy (oAMT) is widely considered to be one of the main contributing factors to the development and spread of resistance to artemisinin and its derivatives.

In May 2007, all Member States endorsed a World Health Assembly resolution that urges Member States to cease the marketing and use of oAMT[1] in both the public and private sectors, and to promote the use of artemisinin-based combination therapy (ACT). Despite comprehensive regulatory action and substantial progress, oAMT is still available in many countries, as discussed in the text.

In view of the latest evidence on artemisinin resistance, intensified action is required to protect the therapeutic life of ACT, which is the mainstay of treatment for malaria caused by *Plasmodium falciparum*. No alternative medicine is ready to enter the market in the next few years to replace ACT.

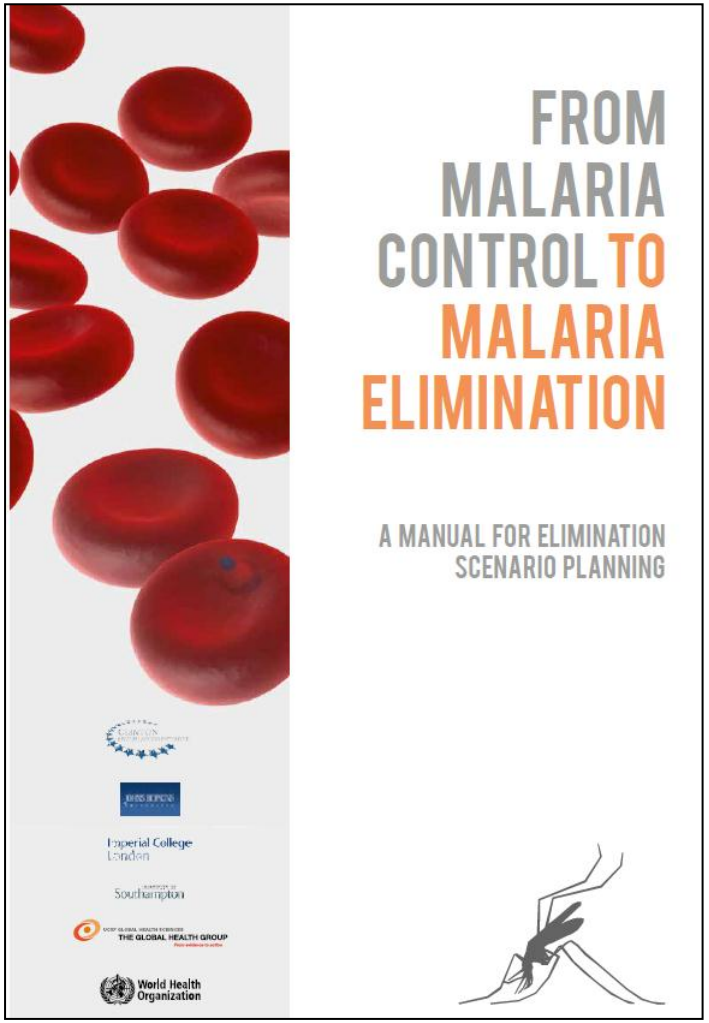
The loss of artemisinin derivatives would have devastating consequences on people's health in malaria-endemic countries and threaten the recent progress in malaria control achieved in many countries.

1. This recommendation refers only to oral artemisinin-based monotherapy. Rectal and injectable formulations (e.g. artesunate suppositories and artesunate injectables) are still required for pre-referral treatment and for the treatment of severe malaria, respectively (*1*). Moreover, in exceptional cases, the manufacture and export of oAMT might still be necessary for co-packaging with a partner medicine in artemisinin-based combination therapy (ACT) products that are not yet available as fixed-dose combinations.

WHO/HTM/GMP/2014.3

GMP Products – Elimination Scenario Planning (April 2014)

- From malarial control to malaria elimination: a manual for elimination scenario planning
- Provides a framework to assess scenarios for moving towards elimination based on programme coverage and funding and helps to set realistic timelines
- Collaboration with Clinton Health Access Initiative, Imperial College, Johns Hopkins University, the University of Southampton and the Global Health Group at UCSF

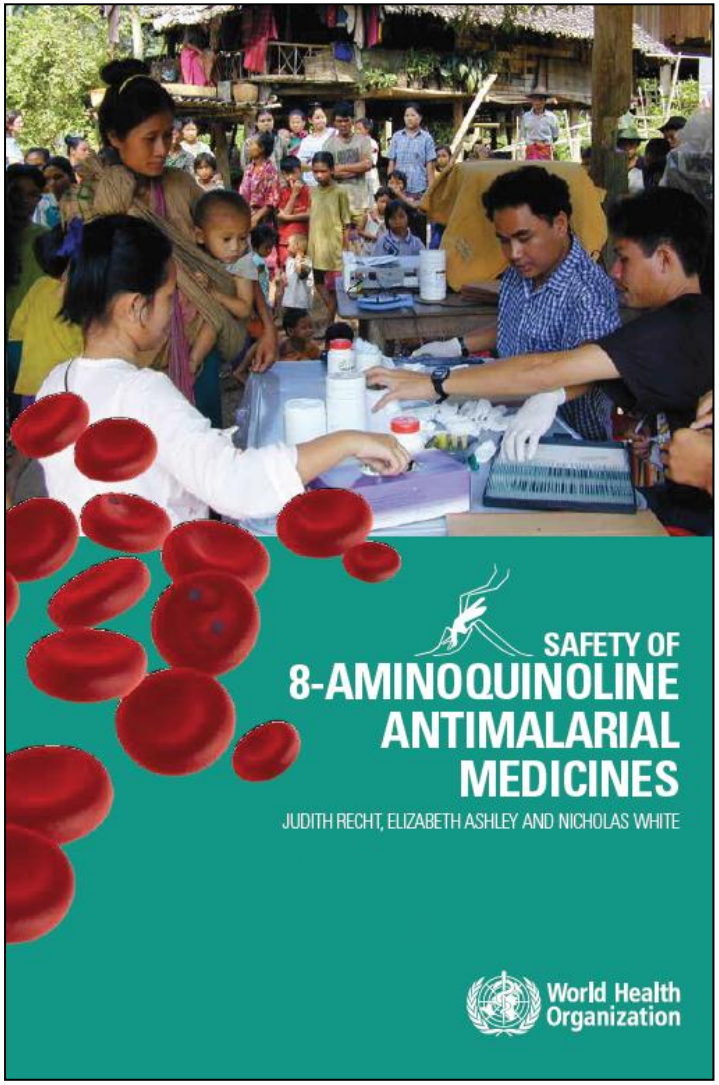


http://www.who.int/malaria/publications/atoz/9789241507028/en/

GMP Products – Safety of 8-aminoquinoline antimalarial medicines (May 2014)

- Report on the safety and effectiveness of single-dose primaquine as a P.f. gametocytocide
- Reviews published and unpublished studies on the safety of primaquine, particularly haemolytic anaemia in G6PD-deficient individuals

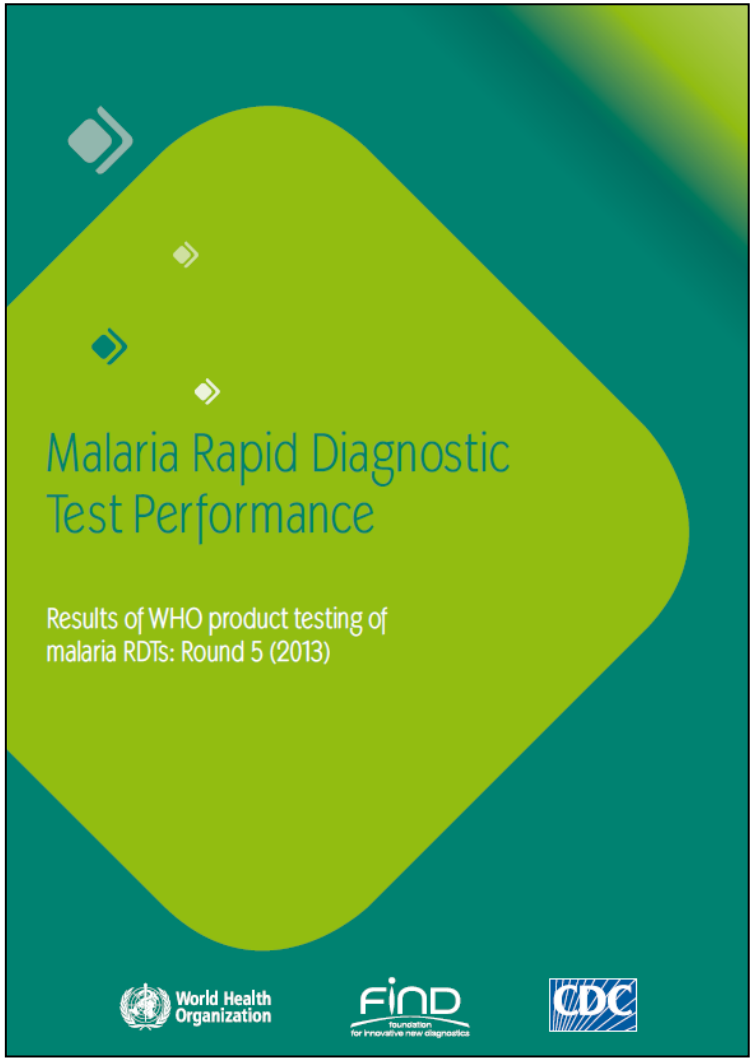
http://www.who.int/malaria/publications/atoz/9789241506977/en/



GMP Products – Results of WHO product testing of RDTs: Round 5 (July 2014)

- Round 5 – 42 products were evaluated including 19 new products and 23 resubmissions
- Overall range of results similar to rounds 1-4; most of the compulsorily retested products were within 10% of initial test
- Funded by WHO and FIND through a grant from UNITAID. Testing performed at CDC

http://www.who.int/malaria/publications/atoz/9789241507554/en/

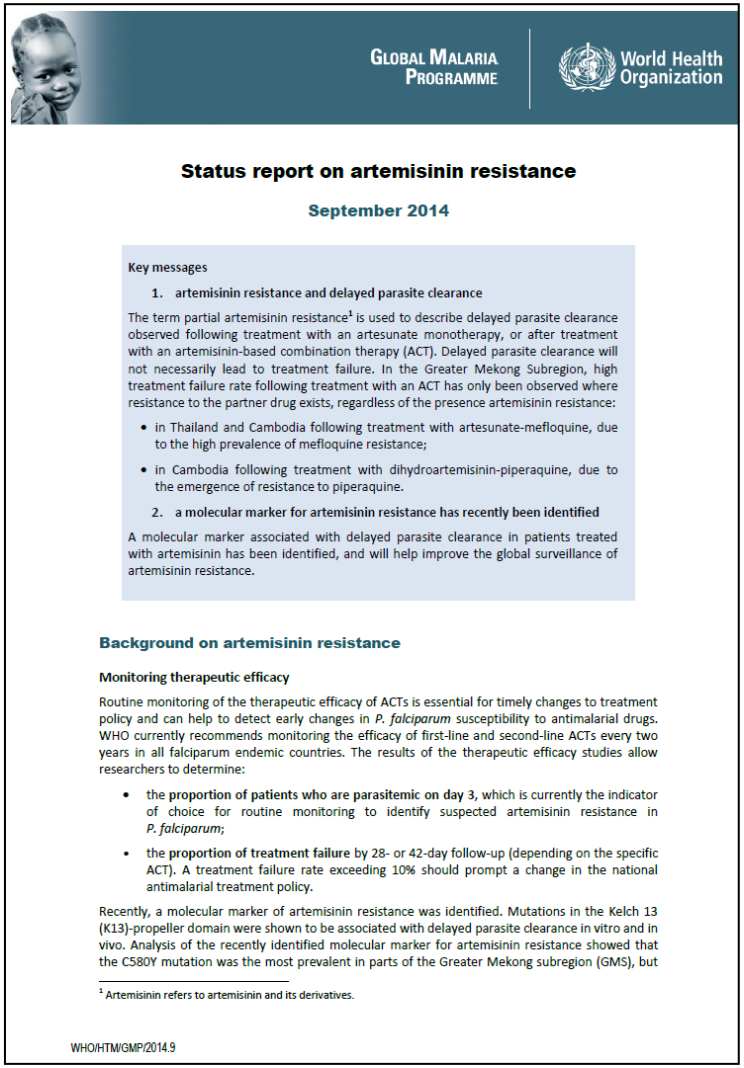


GMP Products – Update on artemisinin resistance (September 2014)

Key messages:

1. Artemisinin resistance and delayed parasite clearance
   - Thailand and Cambodia following treatment with artesunate-mefloquine due to mefloquine resistance;
   - Cambodia following treatment with dihydroartemisinin-piperaquine due to resistance to piperaquine
2. A molecular marker for artemisinin resistance has been identified

http://www.who.int/malaria/publications/atoz/update-artemisinin-resistance-sep2014/en/



Global Malaria Programme | World Health Organization

Status report on artemisinin resistance

September 2014

Key messages

1. **artemisinin resistance and delayed parasite clearance**

The term partial artemisinin resistance[1] is used to describe delayed parasite clearance observed following treatment with an artesunate monotherapy, or after treatment with an artemisinin-based combination therapy (ACT). Delayed parasite clearance will not necessarily lead to treatment failure. In the Greater Mekong Subregion, high treatment failure rate following treatment with an ACT has only been observed where resistance to the partner drug exists, regardless of the presence artemisinin resistance:

- in Thailand and Cambodia following treatment with artesunate-mefloquine, due to the high prevalence of mefloquine resistance;
- in Cambodia following treatment with dihydroartemisinin-piperaquine, due to the emergence of resistance to piperaquine.

2. **a molecular marker for artemisinin resistance has recently been identified**

A molecular marker associated with delayed parasite clearance in patients treated with artemisinin has been identified, and will help improve the global surveillance of artemisinin resistance.

Background on artemisinin resistance

Monitoring therapeutic efficacy

Routine monitoring of the therapeutic efficacy of ACTs is essential for timely changes to treatment policy and can help to detect early changes in *P. falciparum* susceptibility to antimalarial drugs. WHO currently recommends monitoring the efficacy of first-line and second-line ACTs every two years in all falciparum endemic countries. The results of the therapeutic efficacy studies allow researchers to determine:

- the **proportion of patients who are parasitemic on day 3**, which is currently the indicator of choice for routine monitoring to identify suspected artemisinin resistance in *P. falciparum*;
- the **proportion of treatment failure** by 28- or 42-day follow-up (depending on the specific ACT). A treatment failure rate exceeding 10% should prompt a change in the national antimalarial treatment policy.

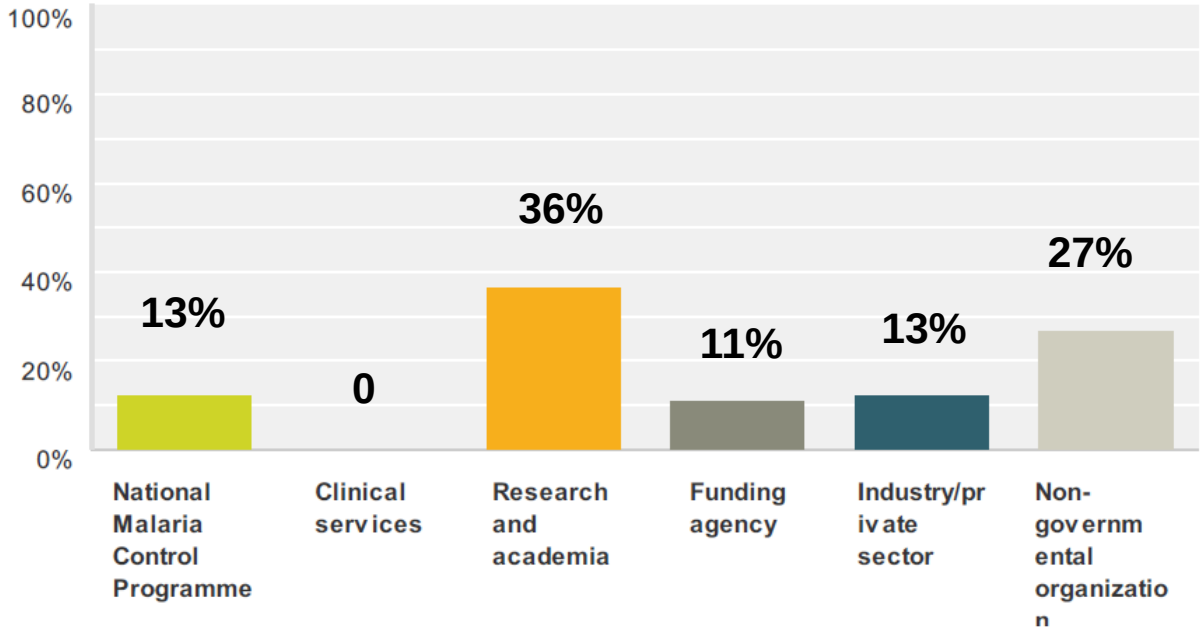
Recently, a molecular marker of artemisinin resistance was identified. Mutations in the Kelch 13 (K13)-propeller domain were shown to be associated with delayed parasite clearance in vitro and in vivo. Analysis of the recently identified molecular marker for artemisinin resistance showed that the C580Y mutation was the most prevalent in parts of the Greater Mekong subregion (GMS), but

[1] Artemisinin refers to artemisinin and its derivatives.

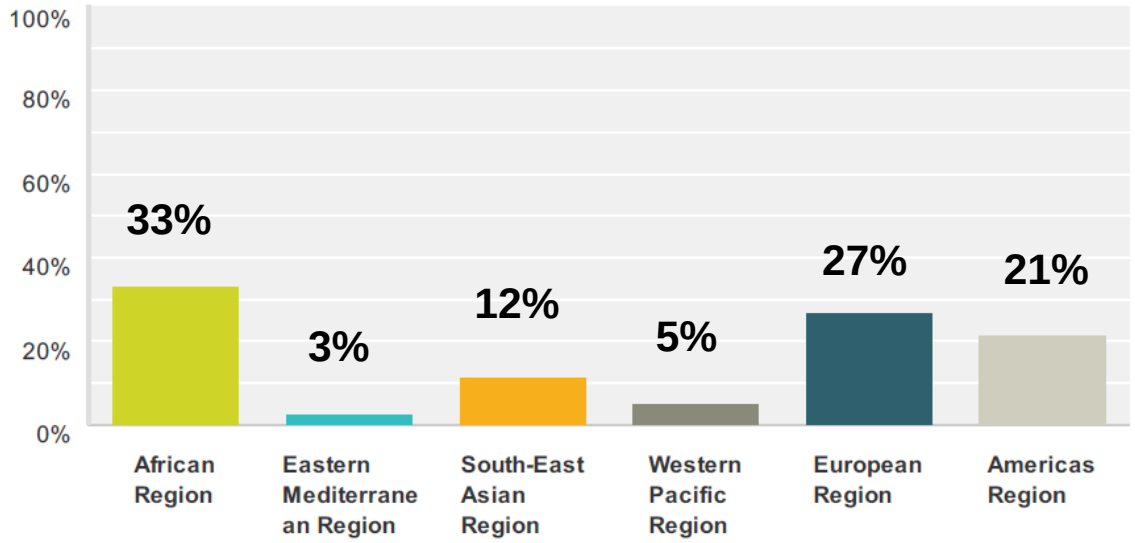
WHO/HTM/GMP/2014.9

MPAC Survey results

- Open monkey survey conducted to determine if the MPAC framework is meeting the needs of NMCPs, partners, donors and other stakeholders
- Advertised through WHO and RBM listservs, the GMP newsletter and by email to several hundred malaria contacts
- 123 responses received with the following affiliations (9 others)

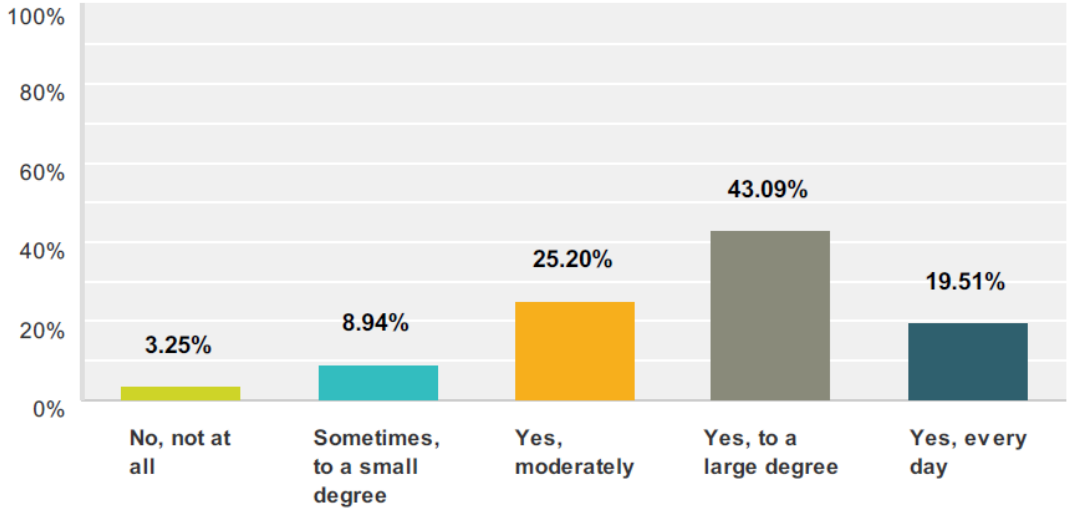


MPAC Survey results



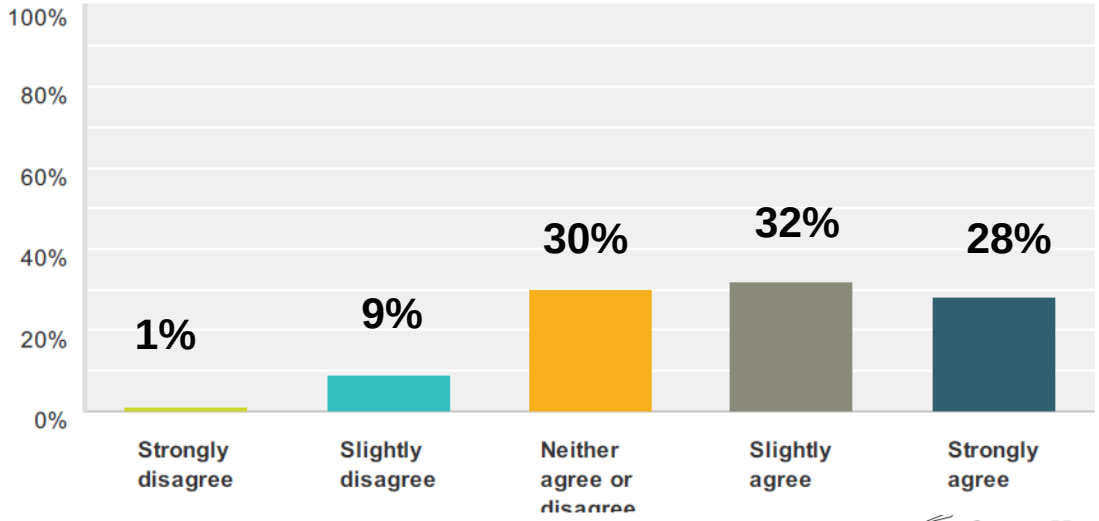
Respondents represented all WHO Regions

Malaria policy recommendations directly impact the work of 88% of respondents; ranging from moderately to every day



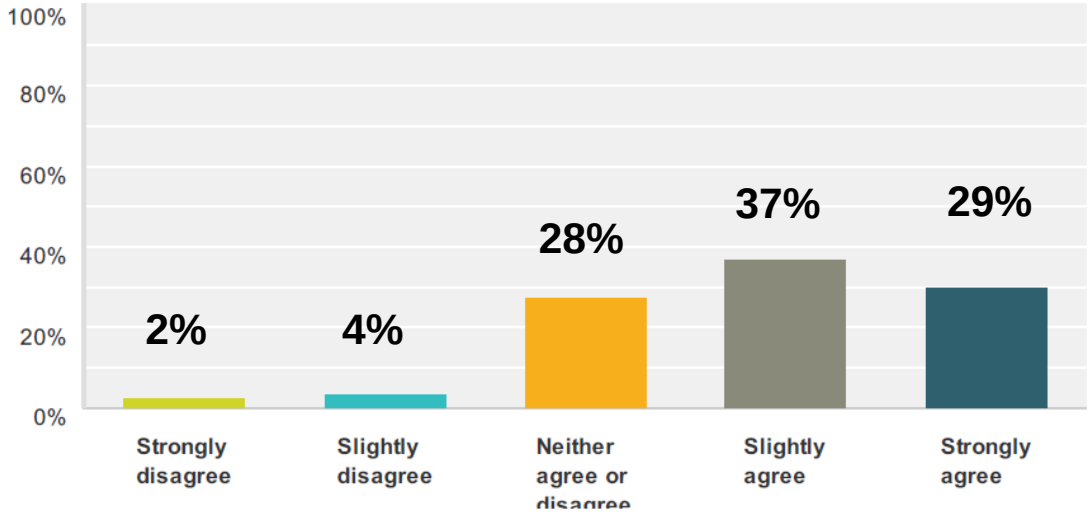
MPAC Survey results

- 72% of respondents were aware that the Malaria Policy Advisory Committee holds regular and open meetings to review and consider malaria policy recommendations
- 66% of respondents agreed that GMP has succeeded in establishing a transparent evidence review and policy setting process through MPAC
  - Comments included: communication should be expedited; the process for setting the agenda is not clear; this survey appears to be the first effort to get the wider community's opinions and involvement
- 60% of respondents agreed that GMP has succeeded in establishing a timely evidence review and policy setting process through MPAC



MPAC Survey results

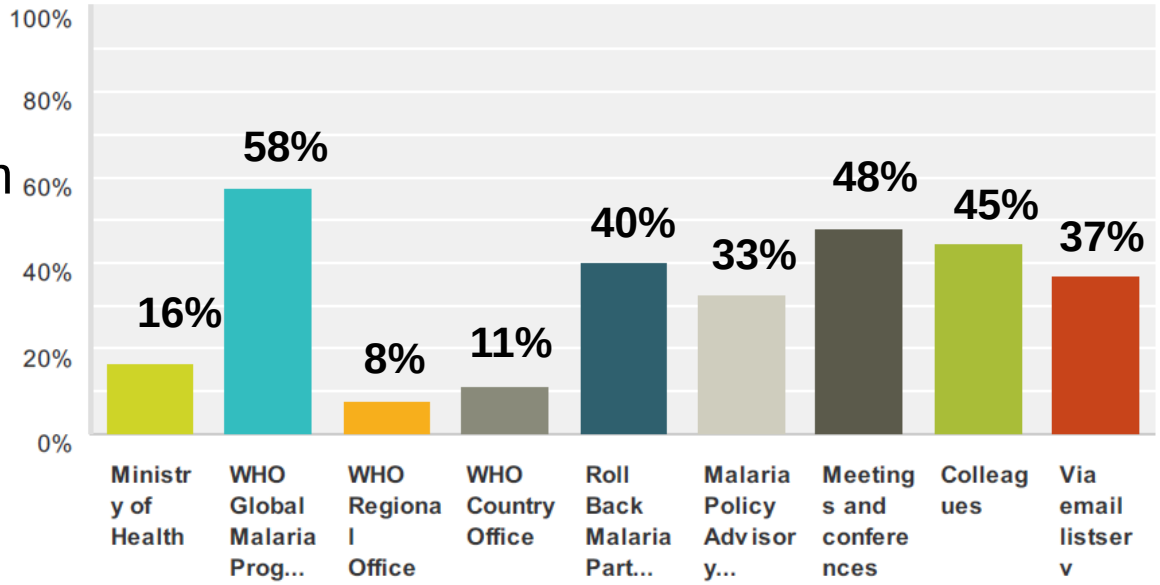
- 66% of respondents agreed that GMP has succeeded in establishing a credible evidence review and policy setting process through MPAC



- Comments included: having insufficient knowledge to answer the question and not sure how MPAC differs in its working process from the business as usual WHO technical expert groups

MPAC Survey results

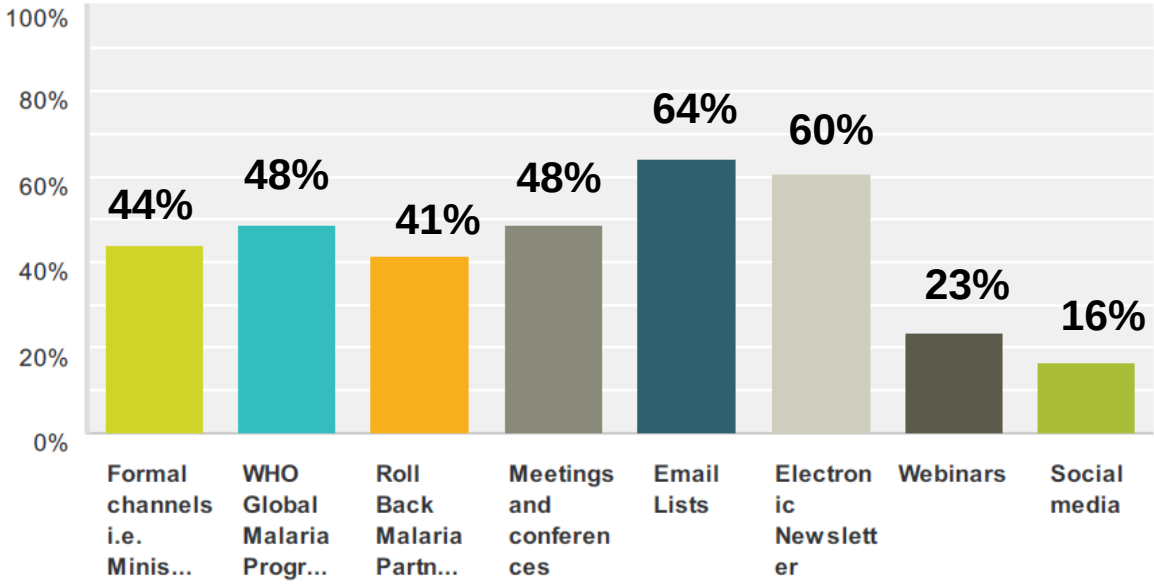
- Respondents hear of new malaria policy recommendations from a variety of sources (respondents could choose multiple sources)



- The GMP website was a resource for 58% of respondents, followed by meetings and conferences, colleagues and Roll Back Malaria Partnership mechanisms
- Other sources included: MMV info, RBM and WHO listserv, Global Fund, and the Malaria group at LSHTM.

MPAC Survey results

- What methods of communication can WHO better use to reach Member States and the global malaria community with important policy updates?



- Email listservs, electronic newletter, GMP website, and meetings and conferences were the top methods for communication
- Additional suggestions included: more rapid translation into French, use of country staff, Malaria World website, active engagement of the target audience is crucial, use of RBM mechanisms and Global Fund to ensure timely integration into proposals.

MPAC Survey results – any other comments

- GMP should translate the recommendations into all UN languages and send them to the WHO Country Offices for dissemination.
- MPAC should pay more attention to innovative developments that can be added to the malaria toolbox and update the RBM strategy.
- WHO field staff have difficulty in explaining policy changes to programmes, the need to implement new guidelines and how to do it.
- MPAC should address case management issues such as the role of molecular diagnostic tools in the context of elimination.
- Consider webcasting the open sessions live.
- MPAC should be given the mandate to also carry out independent reviews instead of depending on review reports presented to them
- WHO policy is better developed by experts in the specific area of interest, not experts in areas of malaria science and implementation
- Make it more clear that engagement from the community is welcome; MPAC is not reaching the engagement level of the SAGE.

GMP Conclusion

- Productive six months since the last MPAC meeting
  - GMP products published
  - Technical Expert Group meetings convened
  - Global Technical Strategy Regional Consultations and Steering Committee meetings held
- MPAC survey indicates some areas for improvement, but overall appreciation for the strengthened policy making process
- All regions report significant progress, but highlight important challenges, including sustained financing
- GMP signed a grant renewal with BMGF for their contribution to MPAC; actively seeking to diversify support
- Looking forward to the incoming leadership of Pedro Alonso as the new Director of GMP next month

Surveillance, Monitoring and Evaluation Technical Expert Group (SME TEG)

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 10 September 2014

David Schellenberg
London School of Hygiene and Tropical Medicine

World Health Organization

GLOBAL MALARIA PROGRAMME

Outline

1. Reminder – what is the SME TEG?
2. Activities so far
3. Plans for the future

What does the SME TEG do?

1. Guidance at global level:
   - Ensure some thought has been given to M&E issues when MPAC makes policy recommendations e.g. indicators for SMC
   - Methodology used for World Malaria Report e.g. burden estimates, programme coverage, financing
   - Methodology used for country assessments e.g. demonstrated impact, certification of elimination, resource allocation formulae
   - Contents of GTS and related documents e.g. choice of indicators

2. Guidance to countries to improve the data base/ use of data:
   - Malaria Programme Reviews/ Malaria Strategic Planning
   - Elimination Field Manual
   - Health facility surveys
   - Core data elements for routine information systems

Composition of SME TEG: Expertise wanted

- Topics
  - Monitoring finances
  - Monitoring vector control
  - Monitoring preventive therapies
  - Monitoring diagnosis and treatment
  - Measurement of morbidity and mortality
  - Tracking progress of elimination
- Methods
  - Health information systems
  - Household surveys
  - Health facility surveys
  - Demographic surveillance systems
- Plus
  - Members working in NMCPs
  - MPAC members

Composition of SME TEG: what we got

	Area of expertise		Institution
1	Monitoring finances	Jessica Cohen	Harvard University, USA
2	Monitoring vector control	Immo Kleinsschmidt	LSHTM, UK
3	Monitoring diagnosis and treatment	Thom Eisele	Tulane University, USA
4	Measurement of morbidity	Pete Gething	Oxford University, UK
5	Tracking progress of elimination	Roly Gosling	UCLA, USA
6	Health Information Systems	Sarah Byakika	MoH, Uganda
7	Household surveys	Fred Arnold	ICF, USA
8	Health facility surveys	Abdisallan Noor	KEMRI, Kenya
9	Demographic surveillance systems	Peter Byass	Umea University, Sweden
10	Member working in NMCPs	Kokou Tossa	NMCP, Togo
11	Member working in NMCPs	Rebecca Kiptui	NMCP, Kenya
12	Member working in NMCPs	Mansour Ranjbar	UNDP, Iran
13	All rounder	Arantxa Roca-Felterer	Malaria Consoritum, Cambodia
14	All rounder	David Schellenberg	LSHTM, UK
15	All rounder	Justin Cohen	CHAI, USA
16	MPAC member	Kamini Mendis	Sri Lanka
17	MPAC member	Salim Abdulla	IHI, United Republic of Tanzania
18	MPAC member	Larry Slutsker	CDC, USA

What have they done? Guidance at global level

- Estimation of global malaria indicators
  - ITN coverage: Recommended to adopt proposed method of MAP
  - Case management indicators: Recommended to adopt proposed method of Tulane University/ University of California, San Francisco
  - Cases and deaths:
    - Recommended to adopt proposed method of MAP for cases in sub-Saharan Africa
    - Will review work on malaria deaths under 5 in Africa
    - Will review work on age distribution of deaths
    - Will review work on *P. vivax* severe cases and deaths

- GTS
  - Reviewed sections on (i) Targets (ii) Measuring progress towards targets (iii) Surveillance section (iv) Costing

- Indicators for Sustainable development goals
  - Made recommendations to WHO on response on SDG indicators proposed by Open Working Group

What have they done? Guidance at country level

- **Chemoprevention indicators** - SMC, IPTi
  - Draft paper on chemoprevention indicators reviewed by TEG
  - Revised draft to be shared with MERG and other implementing partners and finalized by February 2015

- **Manual on programme monitoring** / recommended routine data
  - Draft manual reviewed by TEG
  - Revised draft to be shared with MERG and finalized by February 2015

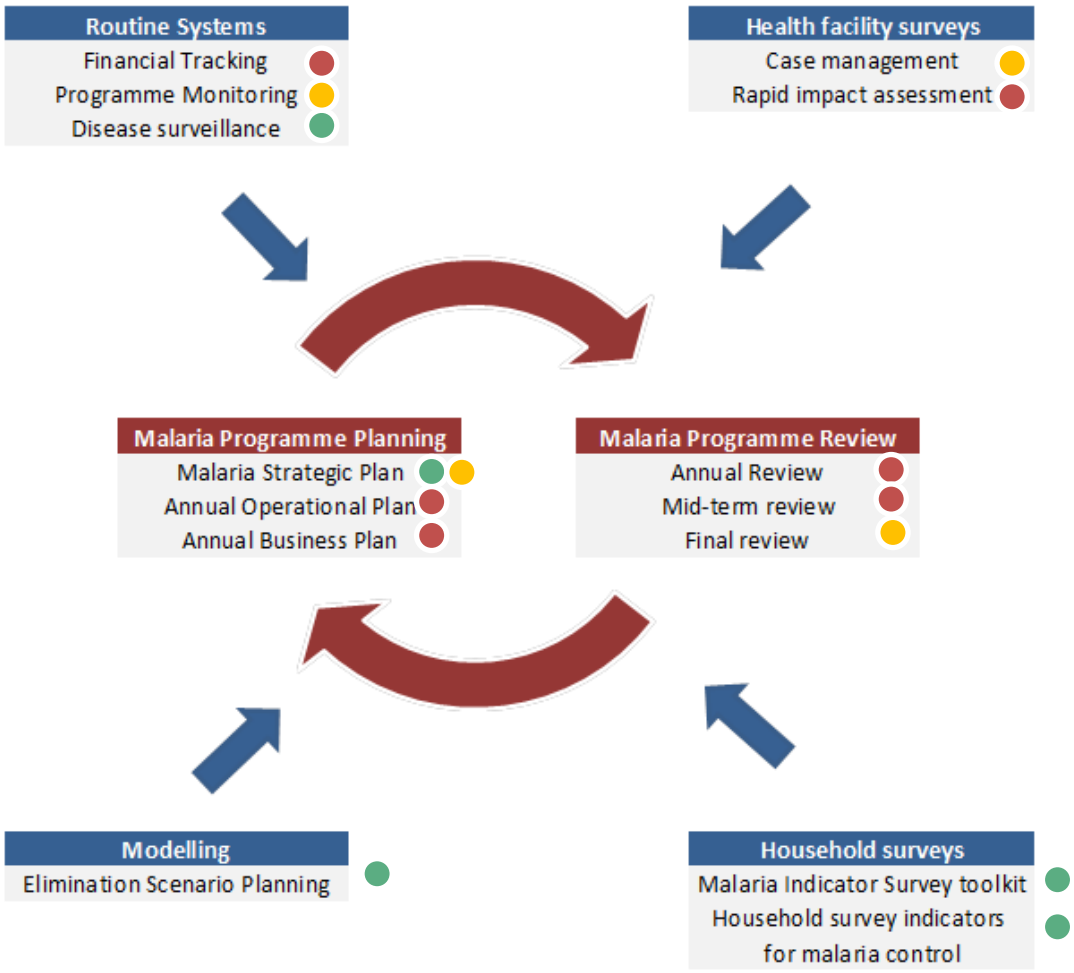
- **Health facility survey manual** - to monitor diagnostic testing and treatment
  - Draft manual reviewed by TEG
  - Revised draft to be shared with MERG
  - Field testing of recommendations as part of SARA in Guinea postponed

- **Malaria Programme Review manual** – especially on assessing impact of interventions
  - Review to be undertaken

Plans for future

- Dictated by the need to monitor and evaluate the GTS at international, and national level
- Immediate priority is to construct a baseline for 2016
  - Ensure guidance is in place
  - Identify what M&E gaps need to be filled
  - Work with WHO regional and country offices, MERG and other partners to fill them
  - Undertake data analysis with available data

Immediate planned guidance



- No guidance
- Guidance under development
- Guidance exists

Plans for future

- DS/ REC to outline a framework of what needs to be done through to December 2015 and beyond

- SME TEG: Two meetings per year: February & August

P. vivax technical brief

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 10 September 2014

Richard Cibulskis & Chansuda Wongsrichanalai
Global Malaria Programme

World Health Organization

GLOBAL MALARIA PROGRAMME

Why is technical brief needed?

P. vivax often features only as an “add-on” to malaria documents:

- 1993 Global Strategy: only broad guidance of malaria control.
- GMAP 2008: some mentioning of *P. vivax*-specific issues but not ‘how.’
- Current WHO guidance for *P. vivax* malaria spread across several documents. No single summary.

In September 2012, MPAC endorsed need to develop a global plan for *P. vivax.*

- To fall under the umbrella of the overall Global Technical Strategy for Malaria Control and Elimination, 2016–2025
- to be commissioned as a separate piece of work to ensure that it is fully developed
- GTS 2016-2025 to include key strategic issues specific for *P. vivax* - but not detailed recommendations

Progress

- Funding: Medicines for Malaria Venture (MMV)
- 1st steering committee meeting in Nov 2012
  - Kevin Baird Chair.
  - Kamini Mendis, MPAC member, to help link PVSP and GTS
- Consultant hired: Chansuda Wongsrichanalai
- Writing Committee established and convened in May and Nov 2013
  - Thematic reviews on biology, epidemiology, Vector control, Diagnosis and treatment, Surveillance and elimination, Cost-effectiveness of interventions, Research priorities
- 10 countries selected for Landscape Briefs (8 completed)
- Strategic directions summary shared with MPAC March 2014
  - recommended a technical brief not a *P. vivax* strategy
- Strategic directions summary shared at regional consultations
- Technical brief drafted July & August, 2014

Not one product but three

- P. vivax Technical Briefing:
  - Summarizes the challenges posed by P. vivax malaria and opportunities for its control and elimination.
  - Summarizes existing WHO guidance on strategies for control and elimination of P. vivax malaria
  - Highlights additional research and development that needs to be undertaken to develop or implement new tools.
- An advocacy piece (to be named) - a companion document of 1. above, but easier to read, less technical, targeting policy makers, etc.
- Journal supplement - a series of 16-17 papers extracted from thematic reviews and landscape briefs.

Launch plans

Plan to launch *P. vivax* Technical Briefing and the Advocacy Piece together.

Options:

1. ASTMH, New Orleans, November 2014
2. World Malaria Day - 25 April 2015
3. Other major events in Southeast Asia during Jan, Feb, Mar 2015

Advantages of release in 2015:

1. Ongoing analysis in GMP on severe *P. vivax* and mortality can be added
2. WHO TEG on G6PD testing will convene in Oct. 2014.
3. WHO Malaria Treatment Guidelines, Third Edition to be published Dec. 2014.

Advice sought

Technical brief a suitable accompaniment to GTS? Or does content and tone need to be changed?

- challenges posed by *P. vivax* malaria and opportunities for its control and elimination.
- WHO guidance on strategies for control and elimination of *P. vivax* malaria
- research and development that needs to be undertaken to develop or implement new tools.

World Health Organization

GLOBAL MALARIA PROGRAMME

Malaria: draft global technical strategy: post-2015

Pedro Alonso, GTS Steering Committee Chair

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 10 September 2014

Global Technical Strategy – Process to date & Next steps

- May 2013: 66th World Health Assembly – Member States supported the development of a **global technical strategy for malaria**
- July 2013: Global Technical Strategy Steering Committee constituted
- March 2014: The first draft was reviewed by MPAC
- March – Jun 2014: Seven Regional Consultations attended by over **400** participants (http://www.who.int/malaria/areas/global_technical_strategy/meetings/en/)
- July 2014: Final Steering Committee meeting
- July – Aug 2014: Open web consultation: **228** people registered, **39** responses received online and **14** responses by email
- September 2014: Final MPAC review, discussion at AFRO Programme Subcommittee and EURO Regional Committee, and submission to EB
- January 2015: Executive Board review
- March 2015: Submission to WHA
- May 2015: World Health Assembly Agenda item

Principles

- All countries can accelerate efforts towards elimination through combinations of interventions tailored to local contexts.
- Country ownership and leadership, with involvement and participation of communities, are essential to accelerating progress through a multisectoral approach.
- Improved surveillance, monitoring and evaluation, as well as stratification of programmes are required to optimize the implementation of malaria interventions.
- Equity in access to services especially for the most vulnerable and hard-to-reach populations is essential.
- Innovation in tools and implementation approaches will enable countries to maximize their progression along the path to elimination.

Vision, Milestones and Goal

- Decision to retain the global targets although dominated by mortality and morbidity
- The timeframe of the goals is now aligned with the SDGs
- Countries will set their own national or subnational goals
- Inclusion of a 4th goal to address prevention of re-establishment in malaria free countries

Vision – A world free of malaria			
	Milestones		Goal
	2020	2025	2030
Reduce malaria mortality rates globally compared with 2015	≥40%	≥75%	≥90%
Reduce malaria case incidence globally compared with 2015	≥40%	≥75%	≥90%
Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
Prevent re-establishment in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

Pathway to malaria elimination

- **Progression towards malaria-free status is continuous**; not independent stages
- At all levels of endemicity, there is significant in-country variation in malaria risk; stratification of programmes will be key to optimizing local responses
- All countries with moderate to high transmission must **ensure maximal reduction of morbidity and mortality through universal access to quality-assured vector control, diagnosis and treatment with support from an efficient surveillance system**
- When programmes reduce transmission to low levels, they should **assess the technical, operational and financial feasibility of malaria elimination**
- As programmes approach elimination or work to **prevent re-establishment of transmission, all cases need to be detected and managed by general health services,** and reported as a notifiable disease to a national malaria registry.

PILLAR 1: Ensure Universal Access to Malaria Prevention, Diagnosis & Treatment - Vector Control

Maximize the impact of vector control

Maintain robust entomological surveillance and monitoring

Manage insecticide resistance & respond to vector behaviour

Strengthen capacity for evidence-driven vector control

PILLAR 1: Ensure Universal Access to Malaria Prevention, Diagnosis & Treatment

- Expand preventive therapies to prevent infection in most vulnerable groups
- Protect all non-immune travellers and migrants
- Ensure universal diagnostic testing of all suspected cases
- Provide quality-assured treatment
- Scale up community-based diagnosis & treatment
- Monitor safety and efficacy of antimalarial medicines & manage antimalarial drug resistance
- Contain antimalarial drug resistance & remove inappropriate antimalarials from markets

PILLAR 2: Accelerate efforts towards elimination and malaria-free status

- Acceleration strategies maximize the impact of existing tools and prioritize reducing the level of malaria transmission by targeting both the parasite and vector
- New tools and approaches are expected to target and clear the undiagnosed infections

Refocus programmes and enact legislation

Renew political commitment and deepen regional collaboration

Reduce the number of undiagnosed infections

Implement targeted malaria vector control

Deploy transmission-blocking chemotherapy

Apply active case detection to control outbreaks, attain elimination or prevent re-introduction

Use antimalarial medicines to reduce the parasite pool

Maintain chemoprophylaxis for travellers

Devise *P. vivax* specific strategies

Use surveillance as an intervention in elimination programmes

PILLAR 3: Transform malaria surveillance into a core intervention

- Surveillance in areas of high transmission
- Surveillance in areas of low transmission
- Surveillance in areas targeted for elimination of malaria
- Functioning routine information systems are critical
- Information necessary for understanding disease trends and overall programme performance
- National strategic plans need to account for epidemiology and heterogeneity
- implementation of national strategic malaria plans should be monitored
- Monitoring the surveillance system

Harnessing Innovations and Expanding Research

Vector Control

- New tools are under development to address insecticide and behavioural resistance of interventions and strategies are being explored to improve delivery and reduce cost

Diagnostic testing and treatment

1. Diagnostics: Detect low-level asymptomatic parasitemia; better species-specific point-of-care RDTs for all non-falciparum malaria and hypnozoites of *P. vivax; and* rapid diagnostics for G6PD status
2. Treatment: Robust pipeline required to manage resistance; safe and effective single-dose treatment that is a radical cure, reduces transmissibility of gametocytes, has prophylactic effect, can be used during pregnancy, and for people with G6PD deficiency

Malaria vaccines

- Malaria vaccines are expected to be a future addition to the core package of interventions.

Surveillance

- Advances in technology and communications offer prospects to improve timeliness of reporting, increased data sharing and enhanced data analysis

Elimination

- Research is need to better define appropriate transmission settings, optimum combinations of approaches, intervals between treatments and methods for monitoring

Strengthening the Enabling Environment

- Increase international and domestic financing
- Ensure robust health sector response
- Strengthen multi-sectoral collaboration
- Improve government stewardship
- Encourage private sector participation
- Enable community leadership and NGO engagement

Measuring global progress and impact

Proposed Outcome Indicators

- Proportion of population at risk who slept under an ITN the previous night
- Proportion of population at risk protected by IRS within the past 12 months
- Proportion of pregnant women who received at least 3 or more doses of IPTp during antenatal care visits during their previous pregnancy (sub-Saharan Africa only)
- Proportion of patients with suspected malaria who receive a parasitological test
- Proportion of patients with confirmed malaria who receive first-line antimalarial treatment according to national policy
- Proportion of health facility monthly reports received at national level
- Proportion of estimated malaria cases detected by surveillance systems
- **Proportion of cases fully investigated (programmes engaged in elimination)**
- **Proportion of foci fully investigated (programmes engaged in elimination)**

Proposed Impact Indicators

- Parasite prevalence: proportion of the population with evidence of malaria infection
- Number of confirmed malaria cases per 1000 persons per year
- Number of malaria deaths per 100 000 persons per year
- **Number of countries that have newly eliminated malaria since 2015**
- **Number of countries that eliminated malaria by 2015 in which malaria was re-established**

Role of the WHO Secretariat

- Set, communicate and disseminate normative guidance, policy advice and implementation guidance, swiftly integrating new tools through the work of the Malaria Policy Advisory Committee
- Provide guidance to Member States to review and update national malaria strategies
- Work with countries to improve management and use of data for decision-making; monitor implementation and progress toward targets (2020, 2025 and 2030).
- Monitor regional and global malaria trends and support efforts to monitor efficacy of drugs and vector control interventions. All data will be made available to countries and global partners.
- Promote research and knowledge generation to accelerate progress toward elimination
- Update the GTS regularly to ensure linkage to the latest policy recommendations

Thank You!

Developing the 2nd Global Malaria Action Plan

Process, structure, content and timelines

Update for the Malaria Policy Advisory Committee meeting

10 September 2014

Swiss TPH | Deloitte. Contracted by Roll Back Malaria

Over 1100 stakeholders consulted to date

- 100+ people completed an **online survey** to assess the current GMAP and gather ideas for GMAP2
- ~250 stakeholders from over 60 countries participated in 6 **regional consultations**
- ~700 + stakeholders participated in 10 **community and country level consultations**. At least 5 more countries will hold consultations to review the draft document.
- 100+ stakeholders participated in **key informant interviews**
- 60+ documents read as part of the **literature review**
- www.gmap2.org launched in English, French & Spanish on World Malaria Day 2014
- 2000+ individual users to date on **GMAP2 web pages**, followers on Twitter and discussions in the GMAP2 LinkedIn group

Consultation page on www.gmap2.org

English Espanol Francais

Home About Consultations Countries GMAP2 Document Participate Timeline

ROLL BACK MALARIA PARTNERSHIP

The GMAP2 Consultative Process

The content of the GMAP2 document will be the result of an extensive consultative process with global, regional and country-level stakeholders from across the RBM constituencies, including Governments, Bilateral & Multilateral Agencies, Foundations, Research & Academia, Civil Society and the Private Sector. Regional consultations are already underway. Plenary presentations, discussions and group work are directly informing the development of the GMAP2. Some of the key areas being covered include how a "business case" can be made for malaria reduction and elimination; how this varies according to the constituency, as well as a country's socio-economic context and its malaria situation. Sessions are also being held on accelerating multisectoral action, engaging the private sector and unleashing the power of civil society to ensure the fight against malaria is won.

Schedule of Regional Consultations March-June 2014

AFRO region (Francophone)	20-21 March	Brazzaville Congo	Report PDF-EN	Report PDF-FR
PAHO region	03-04 April	Panama City Panama	Report PDF-EN	Report PDF-ES
AFRO region (Anglophone)	10-11 April	Harare Zimbabwe	Report PDF-EN	
EMRO region	17-18 April	Casablanca Morocco	Report PDF-EN	
SEARO region	30 Apr.-1 May	New Delhi India	Report PDF-EN	
WPRO region	12-13 June	Manila Philippines	Report PDF-EN	

Countries page on www.gmap2.org

English Espanol Francais

Home About Consultations Countries GMAP2 Document Participate Timeline

ROLL BACK MALARIA PARTNERSHIP

Country and Community Level Consultations

A series of country consultations for GMAP2 have now started. These consultations start with engagement visits to affected communities, followed by a national consultative meeting with a wide spectrum of stakeholders from community to central level, and from different constituencies and sectors. A "toolkit" of all the materials that are needed to run a country consultation is now available. It is comprised of the following documents: Country Consultation Description and Country Consultation Toolkit and Country Consultation Facilitation Guide. By having these tools any potentially interested country can arrange its own consultation. If you would like to find out more about holding such a consultation please contact the GMAP2 focal person at RBM as specified in the Toolkit document. The toolkit is also available in French, Spanish on the respective pages of this site and can be made available in Portuguese upon request.

Community consultation in the Philippines

The engagement visits took place in Rizal and Palawa Provinces.

Community consultation in India

The engagement visits took place in Guwahati and Nagaon District in Assam State.

Schedule of country consultations

The following countries have already indicated a possible timeframe for holding a consultation, others will hopefully follow soon.

Country	Date	Site visits	Location	Convener	Report
Philippines	16-20 June	Rizal & Palawa Provinces	Manila	Philipinas Shell Foundation	
India	16-20 June	Guwahati, Nagaon District, Assam	Delhi	Caritas-India	
Myanmar	23-27 June	Mon State	Yangon	Myanmar Health & Development Consortium	-

Based on the consultative process so far, GMAP2 must accomplish many things

Call for action

- Recognize **progress to date** while highlighting significant **work remaining**
- **Introduce GMAP2 and GTS** – building on the original GMAP, but not the same (the situation has changed since 2008), expanding the call to other sectors

Align and position

- Acknowledge the **external issues that will impact malaria and the global response** through 2030: How malaria fits in the SDGs; the changing financial and political landscape; social, cultural, gender, environmental, biological and health system influences.

Advocate

- **Build the case for investment in malaria, demonstrating the returns**

Accelerate Progress

- Identify the **challenges** that are holding us back, and the **opportunities and efficiencies** that we can take advantage of. Prioritize the **areas most in need of attention** in order to achieve control/elimination goals.
- Provide an **implementation framework** to engage all sectors, create and strengthen partnerships, leverage the key strengths of the different players, and maximize the resources we have available.
- Put **people at the center of the response** and **strengthen accountability**
- Create a structure for a **living document;** eg. a short advocacy section that can be updated at defined intervals.

Proposed Structure: Chapter 1 – Introduction

Chapter 1 will set the stage, call on the malaria community to remain focused, expand the call to the wider health sector, and to other sectors

- Introduce the RBM Partnership, summarize progress under GMAP1
- Show the link between GTS and GMAP2 and how the processes were aligned
- Introduce the common milestones, targets and vision of a malaria-free world
- Outline how GMAP2 and the fight against malaria fit in the post-2015 agenda
- Describe the consultative process through which GMAP2 was developed
- Explain the purpose of GMAP2 and how it can be used

Chapter 2 – Positioning for the future

Chapter 2 will highlight the context that influences malaria and the global response through 2030

- Adapting to the new development agenda/how progress in malaria contributes to the Sustainable Development Goals
- Responding to a changing financial landscape
- Addressing the political elements
- Understanding the social and cultural context
- Managing ecological and environmental factors
- Mitigating biological risks
- Strengthening health systems and integration
- Improving responsiveness and targeting to reach those in greatest need
- Gathering the evidence

Chapter 3 – the case for investing in malaria

Chapter 3 will make the global case for investing in malaria and demonstrate the returns on this investment

- Building the case for investment in malaria
- The economic case – financial returns
- Development, public health and humanitarian returns
- Using the case: advocating for investment in malaria

Chapter 4: Critical actions for improved control and elimination

Chapter 4 picks up the themes raised in chapter 2 and shows how to accelerate to action. Use will be made of case studies from across the RBM constituencies and across the world regions.

- Forging partnership across countries and sectors for sustainable development
- Increasing financial investment in malaria
- Creating enabling policies
- Strengthening health systems and integration
- Keeping people at the center: targeting interventions to those most at need
- Generating data and building a stronger evidence base as we move forward

Chapter 5:Monitoring and evaluation

Chapter 5 may provide a limited number of indicators for the main areas of GMAP2

- Successful partnerships
- Multisectoral collaboration
- Resource mobilization – source/type
- Policy and regulation
- Innovations
- Strengthening the evidence base – data creation, quality, use, sharing etc.

Timelines for the GMAP2 development process

Draft	Approximate Timeframe	Reviewer
Initial Draft	September 12, 2014	Task Force
Draft 2	October 31, 2014	Task Force
Draft 3	December 31, 2014	Task Force
Draft 4	January 31, 2015	General Public
Draft 5	March 31, 3015	Task Force
Final Draft	June 15, 2015	Task Force

Update on GPIRM Implementation: Progress, Challenges and the Way Forward

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 10 September 2014

Vector Control Unit
Global Malaria Programme

World Health Organization

GLOBAL MALARIA PROGRAMME

Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM): Five-Pillar Strategy

Short-term (~3 years)
Preserve susceptibility and slow the spread of resistance on the basis of current knowledge, and reinforce monitoring capability and activities

Medium-term (3–10 years)
Improve understanding of IR and tools to manage it, and adapt strategy for sustainable vector control accordingly

Long-term (≥10 years)
Use innovative approaches for sustainable vector control at global scale

Five pillars of strategy

I. Plan and implement insecticide resistance management strategies in malaria-endemic countries.

II. Ensure proper, timely entomological and resistance monitoring and effective data management.

III. Develop new, innovative vector control tools.

IV. Fill gaps in knowledge on mechanisms of insecticide resistance and the impact of current insecticide resistance management strategies.

V. Ensure that enabling mechanisms (advocacy, human and financial resources) are in place.

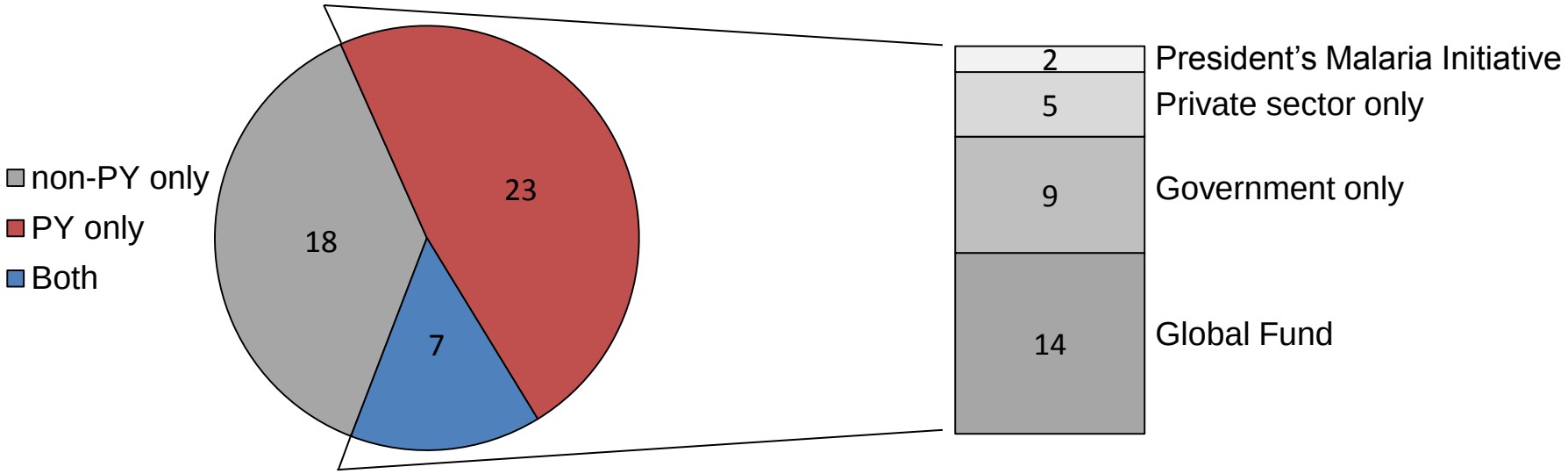
Source: WHO (2012) GPIRM

PILLAR I
Plan and implement IR management strategies (1)

- Insecticide resistance (IR) is spreading geographically and in intensity – especially to pyrethroids (PY)
- Current recommendation is universal coverage of at-risk populations with LLINs or IRS if appropriate. Focal IRS can be implemented with LLINs for resistance management purposes
  - IRS chemicals should be rotated (by mode of action) ideally on an annual basis. Non-PY IRS must be used where LLIN coverage high
  - Mosaics also recommended but are often impractical and difficult to implement. Mixtures not yet available for LLINs or IRS
- Many countries face challenges in adopting these recommendations mainly due to high cost of non-PYs
  - PY = USD2-3* (x 2), carbamate = USD11* (x 3), new organophosphate = USD24* (x 1) - although operational costs differ
- Use of more expensive non-PY IRS has resulted in overall reductions in IRS coverage (with IRS stopped in 2 countries)

PILLAR I
Plan and implement IR management strategies (2)

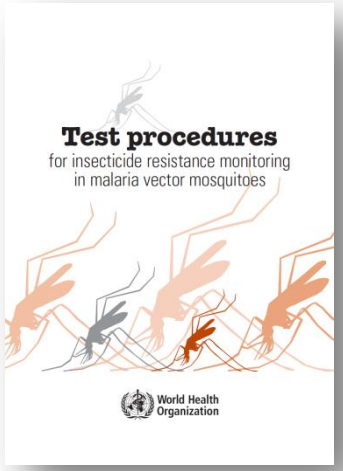
*Countries that implemented IRS by reported insecticide class and funder, 2013**

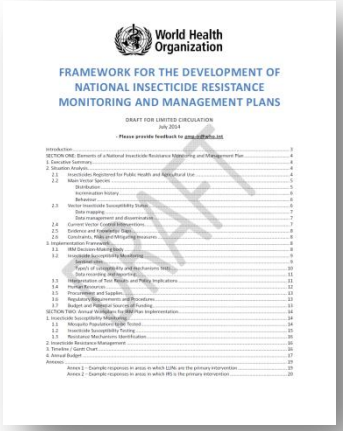


- Many of the 30 countries that used PY for IRS did so in areas where there was high LLIN coverage (despite GPIRM)
- Even when non-PY were used this was mostly due to detection of resistance rather than good management practice of rotation as part of long-term national strategy

PILLAR II. Enhance capacity for routine monitoring of insecticide resistance and data management (1)

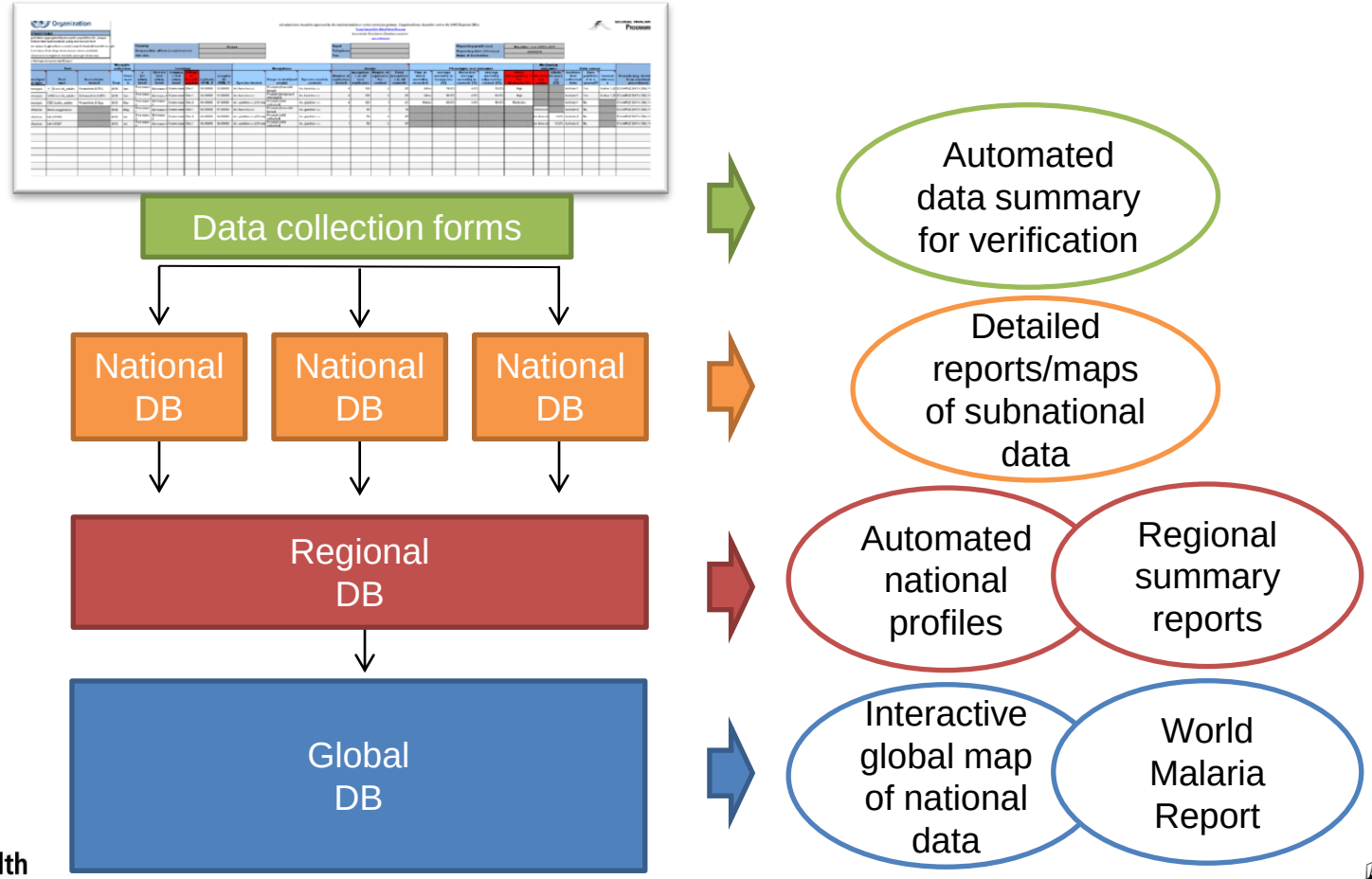
- Key WHO document on procedures for IR monitoring was developed, translated and disseminated with good uptake
- Trainings conducted by WHO and partners to enhance capacity although difficult to document content, participants and outcomes
- Draft framework produced to guide systematic planning and budget of national IR monitoring and management plans for integration into NSPs. Will allow standardization across countries and assist with resource mobilization





PILLAR II. Enhance capacity for routine monitoring of insecticide resistance and data management (2)

- Global tracking system for IR data established with global, regional and national databases under development



PILLAR III
Development and deployment of new tools (1)

- New interventions are needed to address IR - and residual transmission
- Work in this area has been led by the Product Development Partnership of the Innovative Vector Control Consortium and industry
- Vector Control Advisory Group (VCAG) was established by MPAC to review new paradigms/tools/technologies
  - Shorten the process to get products to end users
- *Challenge: How do we prepare countries for rapid and appropriate deployment of new tools?*

PILLAR III
Development and deployment of new tools (2)

IRS

- New long-lasting IRS formulations
  – 2 available (1 PY and 1 non-PY)
- Other non-PY IRS formulations
  – available in 12 - 24 months

LLINs

- First generation LLINs (PY+PBO) with enhanced efficacy but not IR management tools
  – 2 available
- New generation LLINs (multi-insecticides) as true IR management tools
  – several currently in early stage of development, availability forecast 2017 onwards

- Portfolio of novel products - established and expected in 2022

PILLAR IV
Fill gaps in knowledge (1)

Resistance mechanisms

- Understanding mechanisms (especially metabolic) is key to managing IR but identification of metabolic pathways is very complex
- Progress made in reducing the time taken to assess mechanisms – from 6-12 months to a few weeks
- But most malaria endemic countries lack necessary equipment and expertise
  - Need to establish country/regional reference centres of excellence
  - Need to support trained scientists from malaria-endemic countries with necessary resources to apply their skills

PILLAR IV
Fill gaps in knowledge (2)

Impact of resistance on malaria transmission

- While understanding this is essential, it is a difficult task
- Evaluations to date have given differing results
  - How do you design a study that takes into account multiple confounders when resistance is not randomly distributed?
- On-going 5-country project and emerging evidence from Sudan suggest that IR does have an impact on the effectiveness of vector control and hence malaria transmission

PILLAR V
Advocacy for resources to implement GPIRM

- GPIRM launch brought together high-level representatives each of whom made strong statements in support of GPIRM
- Document was translated and widely disseminated
- However, cost of PY alternatives has been one of the limiting factors to managing IR as recommended in GPIRM
- Discussions on price concessions not very successful mainly due to inherent problems in forecasting market demand
- Major priority to maintain traditional funding whilst accounting for GPIRM. Resource mobilization efforts led by WHO and CDC to target non-traditional donors not successful
  - Support for country-driven activities (eg. to collect, analyse, manage and share entomological data including on IR) is especially poor

Call to action

- Preserving the effectiveness of available products and tools is not an option but an imperative → universal access
- We should not wait until we see increase in malaria cases due to IR
- Rotational IRS will remain key to managing IR until we have multi-insecticide LLINs (or mixtures for IRS)
- It is unacceptable to witness a decline in the proportion of population protected or to be unable to conduct resistance management as a result of costly PY alternatives
- Global inaction will essentially deprive affected communities of their basic right of universal access to effective malaria prevention

Thank you!

Update on implementation of the *Global plan for insecticide resistance management in malaria vectors*[1]

- The *Global plan for insecticide resistance management in malaria vectors* (GPIRM) was launched in May 2012 in response to widespread insecticide resistance
- Resistance particularly to pyrethroids has since increased at an alarming rate
- Some progress has been made in implementing GPIRM technical recommendations
- Yet adoption to policy and operational implementation at country level have generally been poor due to a lack of political will coupled with major financial, human and infrastructural resource deficiencies
- Urgent efforts are needed to ensure correct use of existing interventions and availability of new tools in order to maintain the effectiveness of malaria vector control
- A comprehensive situation analysis should be conducted and a global response plan developed

INTRODUCTION

Recent reductions in malaria transmission have largely been achieved due to widespread deployment of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS).[2] However, these are threatened by the rapid increase in the distribution and the intensity of malaria vector resistance to insecticides. This is of particular concern for pyrethroids, which are the only insecticides currently used in LLINs and are widely used for IRS.

The *Global plan for insecticide resistance management in malaria vectors* (GPIRM)[3] was released in May 2012 and outlines a comprehensive five-pillar plan for global, regional and national action. The five pillars of GPIRM are: 1) Plan and implement insecticide resistance management strategies in malaria-endemic countries; 2) Ensure proper, timely entomological and resistance monitoring and effective data management; 3) Develop new, innovative vector control tools; 4) Fill gaps in knowledge on mechansims of insecticide resistance and the impact of current insecticide resistance management strategies; and, 5) Ensure that enabling mechanisms (advocacy, human and financial resources) are in place. This plan is not only for countries with ongoing malaria transmission, but also those for which malaria transmission re-establishment is possible.

In the two years since the launch of GPIRM, the insecticide resistance situation has worsened significantly, particularly in the African Region. Pyrethroid resistance has continued to spread in the major African malaria vectors of *Anopheles gambiae* and *Anopheles funestus*. New resistance mechanisms have been detected in *An. gambiae* from West Africa in addition to those formerly

[1] This document was prepared as a pre-read for the September 2014 meeting of the Malaria Policy Advisory Committee (MPAC) and is not an official document of the World Health Organization.

[2] World Health Organization (2013). *World Malaria Report 2013*. Geneva, Switzerland.

[3] World Health Organization (2012). *Global Plan for Insecticide Resistance Management in malaria vectors*. Geneva, Switzerland.

circulating.[4] This has resulted in levels of resistance elevated by an order of magnitude as well as cross-resistance to additional insecticides,[5] which prompted abandonment of further product development with what was to be a new public health insecticide class.

Against this background of rapidly escalating resistance there has been some progress in the implementation of GPIRM recommendations. This includes an enhancement in capacity for insecticide resistance monitoring, development of new vector control products and the establishment of global and regional insecticide resistance databases. However, while some countries have switched from using pyrethroids in IRS, most have yet to establish insecticide resistance management plans incorporating ongoing rotation of insecticides with different modes of action. Four insecticide classes of only two modes of action remain available for IRS and only one is used for LLINs. GPIRM implementation has been further limited by a lack of political will coupled with major financial, human and infrastructural resource deficiencies.

The objective of this update is to highlight the progress made and the challenges faced in the implementation of GPIRM since 2012, and to propose actions for accelerating its adoption at an operational level.

PILLAR I. Plan and implement insecticide resistance management strategies in malaria endemic countries

Pyrethroid resistance is rapidly spreading geographically and in intensity. To manage insecticide resistance using current tools, GPIRM recommends rotational or mosaic use of insecticides in IRS, and where LLINs are present, combination with targeted IRS using non-pyrethroids.[6] However, the rapidly escalating pyrethroid resistance situation and the paucity of affordable non-pyrethroid alternatives for IRS mean that countries and implementing partners have faced challenges in the adoption of these recommendations.

Of the 55 countries that reported the insecticide class selected for malaria IRS implemented in 2013, 25 used non-pyrethroid insecticides, 30 used pyrethroids and 7 used both.[7] While the continued use of pyrethroid IRS may be justified as part of a resistance management strategy (such as on a rotational basis)[8] and in the absence of LLINs, this was usually not the case. Of the 30 countries that continued to use pyrethroids for IRS in 2013, 14 were supported by the Global Fund,[9] 9 by government, 5 by private sector and 2 by the US President's Malaria Initiative.[10]

For those countries implementing non-pyrethroid IRS, this was often driven by the detection of high level pyrethroid resistance rather than pro-active implementation of good resistance management practice as part of a long-term national strategy. In general, for those countries that changed to non-pyrethroid IRS, there was an associated reduction in the overall proportion of the at-risk population

[4] Mixed function oxidases and *kdr* target site mutations.

[5] Hemingway J (2014). The role of vector control in stopping the transmission of malaria: threats and opportunities. *Phil Trans Roy Soc B* 369 20130431.

[6] Use of mixtures is also recommended but currently no WHO-recommended IRS or LLIN mixture formulations are available.

[7] Data compilation is ongoing by the WHO Global Malaria Programme.

[8] The continued use of pyrethroids in IRS rotations will be heavily dependent on the intensity and mechanisms of resistance in the local vectors and the speed at which resistance reverts once the pyrethroid selection pressure is relaxed.

[9] Scott Filler, personal communication, 25 July 2014.

[10] Christen Fornadel, personal communication, 26 July 2014.

protected by IRS due to the increased cost of procuring and deploying the non-pyrethroid alternatives.[11] For instance, in Liberia the detection of significant pyrethroid and DDT resistance in 2011 led to spraying in 2012 with a pyrethroid and a carbamate in different areas of the country for coverage of 23% of the at-risk population. In 2013, use of a long-lasting organophosphate formulation showed significant entomological impact, but due to the higher cost of this insecticide IRS coverage was reduced to 9.7% of the at-risk population. Subsequent consultations between the national programme and the donor led to a decision to suspend IRS and shift resources to support LLIN procurements. Donor support for IRS has been similarly discontinued in three other countries in Africa due to an inability to achieve economies of scale using a pyrethroid alternative.

While countries are currently at different stages of planning and implementing national insecticide resistance monitoring and management strategies, some have done so in a form that may serve as a useful example to countries undertaking this process. Brief examples are outlined in Annex 1.

PILLAR II. Ensure proper, timely entomological and resistance monitoring and effective data management

GPIRM highlighted the importance of routinely collecting, analysing, managing and sharing data on insecticide resistance to support timely and informed programmatic decision-making. As part of the normative role of WHO, a key document was developed to guide countries and partners on how to conduct insecticide resistance testing and interpret data for informing appropriate vector control.[12] One of the most important functions of this document has been to guide and standardise the reporting of insecticide resistance data in line with GPIRM recommendations to support pre-emptive action for resistance management. However, current procedures for monitoring insecticide resistance are not sufficient for measuring resistance intensity or predicting impact on intervention efficacy, and new test methods are needed.

In order to enhance national capacity to monitor and manage insecticide resistance, countries indicated a need for more concrete guidance on how to systematically plan and budget required activities and how best to integrate these into their national malaria strategic plans. WHO consequently developed a planning framework for insecticide resistance monitoring and management.[13] The document promotes adherence to the objectives of GPIRM and allows standardization across countries in the structure and content of national plans as well as in data collection tools. These plans are meant to form a basis around which to build a more comprehensive entomological monitoring programme that can address issues and answer questions pertaining to the targeting and effectiveness of malaria vector control interventions. Plans can also be used to request financial support from The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and other donors.

An effective global tracking system for insecticide resistance in malaria vectors is in the process of being established by WHO. A baseline survey to obtain data from 2000 to date has been linked to the World Malaria Report data collection process. By December 2014, data from countries will be consolidated into a global database which will be linked to regional databases. The global database will provide data aggregated to the country level and will allow for the online generation of reports and

[11] World Health Organization (2013). *World Malaria Report 2013*. Geneva, Switzerland.

[12] World Health Organization (2013). *Test Procedures for Insecticide Resistance Monitoring in Malaria Vector Mosquitoes*. Geneva, Switzerland.

[13] World Health Organization (2014 - *Draft for limited circulation*). *Framework for the Development of National Insecticide Resistance Monitoring and Management Plans*. Geneva, Switzerland.

maps by users to facilitate a rapid and up-to-date overview of resistance status. Databases managed by WHO regional offices will provide summaries for the countries of respective regions. These platforms will facilitate data sharing and will ensure timely availability of data to guide national and global malaria policy. Whereas in GPIRM the proposal was for the global database to be managed by a partner institution, countries indicated their preference for data management and database hosting to be conducted by WHO. Resources were therefore mobilized by WHO to implement this request from countries. Plans are also underway to include the rich historical data available in the WHO archives.

Development of technical competency through training is also key to supporting insecticide resistance monitoring and management. A number of regional as well as national training courses have been conducted since the launch of GPIRM. Partners, in particular the US President's Malaria Initiative, have been commendably involved in coordinating training workshops and the supply of bottle bioassay kits in countries where they operate. These have focussed on imparting knowledge and skills to national technicians on the collection of insecticide resistance data and on how to correctly analyse and interpret such data. The latter has been identified as a key issue given the complexity of correctly assessing all factors related to resistance required to correctly inform control interventions. In countries where PMI has been operating, capacity has been built in entomological surveillance including insecticide resistance monitoring as well as LLIN distribution and IRS implementation, monitoring and evaluation. Other partners have also supported capacity building and regional initiatives.

Pillar III. Develop new innovative vector control tools

While current resistance management efforts focus on judicious use of insecticides through rotations and combinations, in the medium-term the development of new active ingredients for use in LLINs and IRS based on validated target product profiles is essential. To further reduce the insecticide selection pressure exerted by effective vector control tools, new interventions are needed to address residual transmission maintained by mosquito species exhibiting behaviour that allows them to avoid LLINs and IRS, such as by outdoor biting and resting or early-evening biting. Genetically modified (GM) mosquitoes may provide effective options in the longer term.

In response to the need for improved mechanisms for assessing the public health value of new vector control tools and technologies, and to aid the development of appropriate technical recommendations, the Malaria Policy Advisory Committee constituted the Vector Control Advisory Group (VCAG) in 2012. The group is jointly managed by the WHO Global Malaria Programme and the Neglected Tropical Diseases departments and is responsible for proposing recommendations on new forms/ tools/ technologies of vector control after reviewing their public health benefit. With the initial recommendation, WHOPES will then proceed with the development of product specifications for safety and efficacy by building on relevant data from potential innovators. The outcome of the VCAG process will be to shorten the time it takes to deploy validated vector control tools to protect populations from malaria and other vector-borne diseases.

To date, VCAG has established its working procedures and has reviewed 12 dossiers for potential products from innovators. VCAG is currently preparing guidelines for the minimum data set that will be required for innovators wishing to develop products to address pyrethroid resistance, and the appropriate product claims of effectiveness and resistance management.

The global pipeline of new insecticide-based vector control products has dramatically improved in the past five years, mainly due to the Innovative Vector Control Consortium (IVCC) programme with

industry (See Box 1). Although the different production development initiatives are a major step forward, the successful deployment of the existing core interventions and new products will require multi-sectoral coordination across many stakeholder groups. Specialist technical assistance is a necessity to ensure the limited number of tools available remains effective. Alongside innovation in product development and harmonisation of policy and regulatory processes, the funding mechanisms, cost, efficacy and benefits assessments and supply chains will all need to be managed to achieve a cost-effective and sustainable outcome for vector control.

Pillar IV. Fill gaps in knowledge on mechanisms of insecticide resistance and impact

BOX 1. DEVELOPMENT OF NEW PRODUCTS FOR MALARIA VECTOR CONTROL

Indoor residual sprays: Two new long-lasting formulations of existing IRS insecticides that exceed the 2–4 month established benchmark to last 6–12 months have already reached the market. Other formulations of repurposed agro-chemicals are under development, but are at best 12–24 months from becoming available for deployment. IVCC has established a portfolio of novel active ingredient candidates that should deliver new public health insecticides by 2022. If these novel insecticides are to reach the market in the predicted timeframe, the global and national regulatory framework will need to be adapted in order to avoid delays in availing these insecticides for use.

L*ong-lasting insecticidal nets:* New formulations are in preparation, with the first generation of these containing a pyrethroid plus a synergist or growth regulator. An important step will be to examine potential additional benefits against pyrethroid-resistant *Anopheles*. A second generation of non-pyrethroid multi-insecticide nets is in early stage development but it is likely to be several years before these are available for wide-scale deployment.

Spatial repellents: Currently there are insufficient data to assess whether spatial repellents could play a substantive role in disease prevention. A multi-country coordinated field trial of the effectiveness of repellents is under way which should establish whether repellents work against most or just a small sub-set of mosquito vectors, but this study is unlikely to alone provide sufficient evidence to recommend wide-scale usage of repellent as part of national control programmes. Continued commitment from industry and research groups will be required to identify and validate any promising new candidates.

GPIRM set out some priorities for research in the short-, medium- and long-term, though it was acknowledged that the lack of full information and evidence in some key areas does not preclude immediate action to pre-emptively address insecticide resistance. Progress has been made in some but not in all identified areas.

Evidence on subregional and regional trends in the spread of resistance in locally important vector species. As outlined for Pillar II above, global and regional database are currently being constructed to consolidate all evidence on resistance status and mechanisms in malaria vectors. A regional meeting of the African Network on Vector Resistance is planned for late September 2014 at which representatives from NMCPs, WHO and/or national research institutes will present and discuss resistance data, and share experiences on development of national IRM plans. A similar process is planned for WHO South-East Asia Region in November 2014.

New knowledge on resistance mechanisms. Significant investment in defining and rapidly monitoring metabolic resistance mechanisms have been made by various institutes in recent years. This has essentially reduced the time required to assess the underlying causes of resistance from 6–12 months to a matter of weeks. While the methodology was published in 2011, the complexity of metabolic pathways impedes simplification of the monitoring system. Most malaria endemic countries therefore do not have the capacity for full characterization of resistance mechanisms. Indeed, many have yet to even conduct simple synergist bioassays as an indicator of underlying metabolic mechanisms even though these mechanisms are of vital importance in conferring operationally-significant resistance. The establishment or strengthening of country reference centres where possible, or regional centres of excellence and mechanisms to support malaria endemic scientists with resources will help address this problem.

Impact of resistance on malaria control. Assessing the impact of insecticide resistance on the effectiveness of interventions is an essential but difficult task. A number of studies on LLINs claiming to have evaluated this have yielded differing results. The Roll Back Malaria Partnership, via the Vector Control Working Group, commissioned a systematic review to assess the evidence on the impact of resistance on disease transmission and insecticide-treated net efficacy which was published in 2014.[14] In summary, despite numerous studies there are still insufficient data to ascertain the impact of resistance on disease transmission. Likewise, evaluations of the added impact of IRS in areas with LLINs and resistant *Anopheles* have provided inconsistent results and further evaluations are in progress. [15] Poor standardisation of methodologies, inadequate controls and poor or no characterization of underlying resistance mechanisms in most studies mean that even conclusions on entomological impact are limited.

Accurate assessment of resistance impact requires greater standardisation of methodologies, with studies undertaken of sufficient scale and power to generate meaningful conclusions. To this end, a 5-country project is being implemented in Benin, Cameroon, India, Kenya and Sudan with support from the Bill & Melinda Gates Foundation and coordination by GMP. With completion expected in 2016, interim results indicate the importance of adhering to GPIRM recommendations. They also point to the complexity of insecticide resistance and variations in impact on malaria transmission across different eco-epidemiological settings. (See Box 2 for example data from Sudan)

New evidence on insecticide resistance management methods. There is also a paucity of evidence on the utility of resistance management strategies on restoring the susceptibility of malaria vectors. In addition to studies on resistance impact, there is a need for carefully designed assessments of the operational implications of combination of chemical and non-chemical based interventions. Such strategies include rotational or mosaic application of insecticides of different modes of action in IRS implemented either broadly or on a targeted basis. Outcomes are likely to be dependent on the levels of malaria parasite transmission and the insecticide susceptibility or resistance mechanisms of local mosquitoes. These need to focus on validated cost-effective interventions that can be undertaken at scale within the constraints of the national malaria control programmes.

[14] Strode C, Donegan S, Garner P, Enayati AA, Hemingway J. (2014). The impact of pyrethroid resistance on the efficacy of insecticide-treated bed nets against African anopheline mosquitoes: systematic review and meta-analysis. *PLoS Medicine* 11(3):e1001619.

[15] World Health Organization (2014). *WHO guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets*. Geneva, Switzerland.

BOX 2. EMERGING EVIDENCE ON THE IMPACT OF INSECTICIDE RESISTANCE

In a cluster randomised trial in Sudan, 140 clusters in four study areas were randomly allocated to either full coverage with LLINs, or full coverage with LLINs plus IRS. Entomological indices and malaria prevalence and incidence were measured. Bendiocarb (carbamate) IRS was used in three of the four study areas. In the highest transmission areas of Galabat in Gedarif state, deltamethrin (pyrethroid) was used in 2011 and 2012 with a change to bendiocarb in 2013 following the detection of pyrethroid resistance.

The switch to bendiocarb in Gabalat was associated with a significant decline in malaria incidence, suggesting that resistance was compromising the efficacy of the pyrethroid IRS. While this indicates a higher efficacy of bendiocarb, it may not necessarily have resulted in an impact on the pyrethroid susceptibility status of the local vectors. Rotational application of insecticides should continue on the basis of local data in order to minimize the selection that would result from continuous use of a carbamate. Monitoring of resistance mechanisms is ongoing, and may be used to ascertain the impact of the initial and subsequent rotations resistance.

Pillar V. Ensure that enabling mechanisms (advocacy, human and financial resources) are in place

The GPIRM launch event brought together high-level representatives of all key constituencies within the global malaria community. Speakers urged affected countries and partners to take immediate action to preserve the effectiveness of current vector control tools, and to ensure that new public health interventions are made available soon and at an affordable cost. As part of a wider dissemination plan, the executive summary of GPIRM was translated into three of the six UN official languages and the document was circulated widely. WHO and partners also used every opportunity in both national and international forums to present GPIRM to ensure that it reached all intended audiences.

Attempts by WHO to engage industry partners on potential price concessions for existing or new IRS products have had limited success. The US President's Malaria Initiative also attempted to discuss pricing with industry, and advocated for insecticide manufacturers to look into price elasticity models i.e. if price goes down, quantity purchased goes up to reach an equilibrium point. This has not been successful in part because a high commodity price and single supplier for the only long-lasting, non-pyrethroid IRS formulation has led to a small and chaotic marketplace and low uptake, which results in a lack of reliable, long-term demand forecasting. Using their experience with LLIN procurement, the Global Fund is considering engaging with industry on a new procurement strategy for IRS in 2015. It should be noted that the basic cost of manufacture of the non-pyrethroid alternatives, whatever the volume, will nevertheless be significantly higher than that of pyrethroids.

The result of the ongoing high costs is that at country level there is a lack of access to affordable, quality non-pyrethroid insecticides. This provides a barrier to their widespread use, and means that when they are deployed overall reductions in IRS coverage rates may result. A key factor reinforcing this barrier is the lack of evidence on the cost-effectiveness of different insecticides, and limited capacity at the country level to use such evidence for local decision-making. For example, while pyrethroids are approximately 2–3 US dollars per sachet (requiring two spray rounds in areas with a transmission season beyond six months), bendiocarb is about 11 US dollars per sachet (requiring up to 3 spray rounds in areas with a transmission season beyond 9 months) and the new long-lasting organophosphate (pirimiphos-methyl) formulation is approximately 24 US dollars for a sachet

equivalent (requiring one spray round per season). However, once application costs are taken into account, the cost of spraying one round of the long-lasting organophosphate formulation may be similar to that required for two rounds of a pyrethroid. Unless the factors limiting programme access to non-pyrethroids are addressed, including reduction in costs for overall management and implementation of IRS, it is unlikely that the objective of GPIRM to maintain the effectiveness of vector control will be sustainable. Strategic transitioning of ownership to national programmes and building national capacity for and investment in IRS is vital.

In addition to the wide dissemination of GPIRM, concurrent efforts were undertaken for example by WHO and USA Centers for Disease Control and Prevention to mobilize financial resources. These included approaching traditional donors as well as exploring innovative ways to engage non-traditional donors such as through CDC Foundation for independent management of funds from sources including the private sector. These efforts were largely unsuccessful.

The critical need remains for resources to build the capacity of countries to collect, analyse, manage and share entomological data including on insecticide resistance,[16] as well as use the data appropriately to guide the management of insecticide resistance. The World Malaria Report data collection process will be used to track global progress on GPIRM implementation including capacity building, with the baseline human and infrastructural capacity assessment currently ongoing. Resources are also required within WHO to support countries in coordinating the implementation of technical recommendations outlined in GPIRM and other relevant policies.

Conclusions and the way forward

For most malaria endemic countries, particularly those in Africa south of the Sahara, pyrethroid resistance is spreading and there are increasing reports of resistance to organophosphates, carbamates and DDT. Pre-emptive action, as emphasised in GPIRM, has now been overtaken: immediate measures are needed to address resistance. Even where resistance is yet to be detected, resistance management must be implemented in order to preserve the effectiveness of available insecticide classes. This is imperative given the need for sustained universal access to LLINs and the limited options currently available for malaria vector control.[17]

Until new tools such as the second generation of non-pyrethroid multi-insecticide LLINs are available, insecticide resistance will to a great extent rely on the targeted use of IRS with insecticides of different modes of action in rotation. However, in areas of high pyrethroid resistance, such rotation options are now severely limited. A decline in the global at-risk population protected with IRS from 153 to 135 million (5% to 4%) in 2012[18] was largely attributable to the high cost of non-pyrethroid alternative insecticides. Thus, with the paucity and cost of alternatives as the main barriers to implementing GPIRM technical recommendations, it is vital that affordable options for vector control are urgently explored. Better global forecasting of insecticide requirements, pooled procurement and long term agreements and tax-free incentives have been successfully applied to the LLIN market. These approaches may be feasible to enhance the confidence of IRS chemical manufacturers, help stabilise the market and eventually lead to price reductions. Together, these actions may support the maintenance and/or scale-up of IRS for insecticide resistance management purposes, which must be

[16] Mnzava AP, Macdonald MB, Knox TB, Temu EA, Shiff CJ. (2014). Malaria vector control at crossroads: public health entomology and the drive to elimination. *Trans Royal Soc Trop Med Hyg*. Doi:10.1093/trstmh/tru101.

[17] World Health Organization (2011). *The technical basis for coordinated action against insecticide resistance: preserving the effectiveness of modern malaria vector control. Meeting report 4 – 6 May 2010*. Geneva, Switzerland.

[18] World Health Organization (2013). *World Malaria Report 2013*. Geneva, Switzerland.

conducted in parallel to enhanced entomological surveillance and insecticide susceptibility monitoring. The challenges of introducing IRS in countries with no previous experience should also be taken into account.

Countries and partners are urged to continue to develop and implement national insecticide resistance monitoring and management plans that include contingencies for more expensive alternative IRS insecticides as part of national strategic plans and funding submissions to the Global Fund. They are also encouraged to pursue resource mobilization to secure additional funds from elsewhere to cover the costs of deploying IRS alternatives. As the majority of countries implementing IRS depend heavily on external support - especially in high burden countries in Africa - there is a need to advocate for investments by hosting countries and donors that are coupled with national malaria strategic plans in order to transition to full country ownership and management.

In parallel with these efforts, additional investments should be made to build country capacity to monitor insecticide resistance, including quantifying resistance intensity and assessing its operational impact. Country reference centres run in collaboration with the national malaria control programme should be established, potentially by upgrading existing institutions with the necessary facilities. The complexity of characterizing the underlying resistance mechanisms means that establishing capacity for these assessments will not be practical in all malaria endemic countries. Country, regional or global centres that can rapidly assess mechanisms and feed-back results in a timely manner should be established to work alongside national programmes to ensure optimal uptake and use of information. This will help in building capacity of scientists from developing countries, particularly those working in national malaria control programmes. A mechanism is also needed to ensure that scientists who may have been trained internationally have the opportunity to utilise their technical and management skills to maximum effect in their own countries. Specialised re-entry grants, such as those previously issued by the WHO Special Programme for Research and Training in Tropical Diseases, or similar grant schemes should be implemented to address this.

WHO through MPAC must support these initiatives by building awareness and consensus around the extent of the problem of insecticide resistance - similar to those efforts with artemisinin resistance - and should explore ways to ensure that alternative products for managing insecticide resistance are affordable. The inclusion of a WHA resolution in the upcoming discussion of the draft Malaria Global Technical Strategy will need to request Member States to commit additional financial, infrastructural and human resources to address the threat of insecticide resistance to malaria control and elimination.

With the current knowledge and experience, it would be irresponsible for the global community to wait until malaria programmes report increases in malaria cases due to insecticide resistance before there is a significant response. Moreover, it is unacceptable to merely stand by and witness declines in IRS coverage due to a lack of resources for rotating with more expensive non-pyrethroid alternatives. Global inaction deprives affected communities of their basic right to universal access to effective prevention against malaria. It is therefore recommended that mechanisms are explored to develop a global emergency response plan for insecticide resistance in malaria vectors.

ANNEX 1. Examples of countries with experience in implementing insecticide resistance management

Equatorial Guinea

On Bioko, the main island of Equatorial Guinea, IRS was first conducted using deltamethrin in 2004. While *An. funestus* and *An*. *gambiae*[19] appear to have been eliminated from the island, high levels of a target-site resistance mechanism (L1014F *kdr* alleles) were rapidly detected in *An. Coluzzii.*[20] This resistance mechanism conferred DDT resistance and a low level of cross-resistance to all pyrethroids. The high frequency of this mechanism coupled with an apparent lack of response of the vector to the IRS, prompted the malaria control programme to change from pyrethroid usage. IRS was subsequently conducted with bendiocarb from 2005 to 2012. However, retrospective analysis of bioassay and infection data indicated that the initial deltamethrin IRS had in fact imparted a substantial epidemiological effect and that the *An. gambiae kdr* status alone was not operationally significant.[21] Following continuous bendiocarb usage for 7 years, an annual rotation of insecticides was instigated in 2013 with pyrethroids reintroduced despite a high frequency of *kdr*. For 2014-2015, IRS with both deltamethrin and bendiocarb is planned. Continuous monitoring of insecticide susceptibility and transmission will be undertaken. The national insecticide resistance management plan was finalized in 2012 by the National Malaria Control programme and will be approved by the Ministry of Health in September 2014 and published in both English and Spanish.

India[22]

Implementation of malaria vector control in India is based on data from routine monitoring of insecticide resistance. The National Vector Borne Disease Control Programme has come up with a stratified plan in which DDT is sprayed in a total of 255 districts, malathion in 35 districts and deltamethrin in 111 districts. In Surat district in Gujarat province, the local malaria vector species *An*. *culicifacies* was reported to be resistant to all three of these insecticides. Follow up monitoring showed that vectors were still resistant to DDT and malathion 30 and 9 years after withdrawal of IRS, respectively. On the other hand, susceptibility to deltamethrin returned by 3 years after its withdrawal in the area. It is important that programmes in such a similar situation do not merely switch insecticides but rather rotate the use of insecticides as recommended in GPIRM.

Senegal[23]

IRS was conducted in seven districts of Senegal using the pyrethroids lambda-cyhalothrin (2007 to 2009) and deltamethrin (2010). High levels of resistance to both pyrethroids and DDT were detected in species of *An. gambiae s.l.* but susceptibility to carbamates and organophosphates remained. After reviewing these data, a national technical committee on vector control recommended replacement (not rotation *per se*) of pyrethroids with bendiocarb in 2011. Subsequent routine monitoring of vector susceptibility has indicated a gradual restoration of pyrethroid and DDT susceptibility in some districts. Species composition, *kdr* frequency and data on malaria cases are currently being evaluated. It is hoped that restoration of susceptibility to pyrethroids will allow the inclusion of this insecticide class in future rotations for IRS in Senegal.

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[19] Formerly *An. gambiae* S form.

[20] Formerly *An. gambiae* M form.

[21] Hemingway J, Vontas J, Poupardin R, Raman J, Lines J, Schwabe C, Matias A, Kleinschmidt I. (2013). Country-level operational implementation of the Global Plan for Insecticide Resistance Management. *Proc Natl Acad U USA* 110: 9397-9402.

[22] Raghavendra K, Verma V, Srivastava HC, Gunasekaran K, Sreehari U, Dash AP (2012). Persistence of DDT, malathion & deltamethrin resistance in *Anopheles culicifacies* after their sequential withdrawal from indoor residual spraying in Surat district, India. *Indian J Med Res* 132: 260-264.

[23] Ousmane Faye, personal communication, 18 July 2014.

Sudan

An Intersectoral Steering Committee for Vector Control was established in 2005 that provides the Sudanese Government with policy and operational recommendations on vector control. Membership includes representatives from the National Vector Control Programme, ministries of health, agriculture, environment and industry, as well as regional malaria coordinators. Research and other academic intuitions, WHO technical advisory staff and other relevant experts are also members. Meetings are conducted quarterly to discuss and decide on vector control interventions, and insecticide resistance data are reviewed at least annually in order to inform operational planning. Further detail can be found in Box 2 on research to assess the impact of insecticide resistance on malaria transmission.

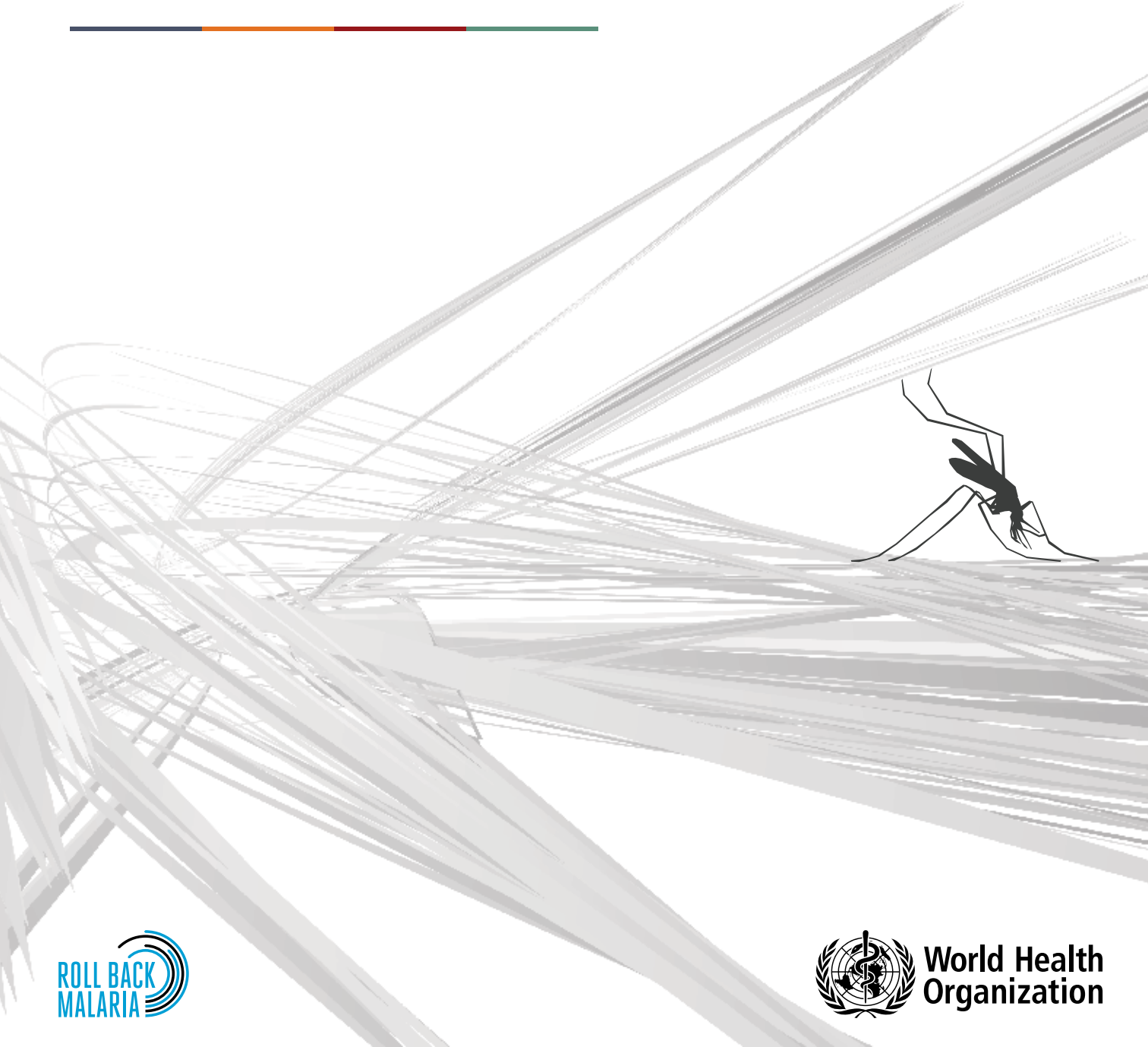
Zambia

Zambia has formed a multi-sectoral insecticide resistance management technical working group, under the auspices of the National Malaria Control Centre. This group includes research and academia, public and private sector, donors and other partners. They review all published and unpublished data for the three main malaria vectors (*An*. *gambiae*, *An*. *arabiensis* and *An*. *funestus*) and have established a long term resistance management plan against which progress is monitored[6]. Spatio-temporal national maps of resistance are produced by combining all data from numerous sources. Based on a review of these data, a country-level mosaic of IRS driven by the local vector susceptibility profiles has been instigated, with bendiocarb IRS in the Copperbelt and pirimiphos-methyl in Eastern provinces. The impact of rotating the IRS insecticides is being closely monitored.

WHO GLOBAL MALARIA PROGRAMME

GLOBAL PLAN FOR INSECTICIDE RESISTANCE MANAGEMENT

IN MALARIA VECTORS



ROLL BACK MALARIA

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CONTENTS

NAVIGATING THE GPIRM

Executive summary: provides a brief but comprehensive overview of the GPIRM.

It is recommended that all readers first examine this summary, which is intended as a guide for the main aspects of the document.

Part 1: ***The threat of insecticide resistance*** explains what insecticide resistance is and why it is a concern for malaria control; it also presents the available strategies for managing resistance.

This section will be particularly helpful for readers who wish to gain an indepth understanding of the threat of resistance (e.g. extent, trajectory, operational impact) and interesting for those who have a good level of knowledge on this topic.

Part 2: ***Collective strategy against insecticide resistance*** outlines the activities necessary to preserve the effectiveness of malaria vector control.

Insecticide resistance management must be a collective response, and all stakeholders have a role to play in making the strategy successful. It is important that stakeholders understand the overall strategy, at both global and country levels.

Part 3: ***Technical recommendations for countries*** outlines a framework for policy-making to manage insecticide resistance, depending on the type of vector control interventions already in place and on the mechanism and level of resistance. This framework will be refined during further consultations as new evidence becomes available.

This section considers different scenarios at country level and contains tables of consensus recommendations on how to address each of these scenarios (pages 79 to 87). The section will be most helpful for managers of national malaria control and vector control programmes, WHO regional and country staff and agencies involved in planning and implementing vector control strategies.

Part 4: ***Near-term action plan*** describes the roles of each stakeholder group and lists concrete activities that should be undertaken in the short term (particularly within the next 12 months) to implement the strategy.

All stakeholder groups should read this section in order to understand their respective roles in preserving effective malaria vector control.

ACRONYMS AND ABBREVIATIONS

DDT	dichlorodiphenyltrichloroethane
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GPIRM	Global Plan for Insecticide Resistance Management in malaria vectors
IRM	insecticide resistance management
IRS	indoor residual spraying
ITN	insecticide-treated net
kdr	knock-down resistance gene
LLIN	long-lasting insecticidal net
PMI	President's Malaria Initiative
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme

CONTRIBUTORS

The Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM) was prepared in consultation with members of each of the constituencies of the Roll Back Malaria Partnership. The WHO Global Malaria Programme would like to thank the many individuals and institutions that participated in preparation of the GPIRM for their invaluable advice provided in interviews and consultations, comments on the initial fact base or review of the final document.

Tarekegn Abeku, Malaria Consortium, London, United Kingdom of Great Britain and Northern Ireland

Rabindra Abeyasinghe, WHO Country Office for Papua New Guinea, Port Moresby, Papua New Guinea

Nicole Achee, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

Doreen Ali, National Malaria Control Programme, Lilongwe, Malawi

Pedro Alonso, Barcelona Centre for International Health Research, Barcelona, Spain

Chioma Amajoh, National Malaria Control Programme, Abuja, Nigeria

Birkinesh Ameneshewa, WHO Regional Office for the African Region, Inter-country Support Team East and Southern Africa, Harare, Zimbabwe

Hoda Atta, WHO Regional Office for the Eastern Mediterranean Region, Cairo, Egypt

Rifat Atun, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

Kate Aultman, Bill & Melinda Gates Foundation, Seattle, Washington, USA

Sam Awolola, Institute for Medical Research, Lagos, Nigeria

Magaran Bagayoko, WHO Office for the African Region, Brazzaville, Congo

Suprotik Basu, Office of the United Nations Secretary-General's Special Envoy for Malaria, New York City, New York, USA

Gregory Beavers, Armed Forces Pest Management Board, Washington, District of Columbia, USA

Allison Belemvire, United States President's Malaria Initiative, United States Agency for International Development, Washington, District of Columbia, USA

David Brandling-Bennett, Bill & Melinda Gates Foundation, Seattle, Washington, USA

William Brogdon, United States President's Malaria Initiative, United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Valentina Buj, United Nations Children's Fund (UNICEF), New York City, New York, USA

Nichola Cadge, United Kingdom Department for International Development, London, United Kingdom of Great Britain and Northern Ireland

Kate Campana, Malaria No More, New York City, New York, USA

Kent Campbell, Malaria Control and Evaluation Partnership in Africa (MACEPA), Seattle, Washington, USA

Pierre Carnevale, Institut de recherche pour le développement, Montpellier, France

Keith Carter, WHO Regional Office for the Americas, Washington, District of Columbia, USA

Emanuel Chanda, National Malaria Control Programme, Lusaka, Zambia

Fabrice Chandre, Institut de recherche pour le développement, Montpellier, France

Chang Moh Seng, WHO Regional Office for the Western Pacific, Manila, Philippines

Desmond Chavasse, Population Services International (PSI), Nairobi, Kenya

John Chimumbwa, RTI International, Nairobi, Kenya

John Chipwanya, National Malaria Control Programme, Lilongwe, Malawi

Eva Christophel, WHO Regional Office for the Western Pacific, Manila, Philippines

Thomas Churcher, Infectious Disease Epidemiology, Imperial College London, London, United Kingdom of Great Britain and Northern Ireland

Richard Cibulskis, Global Malaria Programme, WHO, Geneva, Switzerland

Alison Clements-Hunt, WHO Consultant, Geneva, Switzerland

Maureen Coetzee, Malaria Entomology Research Unit, Wits University, Johannesburg, South Africa

Justin Cohen, Clinton Health Access Initiative, Boston, Massachusetts, USA

Jide Coker, National Malaria Control Programme, Abuja, Nigeria

Mike Coleman, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

Frank Collins, University of Notre Dame, South Bend, Indiana, USA

Marc Coosemans, Institute of Tropical Medicine, University of Antwerp, Antwerp, Belgium

Vincent Corbel, Institut de recherche pour le développement, Cotonou, Benin

Allen Craig, United States President's Malaria Initiative, United States Centers for Disease Control and Prevention, Lusaka, Zambia

Janice Culpeper, Bill & Melinda Gates Foundation, Seattle, Washington, USA

Aditya Prasad Dash, WHO Regional Office for South-East Asia, New Delhi, India

Peter DeChant, Valent BioSciences, Libertyville, Illinois, USA

Akshay Dhariwal, National Vector Borne Disease Control Programme, New Delhi, India

Abdoulaye Diop, Programme National de Lutte contre le Paludisme, Dakar, Senegal

Thomas Eisele, Tulane University, New Orleans, Louisiana, USA

Mikhail Ejov, WHO Regional Office for Europe, Copenhagen, Denmark

Salaheldin Elkhalifa, WHO Regional Office for the Eastern Mediterranean Region, Cairo, Egypt

Khalid El Mardi, National Malaria Control Programme, Khartoum, Sudan

Rainier Escalada, WHO Regional Office for the Americas, Washington, District of Columbia, USA

Scott Filler, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

Christen Fornadel, United States President's Malaria Initiative, United States Agency for International Development, Washington, District of Columbia, USA

Azra Ghani, Infectious Disease Epidemiology, Imperial College London, London, United Kingdom of Great Britain and Northern Ireland

John Gimnig, United States President's Malaria Initiative, United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

David Gittelman, United States President's Malaria Initiative, United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

John Govere, WHO Regional Office for the African Region, Inter-country Support Team East and Southern Africa, Harare, Zimbabwe

Joanne Greenfield, Australian Agency for International Development, Canberra, Australia

Stephanie Guillaneux, Global Malaria Programme, WHO, Geneva, Switzerland

Pierre Guillet, Vector Health International, Arusha, Tanzania

Ahmad Ali Hanafi, School of Public Health, Teheran, Islamic Republic of Iran

Janet Hemingway, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

Jeffrey Hii, WHO Regional Office for the Western Pacific, Manila, Philippines

Atsuko Hirooka, Sumitomo Chemical, Tokyo, Japan

Mark Hoppe, Syngenta, Stein, Switzerland

Stefan Hoyer, Global Malaria Programme, WHO, Geneva, Switzerland

John Invest, Sumitomo Chemical UK, London, United Kingdom of Great Britain and Northern Ireland

Fumiharu Ishige, Sumitomo Chemical, Tokyo, Japan

Elissa Jensen, United States President's Malaria Initiative, United States Agency for International Development, Washington, District of Columbia, USA

Patrick Kachur, United States President's Malaria Initiative, United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Mulakwa Kamuliwo, National Malaria Control Programme, Lusaka, Zambia

Njagi Kiambo, Kenya Ministry of Health, Nairobi, Kenya

Georges-Alfred Ki-Zerbo, WHO Regional Office for the African Region, Brazzaville, Congo

Immo Kleinschmidt, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

William Kisinza, Amani Medical Research Centre, Muheza, United Republic of Tanzania

David Larsen, Tulane University, New Orleans, Louisiana, USA

Kristen Latona, United States President's Malaria Initiative, United States Agency for International Development, Washington, District of Columbia, USA

Ng Lee Ching, Environmental Health Institute, National Environment Agency, Singapore

Christian Lengeler, Swiss Tropical and Public Health Institute, Basel, Switzerland

Kimberley Lindblade, United States President's Malaria Initiative, United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Jonathan Lines, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Manuel Lluberas, H.D. Hudson Manufacturing Company, Chicago, Illinois, USA

Kitsos Louis, Institute of Molecular Biology and Biotechnology, Heraklion Crete, Greece

John Lucas, Sumitomo Chemical UK, London, United Kingdom of Great Britain and Northern Ireland

Matthew Lynch, Center for Communication Programs, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

Michael Macdonald, United States President's Malaria Initiative, United States Agency for International Development, Washington, District of Columbia, USA

Lucien Manga, WHO Regional Office for the African Region, Brazzaville, Congo

Gamini Manuweera, Secretariat of the Stockholm Convention on Persistent Organic Pollutants, United Nations Environment Programme, Geneva, Switzerland

Fred Masaninga, WHO Country Office for Zambia, Lusaka, Zambia

Charles Mbogo, Kenya Medical Research Institute, Kilifi, Kenya

Tom McLean, Innovative Vector Control Consortium, Liverpool, United Kingdom of Great Britain and Northern Ireland

Sylvia Meek, Malaria Consortium, London, United Kingdom of Great Britain and Northern Ireland

Nobuaki Mito, Sumitomo Chemical, Tokyo, Japan

Tatsuo Mizuno, Sumitomo Chemical, Tokyo, Japan

Abraham Mnzava, Global Malaria Programme, WHO, Geneva, Switzerland

Patrick Moonasar, National Malaria Control Programme, Department of Health, Pretoria, South Africa

Bruno Moonen, Clinton Health Access Initiative, Nairobi, Kenya

Joanne Mulligan, United Kingdom Department for International Development, London, United Kingdom of Great Britain and Northern Ireland

Sivakumaran Murugasampillay, Global Malaria Programme, WHO, Geneva, Switzerland

José Najera, Independant Consultant, Nyon, Switzerland

Ralf Nauen, Bayer CropScience, Manheim, Germany

Robert Newman, Global Malaria Programme, WHO, Geneva, Switzerland

Ray Nishimoto, Sumitomo Chemical, Tokyo, Japan

Jose Nkuni, Global Malaria Programme, WHO, Geneva, Switzerland

Donald Ordu, Ministry of Health, Abuja, Nigeria

Leonard Ortega, WHO Regional Office for South-East Asia, New Delhi, India

John Otshudiema, Université Cheikh Anta Diop, Dakar, Senegal

Helen Pates Jamet, Vestergaard Fransen, Lausanne, Switzerland

Mushfiqur Rahman, WHO Regional Office for South-East Asia, New Delhi, India

Hilary Ranson, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

Melanie Renshaw, African Leaders Malaria Alliance (ALMA), Nairobi, Kenya

Pascal Ringwald, Global Malaria Programme, WHO, Geneva, Switzerland

Donald Roberts, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

Mark Rowland, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Trent Ruebush, United States President's Malaria Initiative, United States Agency for International Development, Washington, District of Columbia, USA

Marina Ruta, Water Environment Federation, United Nations Environment Programme, Geneva, Switzerland

Ryo Sato, Sumitomo Chemical, Tokyo, Japan

Ranjander Sharma, Vector Borne Disease Control Programme, New Delhi, India

Erin Shutes, Bill & Melinda Gates Foundation, Seattle, Washington, USA

Laurence Slutsker, United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Richard Steketee, Malaria Control and Evaluation Partnership in Africa (MACEPA), PATH, Atlanta, Georgia, USA

Zsofia Szilagyi, Global Malaria Programme, WHO, Geneva, Switzerland

Hiroshi Tanaka, Sumitomo Chemical, Tokyo, Japan

Thomas Teuscher, Roll Back Malaria Partnership Secretariat, Geneva, Switzerland

Moussa Thior, National Malaria Control Programme, Dakar, Senegal

Hmooda Toto Kafy, National Malaria Control Programme, Khartoum, Sudan

Yeya Touré, Special Programme for Research and Training in Tropical Diseases (TDR), WHO, Geneva, Switzerland

Jan Van Erps, Roll Back Malaria Partnership Secretariat, Geneva, Switzerland

Hassan Vatandoost, School of Public Health, Tehran, Islamic Republic of Iran

Raman Velayudhan, Department of Neglected Tropical Diseases, WHO, Geneva

Mikkel Vestergaard, Vestergaard Fransen, Lausanne, Switzerland

Mohamoud Wais, WHO Country Office for Sudan, Khartoum, Sudan

Julie Wallace, United States President's Malaria Initiative, United States Agency for International Development, Washington, District of Columbia, USA

Egon Weinmueller, BASF, Limburgerhof, Germany

Jacob Williams, RTI International, Durham, North Carolina, USA

Ryan Williams, Global Malaria Programme, WHO, Geneva, Switzerland

Robert Wirtz, United States President's Malaria Initiative, United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Rajpal Yadav, Department of Neglected Tropical Diseases, WHO, Geneva, Switzerland

Joshua Yukich, Tulane University, New Orleans, Louisiana, USA

Morteza Zaim, Department of Neglected Tropical Diseases, WHO, Geneva, Switzerland

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For more information, please contact: Vector Control Unit, Global Malaria Programme, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland; or by email at infogmp@who.int; or visit the Global Malaria Programme website at http://www.who.int/malaria.

FOREWORD

The past decade has seen unprecedented progress in malaria control, resulting in major declines in malaria mortality rates globally. This progress is attributed to a significant scale-up of vector control interventions, as well as better diagnostic testing and a wider availability of effective medicines to treat malaria. But 99 countries still have ongoing malaria transmission, and the disease killed an estimated 655 000 people in 2010, mostly children under five years of age. International funding committed to malaria, while now substantial, has fallen short of the amounts needed to meet global targets. In recent years, resistance to artemisinins and other antimalarial medicines in the Mekong sub-region of Asia has become a major concern.

The next few years will be critical in the fight against malaria. Vector control, primarily through the use of indoor residual spraying and long-lasting insecticidal nets, will remain a central pillar in our efforts. The good news is that tools for controlling malaria vectors remain highly effective in almost all settings. Unfortunately, this good news is under threat: mosquitoes are developing resistance to insecticides. Insecticide resistance among *Anopheles* malaria vectors has been identified in 64 countries with ongoing malaria transmission, affecting all WHO Regions. Countries in sub-Saharan Africa and India are of greatest concern. These countries are characterized by high levels of malaria transmission and widespread reports of resistance. In some areas, resistance to all four classes of insecticides used for public health vector control has been detected.

The global malaria community takes this threat seriously. The Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM) is evidence of a broad commitment to act before insecticide resistance compromises current vector control strategies. The main factor driving resistance has been the heavy reliance by vector control programmes on a single class of insecticides, the pyrethroids. In some endemic areas, the use of insecticides in agriculture also appears to have contributed to the rise of resistant mosquitoes. Urgent action is required to prevent resistance from emerging at new sites, and to maintain the effectiveness of vector control interventions in the short, medium and long term.

This GPIRM was developed in response to requests from both the World Health Assembly and the Board of the Roll Back Malaria Partnership. The WHO Global Malaria Programme gathered, analysed and synthesized input from over 130 stakeholders representing all the constituencies of the malaria control community. These include national malaria control programmes, vector control specialists, major donor organizations and multilateral and implementing agencies, as well as representatives of academic institutions, product development partnerships and industry. We trust that the GPIRM will trigger coordinated action from all stakeholders and will lay the foundations for integrated practices for managing insecticide resistance in all malaria-endemic countries.

The GPIRM puts forward a comprehensive strategy for global and country levels, including a short-term action plan with clear responsibilities, and sets out research and development priorities for academia and industry. We urge affected countries and stakeholders to take immediate action to preserve the effectiveness of current vector control methods, and to ensure that a new generation of public health insecticides is made available as soon as possible. Close collaboration between malaria control programmes and the agricultural sector will also be crucial. In addition, targeted communication and educational activities will be needed to make communities aware of the problem.

Similar to the efforts to contain emerging drug resistance, implementing the GPIRM will have cost implications in the near term, for which many malaria endemic countries will need support. We are convinced, however, that such investment now will result in significant savings in the long run, improving the sustainability and public health impact of malaria interventions, especially on maternal and child health. We have the tools at hand to end deaths from malaria. But only through concerted action will we manage to maintain the effectiveness of our existing package of interventions. If our efforts succeed, we can overcome resistance to insecticides, and save millions of lives.

Dr Margaret Chan
Director-General
World Health Organization

EXECUTIVE SUMMARY

PART 1 THE THREAT OF INSECTICIDE RESISTANCE

1.1 MALARIA VECTOR CONTROL TODAY

The control of malaria currently relies on a handful of insecticide classes and on pyrethroids in particular.

Vector control is a central, critical component of all malaria control strategies. It relies primarily on two interventions: long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). Use of both has increased significantly during the past 10 years as part of a drive towards universal coverage of all populations at risk, saving hundreds of thousands of lives.

The active ingredients of all WHO-recommended products for IRS come from only four classes of insecticide: pyrethroids, organochlorines (dichlorodiphenyltrichloroethane, DDT), organophosphates and carbamates. All currently recommended LLINs are treated with pyrethroids. From the points of view of both safety and effectiveness, pyrethroids are the best insecticides ever developed for public health use. They accounted for the majority of IRS coverage worldwide in 2009 and were used in all LLINs (*1*). The reliance of modern malaria control on pyrethroids and the increasing resistance of malaria vectors to these products put current global efforts at risk.

For these reasons, a group of experts was convened by WHO in 2010 to identify technical strategies for preserving the effectiveness of the insecticides used for malaria control (*2*). The Global Plan for Insecticide Resistance Management in malaria vectors is a further stage in preparing a global strategy, setting out the rationale and an action plan for insecticide resistance management (IRM) by a broad-based stakeholder community.

1.2 STATUS OF INSECTICIDE RESISTANCE

Insecticide resistance is widespread: it is now reported in nearly two thirds of countries with ongoing malaria transmission. It affects all major vector species and all classes of insecticides.

The significant increase in insecticide-based malaria vector control in the past decade has resulted in increasing resistance among malaria vectors because of the selection pressure placed on resistance genes. Data are still limited and difficult to consolidate as many countries have not yet carried out adequate routine susceptibility testing. But at the time of this report's publication, resistance to at least one insecticide had been identified in 64 countries with ongoing malaria transmission. Resistance to pyrethroids seems to be the most widespread.

For the time being, existing vector control tools remain highly effective in most settings but their effectiveness can only be maintained through urgent and concerted action by the global malaria community. Countries in sub-Saharan Africa and India are of greatest concern because of the combination of widespread reports of resistance—in some areas to all classes of insecticides—and high levels of malaria transmission.

Managing insecticide resistance is complex, in part because resistance takes a variety of forms. Therefore, local strategies must be tailored to the type of resistance present. The two main mechanisms—metabolic resistance[1] and target-site resistance[2]—include multiple forms[3], which are of varying importance for different classes of insecticide. A further complication is 'cross-resistance' between insecticides that have the same mode of action for killing mosquitoes. For example, vectors that are resistant to pyrethroids and have *kdr* target-site resistance will probably also be resistant to DDT. Cross-resistance restricts the choice of alternative insecticide available for resistance management.

Most experts consider that insecticide resistance will likely have significant operational impact if no pre-emptive action is taken.

There has been one broadly accepted case of control failure due to metabolic resistance to pyrethroids used in an IRS programme in South Africa in 2000. Data from experimental hut trials also suggest that resistance could contribute to a lower-than-expected level of control. Some experts are concerned there may be other such examples that have gone undetected because of the difficulty in linking increases in malaria cases to evidence of resistance. While further evidence is clearly needed to understand more about the operational impact of insecticide resistance on the effectiveness of vector control interventions, this should not prevent the malaria community from taking action now.

The evolution of insecticide resistance is of great concern; we must act early, before resistance becomes stable in the vector populations.

Immediate action is particularly important given the evolution of resistance. Resistance genes have spread rapidly in malaria vector populations over large areas. Data also suggest that resistance can evolve swiftly, occurring at low frequency for many years without being detected and then increasing rapidly to very high levels, to a stage at which it becomes less likely or even impossible to reverse the trend. Resistance can probably be reversed only if the vector incurs a 'fitness cost' for being resistant (if the resistance gene confers some disadvantage on these vectors in comparison with susceptible populations). Once the insecticide is changed, these resistant mosquitoes will no longer have an advantage, and will die out.

Some IRM strategies (e.g. rotations) are based on this concept — that removing selection pressure will reverse resistance, and that it may therefore be possible at some point to reintroduce the original insecticide into vector control programmes. Insecticide resistance management strategies must, however, be implemented before the resistance gene becomes common and stable in the population; otherwise, the resistant gene will not recede even if use of the insecticide causing selection pressure is discontinued.[4]

Current monitoring of insecticide resistance is inadequate and inconsistent in most settings in which vector control interventions are used. Often, monitoring is performed reactively or ad hoc, depending on local research projects being conducted. In addition, the limited availability of reliable routine monitoring data from epidemiologically representative sites makes decision-making on managing insecticide resistance difficult.

1 Metabolic resistance is mediated by a change in the enzyme systems that normally detoxify foreign materials in the insect; resistance can occur when increased levels or modified activities of an enzyme system cause it to detoxify the insecticide much more rapidly than usual, thus preventing it from reaching its intended site of action.

2 Target-site resistance occurs when the molecule that the insecticide normally attacks (typically within the nervous system) is modified, such that the insecticide no longer binds effectively to it, and the resistant insect is therefore unaffected, or less affected, by the insecticide.

3 At the target site, resistance mutations can affect either acetycholinesterase or voltage-gated sodium channels. The gene for this type of resistance is known as *knock-down resistance (kdr)*. For metabolic resistance, three enzyme systems are important: esterases; mono-oxygenases and glutathione *S*-transferases.

4 As demonstrated by a study of blowflies by McKenzie and Whitten in 1982 (*3*), fitness cost is not an intrinsic property of the gene. Therefore, if that gene is allowed sufficient time to become common in a population, the rest of the genome will adapt to incorporate it without a significant fitness cost. At this point, even if the selection pressure is removed, the resistance gene will remain in the population.

1.3 POTENTIAL EFFECT OF RESISTANCE ON THE BURDEN OF MALARIA

If nothing is done and insecticide resistance eventually leads to widespread failure of pyrethroids, the public health consequences would be devastating: much of the progress achieved in reducing the burden of malaria would be lost.[1]

For example, current coverage with LLINs and IRS in the WHO African Region is estimated to avert approximately 220 000 deaths among children under 5 years of age[2] every year. If pyrethroids were to lose most of their efficacy, more than 55% of the benefits of vector control would be lost, leading to approximately 120 000 deaths not averted.[3] If universal vector control coverage were achieved, insecticide resistance at this level would be even more detrimental if pyrethroids failed, with approximately 260 000 deaths of children under 5 years of age not averted every year.

The community currently has a window of opportunity to act, to ensure that malaria vector control interventions continue to be a pivotal component of malaria control, as endemic countries attain universal coverage with sustained malaria control and elimination.

1.4 AVAILABLE STRATEGIES FOR MANAGING RESISTANCE

Strategies to preserve the efficacy of insecticides have already been used in public health and agriculture; there is no magic wand to break resistance, but several strategies of proven use could delay the spread of resistance, at least until new classes of insecticides and new tools become available.

With the potential impact on the malaria burden in mind, action can and should be taken now. IRM, with the objective of preserving or prolonging the susceptibility of malaria vectors to insecticides in order to maintain the effectiveness of vector control interventions, is not a novel concept; it was used effectively in agriculture during the past century as well as in public health (e.g. in the Onchocerciasis Control Programme in the 1980s). As continued exposure to a given insecticide eventually results in resistance to that insecticide, IRM strategies and judicious use of insecticides are required in any programme in which insecticides are used.

Several strategies exist for IRM for vector control, based on the use of IRS and LLINs. They include: rotations of insecticides, use of interventions in combination, and mosaic spraying. Potential future strategies include use of mixtures. In some settings, resistance management strategies may be implemented in the broad context of integrated vector management. These strategies can have several effects on populations of resistant vectors: they can delay the emergence of resistance by removing selection pressure (e.g. rotations) or kill resistant vectors by exposing them to multiple insecticides (e.g. mixtures, when they become available).

1 All assumptions for the estimates provided here can be found in this document.
2 Current coverage with LLINs and IRS interventions as reported in the WHO *World Malaria Report 2010* and assuming an estimated efficacy of IRS and LLINs of ~55% on malaria-related child mortality
3 Assuming 25% efficacy for LLINs, 10% for pyrethroid-based IRS, 55% for non-pyrethroid-based IRS; sensitivity analysis included in this document

PART 2 COLLECTIVE STRATEGY AGAINST INSECTICIDE RESISTANCE

2.1 OVERALL MALARIA COMMUNITY STRATEGY

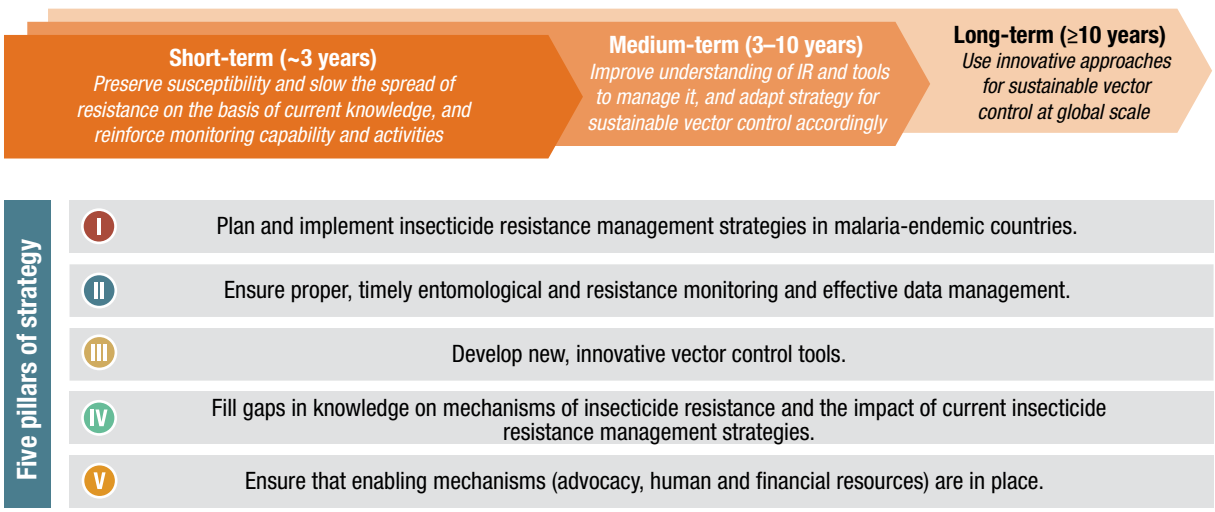
The global strategy consists of five activities (described as five 'pillars') spanning the short, medium and long term. Although some will be led by countries and others at global level, implementing all five pillars is the shared responsibility of all members of the malaria community.

The long-term goal of the malaria community is to maintain the effectiveness of vector control. It is our collective obligation to act in a coordinated manner against insecticide resistance immediately, in order to ensure the continued effectiveness of current and future malaria vector control tools to prevent malaria transmission, morbidity and mortality.

In the near term, prudent action should be taken to preserve the susceptibility of major malaria vectors to pyrethroids and other classes of insecticides, while making investments to ensure that new options for large-scale vector control become available as rapidly as possible.

The five pillars of the GPIRM are illustrated in Figure 1. Some of the activities (particularly pillars I and II) must be country driven but will require strong support from international partners. Although all countries are important to the success of the global strategy to manage insecticide resistance, in a resource-constrained environment, action is especially urgent in some high-priority areas,[1] particularly in sub-Saharan Africa.

Figure 1: Five pillars of the Global Plan for Insecticide Resistance Management in malaria vectors



IR, insecticide resistance

1 Including areas in which there is evidence of control failure, areas with significant resistance to pyrethroids, areas with a high malaria burden and intensive use of pyrethroid-based vector control interventions (so that control failure would have devastating consequences) or areas with unknown status of resistance.

2.2 COUNTRY ACTIVITIES

Pillar I. Plan and implement insecticide resistance management strategies in malaria endemic countries.

Countries should determine how their current vector control programmes should be modified to take account of insecticide resistance. The starting point is to establish the baseline of insecticide resistance and conduct a comprehensive situation analysis. This will require collecting available background data and, if necessary, conducting additional tests on vector susceptibility and on resistance mechanisms. The preparation and implementation of an IRM strategy should not, however, be delayed in order to complete a fully comprehensive situation analysis. Interpretation of the data must take into account the resistance situation in neighbouring countries as well as previous experience elsewhere with the same type of resistance mechanisms.

A national IRM strategy should be based on this analysis, with input from national, regional and global expertise as required. The strategy will determine the modifications necessary for current vector control practices. The national strategy for malaria vector control should be designed on the basis of the WHO policy framework for IRM as outlined in *The technical basis for coordinated action against insecticide resistance* (*2*) and further elaborated in the GPIRM (See Part 3, Technical recommendations for countries). WHO will regularly convene relevant experts to update the recommendations in the light of new evidence and vector control tools. In the long term, IRM should be an integral part of any vector control programme and not a 'stand alone' strategy. Part 3 gives an overview of technical recommendations for IRM at country level, depending on the type of intervention in place and the state of resistance.

Pillar II. Ensure proper, timely entomological and resistance monitoring and effective data management.

Sound IRM strategies must be based on robust, routine, and reliable data. Countries should design a monitoring plan that includes data on vector distribution and relevant vector attributes for transmission and control (biting and resting preferences), on susceptibility (and thus resistance) to currently used insecticides, and on the quality of vector control interventions. Other information, such as epidemiological data, will be necessary for decision-making. At the same time, country capacity and expertise should be built for designing monitoring plans and collecting and interpreting data. An aggregated global database should be created to provide global direction on IRM.

2.3 RESEARCH AGENDA

Pillar III. Develop new, innovative vector control tools.

Given the current reliance on insecticide-based strategies for vector control and the inevitability of insecticide resistance arising if selection pressure is maintained, sustained investment is required to develop new active ingredients with different modes of action. Ultimately, these new compounds will be required to manage resistance. The purpose of the IRM strategies discussed above is to delay the spread of resistance and preserve susceptibility to insecticides, at least until these new classes or molecules are available.

This is essential for LLINs, for which pyrethroids are currently the only class of insecticides used: nets with new active ingredients are urgently needed. IRS and LLIN products containing a mixture of novel active ingredients could be effective in delaying the evolution of insecticide resistance. Two new products—a reformulation of an existing active ingredient and an active ingredient 'repurposed' from agricultural use—are expected to become available for IRS in the near future, which will facilitate the adoption of rotation strategies.

New, non-insecticide-based vector control tools may also be important in the long term to reduce the reliance on insecticides in controlling malaria transmission.

Pillar IV. Fill gaps in knowledge on mechanisms of insecticide resistance and the impact of current insecticide resistance management strategies.

Current understanding of insecticide resistance is sufficient to justify immediate action to preserve the susceptibility of malaria vectors to pyrethroids and other insecticide classes. Scientific theory and experience from agriculture provide enough encouraging information on currently available IRM strategies to allow the design of such strategies for malaria vectors.

Nevertheless, there are important gaps in current knowledge; while these gaps should not preclude immediate action, additional information and evidence will be needed to further refine IRM strategies. In particular, little is known about the link between resistance and control failure (including the impact of the different resistance mechanisms). Furthermore, methodologies need to be developed to measure the effectiveness of IRM strategies and to determine the conditions under which these strategies are likely to be cost-effective in the long run. The GPIRM sets out some priorities for research in the short, medium and long term.

2.4 ENABLING MECHANISMS

Pillar V. Ensure that key enabling mechanisms (advocacy, human and financial resources) are in place.

Several elements are required for successful implementation of the GPIRM. Firstly, advocacy: the importance of insecticide resistance and its threat should be communicated to major donors and national political leaders to ensure that human and financial resources are mobilized and allocated to IRM. Secondly, further modelling is needed of the health and financial impacts of insecticide resistance, building on the initial estimates in this document. Thirdly, resource mobilization is essential both today and tomorrow. It should include:

- financial resources to monitor insecticide resistance and to prepare and implement IRM plans and conduct research;
- human capacity and technical expertise (particularly entomological) in countries to plan and implement monitoring and management of insecticide resistance; and
- capacity at global level and within partner organizations to fulfil their roles in IRM.

2.5 FINANCIAL COST

Monitoring and managing insecticide resistance will have a significant short-term cost. Most experts agree that although pre-emptive IRM will increase costs in the short term, it should result in long-term savings by preserving the effectiveness of insecticides and sustaining their usability. The GPIRM is based on this expectation.

Managing insecticide resistance often implies modifying current vector control practices by adding an insecticide with a different mode of action. Results from models[1] indicate that changing from IRS with only pyrethroids to a rotation that includes organophosphates and carbamates could increase the cost by approximately 20% and 45% in areas with short and long malaria transmission seasons, respectively. Where LLINs are used, combining non-pyrethroid IRS with LLINs while waiting for bednets with new active ingredients or mixtures would have high associated costs but could be targeted to areas with very high, confirmed levels of resistance.

It is assumed that such pre-emptive IRM strategies will delay the evolution of resistance, lengthen the usefulness of current insecticides and even reverse resistance in some settings. Experience suggests that, if nothing is done, resistance will stabilize in the vector population and reversal will be difficult or even impossible, so that some of the most effective insecticides will no longer be usable. Hence, the GPIRM includes not only estimates of the cost of pre-emptive action but a comparison with the cost of acting after control failure has already occurred. For instance, the above-mentioned 20% and 45% increases in the cost of IRS rotations would increase to ~30% and ~70% if action were delayed until pyrethroids were no longer usable.

The overall cost of implementing the five pillars of the GPIRM is expected to be about US$ 200 million per year. This calculation takes into account: implementation of IRM strategies (which would provide at least the same vector control coverage as today); capacity-building for monitoring at country level (assuming that these activities will be performed in all countries); costs of operational research into insecticide resistance; increased investment in research and development for new vector control products; and increased coordination and capacity at global level to support implementation of the GPIRM. This overall estimate is for a 'fully loaded' annual cost at its peak: if all countries were able to implement all GPIRM recommendations on IRM, insecticide resistance monitoring, capacity building and global activities.

There are obvious parallels between mosquito resistance to insecticides and parasite resistance to drugs. Combating antimalarial drug resistance involved the transition to artemisinin-based combination therapies. This required rapid development and adoption of new combination products and of new treatment policies at global and country levels, despite fears of a massive increase in unit costs, with consequent concerns of adequate supply and coverage. Ultimately, the price increase and the supply shortages were not nearly as large as had been predicted, and artemisinin-based combination therapies quickly became accepted as both the standard of care and an essential step in preserving the susceptibility of *Plasmodium falciparum* to our most valuable treatments. Now, the malaria community must tackle the threat of insecticide resistance, giving the highest public health priority to coordinated, pre-emptive action to preserve vector susceptibility to insecticides.

1 All assumptions for the estimates provided here can be found in Part 2.5 of the main document.

PART 3 TECHNICAL RECOMMENDATIONS FOR COUNTRIES

Defining the appropriate IRM strategy for a given situation is highly complex, as it depends on multiple entomological, ecological, epidemiological and operational considerations. The technical recommendations proposed in the GPIRM are built on the recommendations initiated in the WHO document, *The technical basis for coordinated action against insecticide resistance: preserving the effectiveness of modern malaria vector control* (2). The GPIRM recommendations are valid as of May 2012. They are initial working proposals for IRM strategies and will be revised as more evidence and research results become available. Updated versions of these recommendations will be available at http://www.who.int/malaria.

Ultimately, new active ingredients are needed for both LLINs and IRS for the management of insecticide resistance in the medium to longer term. As soon as they become available, bednets with non-pyrethroid active ingredients should be used; if possible, these new active ingredients could be used in a mixture in order to delay the spread of resistance to the new insecticide. In the meantime, a pragmatic approach is proposed to prevent and manage insecticide resistance with the tools currently available. Specific IRM strategies for each geographical area should be based on current vector control interventions, the status of resistance and the epidemiological context.

For IRS, the recommendations focus on pre-emptive use of rotations. For LLINs, the options are more limited, and IRM strategies will require consideration on a case-by-case basis. As described in the GPIRM, the response should focus on areas where resistance is of greatest concern. Wherever possible, countries should introduce focal IRS with non-pyrethroids in addition to LLINs in resistance 'hot spots'.

PART 4 NEAR-TERM ACTION PLAN

4.1 ROLE OF EACH STAKEHOLDER GROUP

Successful implementation of a collaborative plan requires a clear, common understanding of the roles of different partners. Therefore, the GPIRM outlines the main responsibilities of all partners in malaria control and elimination (Figure 2), including all constituencies of the Roll Back Malaria Partnership, in the management of insecticide resistance. Implementation of the plan must be monitored in order to determine global progress.

4.2 ACTION PLAN

A near-term action plan has been prepared to clarify priorities, particularly for the next 12 months. These activities are important prerequisites for proper implementation of the recommendations and are aligned with the five pillars of the strategy. The suggested timeframe for specific activities will serve as an indicator, allowing the malaria community to monitor progress in implementation of the recommendations.

In Figure 3, three colours are used: activities shown in green are needed in malaria-endemic countries, usually under the responsibility of the national malaria control programme; activities shown in blue represent regional or global activities to support countries; and activities in brown should be carried out at all levels (country, regional and global).

Figure 2: Main roles and responsibilities of each stakeholder group

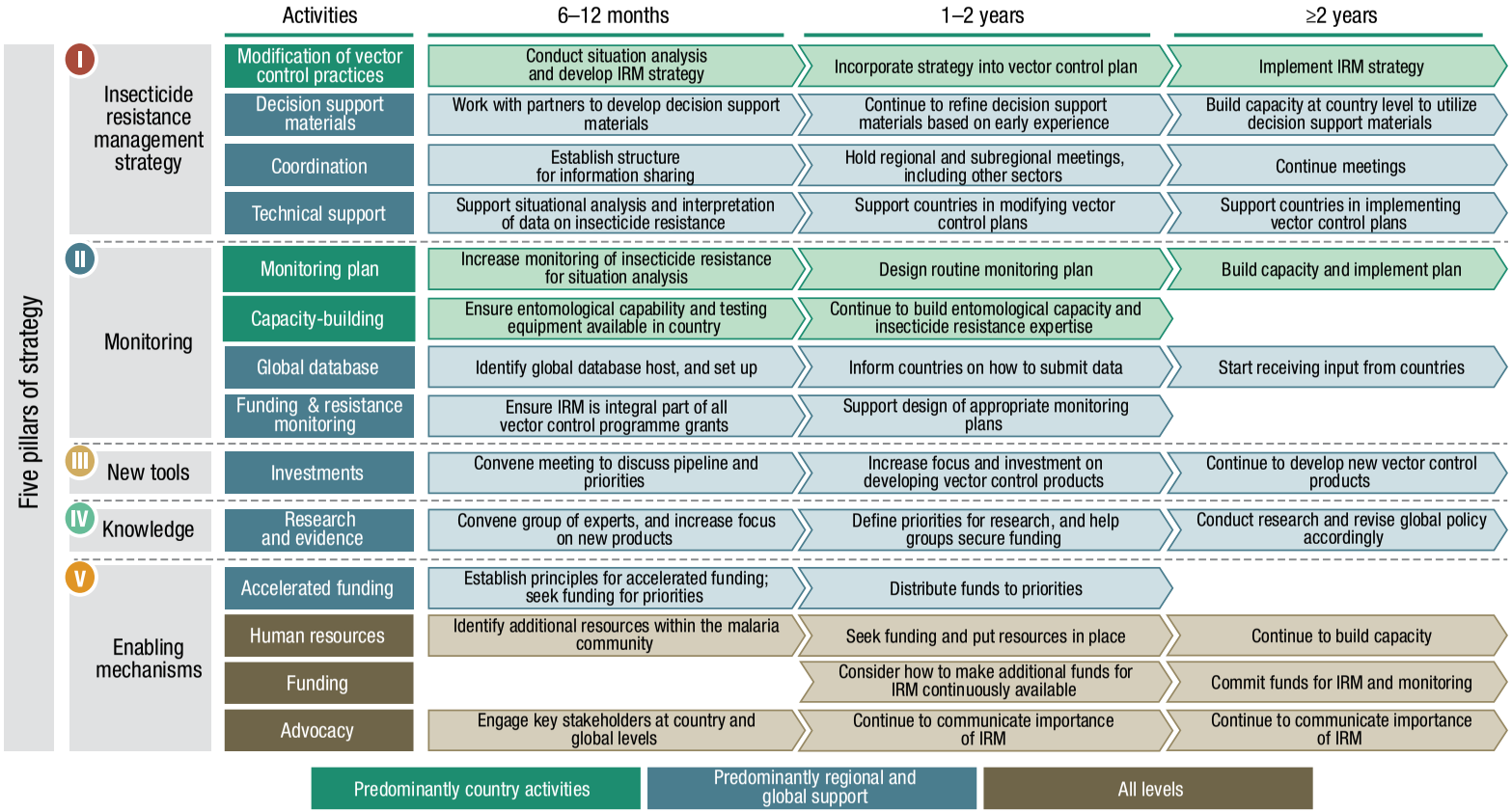
	Global norms and guidelines	Designing IRM strategies	Implementation	Evaluating IRM strategy	Monitoring	Coordination of action / info	IR research	R&D	Resource mobilization	Advocacy
NMCPs and other VBD programmes	✓	✓	✓	✓	✓	✓	✓		✓	✓
Senior government officials			✓			✓			✓	✓
Other health programmes and agricultural sector					✓	✓	✓			
Implementation agencies / NGOs		✓	✓	✓	✓	✓			✓	✓
WHO GMP	✓	✓	✓	✓	✓	✓	✓		✓	✓
WHO regional and country offices	✓	✓	✓	✓	✓	✓			✓	✓
Multilateral agencies		✓	✓						✓	✓
Funding agencies and bilateral donors					✓		✓	✓	✓	✓
WHOPES	✓			✓			✓	✓	✓	✓
Research Institutes and academia		✓		✓	✓		✓			✓
Manufacturers of VC products / PDPs				✓				✓	✓	✓

✓ Primary role ✓ Secondary role: support

NMCP, national malaria control programme; VBD, vector-borne disease; NGO, nongovernmental organization; GMP, Global Malaria Programme; WHOPES, WHO Pesticide Evaluation Scheme; VC, vector control; IRM, insecticide resistance management; IR, insecticide resistance; R&D, research and development; PDPs, Product Development Partnerships

Figure 3: What should we do during the next 12 months and beyond?

Overview of activities required to implement the GPIRM in the near future



IRM, insecticide resistance management

PART 1

THE THREAT OF INSECTICIDE RESISTANCE

1.1 MALARIA VECTOR CONTROL TODAY

1.1.1 LONG-LASTING INSECTICIDAL NETS AND INDOOR RESIDUAL SPRAYING: MAINSTAYS OF MALARIA CONTROL

Vector control is a critical facet of malaria control today and is expected to continue to be so. Vector control today relies primarily on the use of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). Vector control remains the single largest category of spending for malaria control by donors. For example, approximately 39% of malaria expenditures by the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) in 2009 and 59% of the expenditures by the United States President's Malaria Initiative (PMI) in 2010 were dedicated to LLINs and IRS (*4*). (See Annex 1 for more details of past use of malaria vector control tools.)

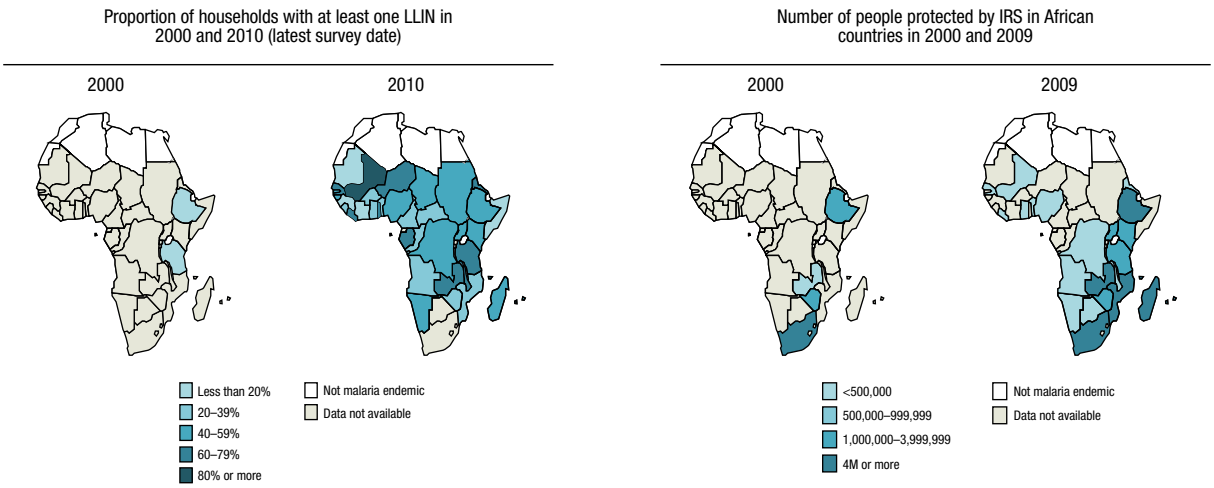
LLINs and IRS are the mainstay of any malaria vector control programme because they are highly effective, have a relatively low cost, and their manufacture and distribution can be rapidly scaled up. Other interventions such as environmental management and larviciding can be useful but only under certain conditions, depending on the target vector and the local situation. (See Annex 2 for more detail on the efficacy and scalability of LLINs, IRS and other vector control interventions.)

Progress in coverage with IRS and bednets over the past decade has been remarkable.

In Africa, where about 81% of all cases of malaria occur, 50% of households at risk owned at least one LLIN in mid-2010 whereas only 3% owned one in 2000. Similarly, the proportion of people protected by IRS in the WHO African Region was estimated to be 11% in 2010 but less than 5% in 2005 (*5*) (Figure 4).

Outside Africa, vector control has also been significantly scaled up. About 60 million LLINs were distributed outside Africa between 2008 and September 2011, with 40 million distributed in six countries (14 million in India, 8 million in Indonesia, 6 million in Afghanistan and about 3 million each in Pakistan, Papua New Guinea and the Philippines). IRS coverage in the Western Pacific Region increased from less than 1% of the population at risk in 2008 to nearly 5% in 2010, largely due to greater coverage with IRS in China; the rate is now equivalent to coverage in the South-East Asia Region (*5*).

Figure 4: Progress in vector control coverage in sub-Saharan Africa (2000-2010)



From reference (*6*), with adjustments from Global Malaria Programme
The maps present survey data available at the end of the specified year and may therefore include data for earlier periods.

1.1.2 DEPENDENCE ON FOUR INSECTICIDE CLASSES, AND IN PARTICULAR ON PYRETHROIDS

Only four classes of insecticide that target adult mosquitoes are currently recommended for IRS and LLINs:

- pyrethroids;
- organochlorines;[1]
- organophosphates; and
- carbamates.

All four classes can be used for IRS, but only pyrethroids are used in currently recommended LLINs. With the available formulations and prices, pyrethroids perform better than other insecticide classes in terms of safety, durability, efficacy and cost. In 2009, pyrethroids were estimated to account for about 75% of IRS coverage, while DDT was the second most widely used insecticide for malaria vector control; carbamates and organophosphates represented only small percentages of global usage (*1*).[2] As the most recent data on worldwide insecticide use in vector control date from 2009, their use in IRS might have changed subsequently because of increasing evidence of insecticide resistance and, in particular, the WHO consultation on this topic in 2010 (*2*).[3]

Given the importance of effective vector control and the reliance on a limited number of insecticides, preserving the susceptibility of malaria vectors to pyrethroids and to the other three classes of insecticides is critical in order to maintain effective malaria control. The evolution of insecticide resistance could jeopardize current and future gains in controlling malaria.

1 Organochlorines are used in IRS in the form of DDT.

2 Global coverage numbers calculated based on WHOPES base data (1) on the kilograms of each insecticide class used in malaria control for the purpose of residual spraying. For each class, an assumption for grams per square meter sprayed was determined: 0.03 g/m² for pyrethroids, 2.00 g/m² for organochlorines, 2.00 g/m² for organophosphates, and 0.40 g/m² for carbamates.

3 For example, the PMI used pyrethroids for IRS spraying in 13 of 15 countries in 2009 but in only 12 of 16 countries in 2010 and sprayed non-pyrethroid insecticides in nearly half the countries they supported in 2011.

Attributes of the four classes of insecticides used for IRS and LLINs

Pyrethroids. Pyrethroids are used for both IRS and LLINs in the form of α-cypermethrin, bifenthrin[1], cyfluthrin, deltamethrin, permethrin, λ-cyhalothrin and etofenprox[2] (*7*). These have been the chemicals of choice in public health for the past few decades because of their relatively low toxicity to humans, rapid knock-down effect, relative longevity (3–6 months when used for IRS) and low cost. They are the only insecticides used currently in WHO recommended LLINs (*7*). Pyrethroids have many modes of action on the mosquito vector. They open sodium channels, leading to continuous nerve excitation, paralysis and death of the vector (*8*); they also have an irritant effect, causing an excito-repellency response, resulting in hyperactivity, rapid knock-down, feeding inhibition, shorter landing times and undirected flight, all of which reduce the ability of vectors to bite.

Organochlorines. Organochlorines are used in IRS in the form of DDT, which was the insecticide used predominantly in the eradication campaigns of the 1950s[3] (*9*). At the Stockholm Convention on Persistent Organic Pollutants in 2001, use of DDT was banned for all applications except disease control, because of its environmental effects when used in large volumes in agriculture. As the number of equally effective, efficient, alternative insecticides for public health is limited, continued use of DDT was permitted until "locally safe, effective, and affordable alternatives are available for a sustainable transition from DDT". A WHO position statement in 2006 (*10*) reasserted the public health value of DDT when used for IRS.

Like pyrethroids, DDT has been popular because of its rapid knock-down effect, relative longevity (6–12 months when used for IRS) and low cost. Despite chemical structural differences, DDT and pyrethroids have similar modes of action (*8*).

Organophosphates. Organophosphates comprise a vast range of chemicals, but those recommended for use for IRS vector control are fenitrothion, malathion and pirimiphos-methyl (*11*). The insecticides in this class are highly effective but do not induce an excito-repellency response from the vector, and in their current formulations have shorter residual activity (2–3 months when used for IRS) than pyrethroids and DDT.[4] In addition, the organophosphates currently used for malaria control are significantly more expensive than other insecticides. For some compounds, toxicological monitoring is required for accidental overexposure during IRS.

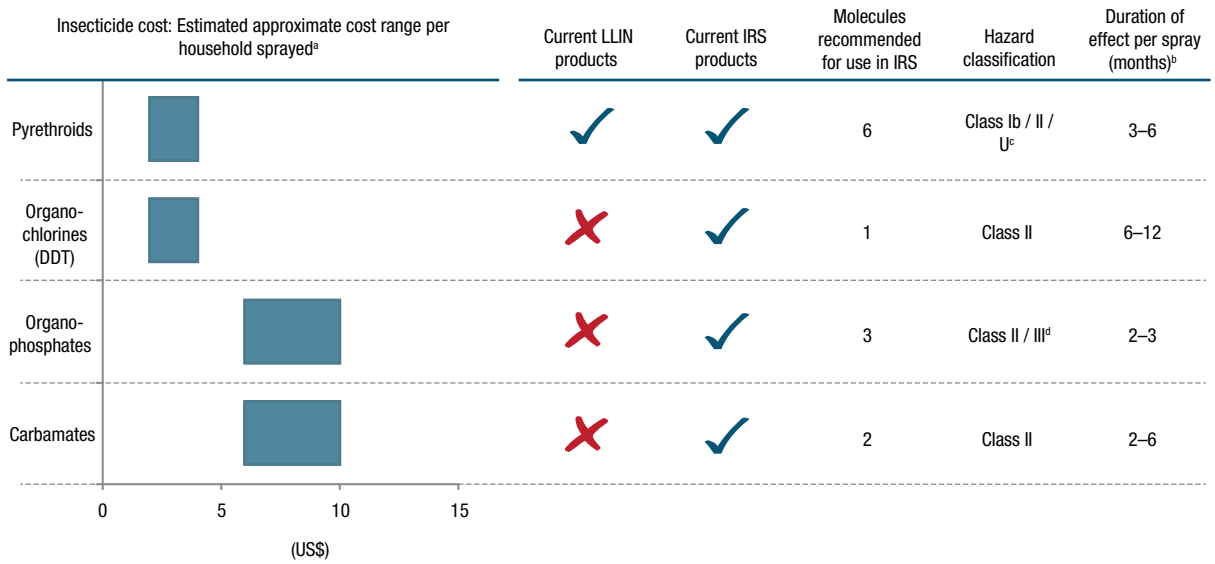
Organophosphates act on the mosquito vector by inhibiting cholinesterase, preventing breakdown of the neurotransmitter acetylcholine, resulting in neuromuscular overstimulation and death of the vector (*8*).

Carbamates. Carbamates are used for IRS vector control in the form of bendiocarb (*11*). Like organophosphates, this compound is highly effective and induces little or no excito-repellency response from the vector. It has short residual activity (2–6 months when used for IRS) and is more expensive than pyrethroids and DDT. The mode of action of carbamates is similar to that of organophosphates (*8*).

1 Bifenthrin is not yet recommended for use in LLINs.
2 Etofenprox is a 'pseudo-pyrethroid' with the same mode of action but different chemical structure.
3 A wider range of organochlorines was previously used for IRS, but many were banned because of their toxicity.
4 Pirimiphos-methyl is now available in capsule suspension formulation with a duration of action of over 8 months.

The characteristics of the four classes of insecticide currently recommended for IRS and LLINs are summarized in Figure 5.

Figure 5: Characteristics of the four classes of insecticide currently recommended for indoor residual spraying and long-lasting insecticidal nets



From references (*12-14*)

LLIN, long-lasting insecticidal net; IRS, indoor residual spraying

Hazard classification (active ingredient): Class Ib: Highly hazardous; Class II: Moderately hazardous; Class III: Slightly hazardous; Class U: Unlikely to present acute hazard in normal use

a Analysis calculated for a household of 5 people (150 m^2 sprayed) and based on WHOPES spraying guidelines and PMI cost data *(14)*.

b Duration as based on typical formulation for use in malaria control.

c Cyfluthrin is WHO class Ib, Alpha-cypermethrin, Bifenthrin, Deltamethrin, Lambda-cyhalothrin and Permethrin are WHO class II and Etofenprox is WHO class U.

d Fenitrothion and Pirimiphos-methyl are class II and Malathion is class III.

1.2 STATUS OF INSECTICIDE RESISTANCE

1.2.1 DEFINITIONS AND TYPES OF RESISTANCE

There are three ways of looking at insecticide resistance, each of which is useful in a different context.

Insecticide resistance is the term used to describe the situation in which the vectors are no longer killed by the standard dose of insecticide (they are no longer susceptible to the insecticide) or manage to avoid coming into contact with the insecticide. The emergence of insecticide resistance in a vector population is an evolutionary phenomenon.

Molecular genotyping of resistance is the identification of the underlying genes that confer the inherited trait of resistance (*15*). Identification of a resistance gene provides evidence of the underlying evolutionary process. Depending on the type of resistance mechanism, this provides understanding of both the degree of resistance expressed in individual insects with the resistance gene, and the frequency of such insects in the population.[1]

Phenotypic resistance is the basic expression of the genetic cause of resistance, shown by a vector's ability to resist and survive the effects of the insecticide. Phenotypic resistance is measured in a susceptibility test of vector mortality when subjected to a standard dose of the insecticide. WHO has defined phenotypic resistance as "development of an ability, in a strain of insects, to tolerate doses of toxicants, which would prove lethal to the majority of individuals in a normal population of the same species" (*16*). Phenotypic resistance is the phenomenon most commonly referred to in public health.

Resistance leading to control failure - while phenotypic resistance provides an indication of the effects of resistance on the vector, the most informative way of looking at resistance is as an epidemiological phenomenon, in which resistance is identified as the cause of increasing malaria transmission. In the notion of resistance leading to control failure, evidence of resistant vectors is linked directly to the failure of vector control programmes in the field. Resistance leading to control failure can be defined as the "selection of heritable characteristics in insect population that results in repeated failure of an insecticide product to provide intended level of control when used as recommended."[2] (*15*) Resistance leading to control failure is the phenomenon most commonly referred to in agriculture. National malaria control programmes should not, however, wait for control failure to occur before implementing strategies to manage insecticide resistance. There is no acceptable level of control failure in public health, and waiting could result in delaying action until it is too late.

Four types of resistance mechanisms have been identified.

Resistance mechanisms can be grouped into four categories, target-site resistance and metabolic resistance being the primary focus of this document.

Target-site resistance occurs when the site of action of an insecticide (typically within the nervous system) is modified in resistant strains, such that the insecticide no longer binds effectively and the insect is therefore unaffected, or less affected, by the insecticide. Resistance mutations, known as knock-down resistance *(kdr*) mutations, can affect acetylcholinesterase, which is the molecular target of organophosphates and carbamates, or voltage-gated sodium channels (for pyrethroids and DDT) (*15*, *17*).

Metabolic resistance is related to the enzyme systems that all insects possess to detoxify foreign materials. It occurs when increased or modified activities of an enzyme system prevent the insecticide from reaching its intended site of action. The three main enzyme systems are: esterases, mono-oxygenases and glutathione *S*-transferases. While metabolic resistance is important for all four insecticide classes, different enzymes affect different classes[3] (*15*, *17*).

Although most resistance mechanisms (especially *kdr* resistance) have been studied for decades in previous cases of resistance, the detailed study of mono-oxygenase metabolic resistance is relatively new, and our understanding of it is fairly limited. Indeed, cases of mono-oxygenase resistance in mosquitoes were unknown before its identification in South Africa in 2000–2001 (see section 1.2.3 for details).[4]

As described below, metabolic and target site resistance can both occur in the same vector population and sometimes within the same individual mosquito. The two types of resistance appear to have different capacities to reduce the effectiveness of insecticide-based vector control interventions, with metabolic resistance being the stronger and more worrying mechanism (see section 1.2.3 for details).

1 Different resistance mechanisms have different strengths and possibly different capacity to drive control failure.

2 Definition from the Insecticide Resistance Action Committee (IRAC).

3 The most important enzyme systems are mono-oxygenases and then esterases for pyrethroids, glutathione *S*-transferases and then mono-oxygenases for DDT and carbamates, and esterases and mono-oxygenases for organophosphates.

4 Mono-oxygenase resistance is exceptionally difficult to study because more than 100 candidate resistance genes could be responsible for resistance and specific mutations are often difficult to locate. Metabolic resistance genes occur when the specificity of an enzyme is altered, when genes are duplicated or when there is a promoter gene. The last is particularly difficult to identify.

Behavioural resistance is any modification in insect behaviour that helps it to avoid the lethal effects of insecticides. Several publications have suggested the existence of behavioural resistance and described changes in vectors' feeding or resting behaviour to minimize contact with insecticides. Studies in New Guinea and the Solomon Islands showed that *Anopheles farauti* vectors stopped biting later in the night (23:00–03:00) after the introduction of indoor DDT spraying and instead bit only in the earlier part of the evening, before humans were protected by sleeping in a sprayed room (*18*). In most cases, however, there are insufficient data to assess whether behavioural avoidance traits are genetic or adaptive; genetic traits could have major implications for the types of vector control interventions needed. All behavioural traits, however, may not be negative, as they could lead mosquitoes to feed on non-human animals. It is also possible to initially mistake the decline of a vector species as behavioural resistance.

Cuticular resistance is reduced uptake of insecticide due to modifications in the insect cuticle that prevent or slow the absorption or penetration of insecticides. Examples of reduced penetration mechanisms are extremely limited and only one study has suggested correlation between cuticle thickness and pyrethroid resistance in *An. funestus (19*). Microarray experiments have identified two genes that encode cuticular proteins that are up-regulated in pyrethroid-resistant strains of *Anopheles* mosquitoes. Experience with other insects suggests that if cuticular resistance emerges in mosquitoes it could have a significant impact when combined with other resistance mechanisms.

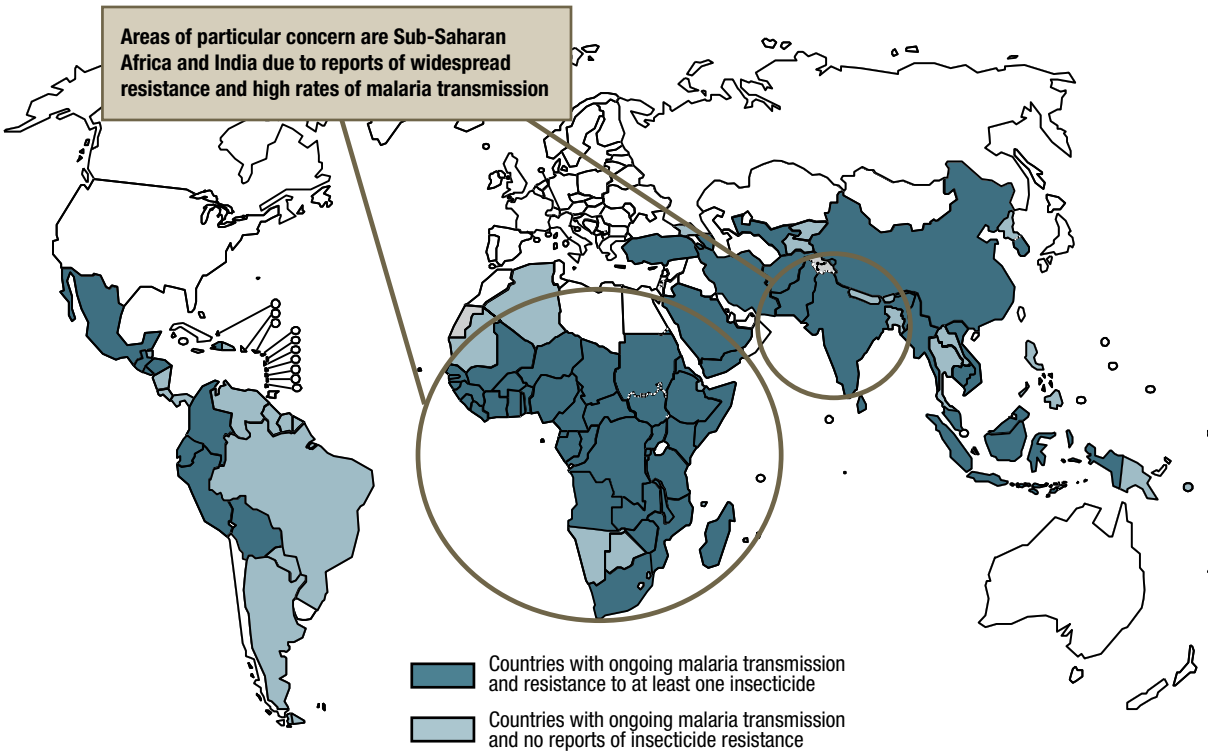
Behavioural and cuticular resistance mechanisms are rarer than the other mechanisms and are perceived by most experts to be a lesser threat than chemical resistance. They are therefore not further discussed in this document. Some experts, however, consider behavioural resistance to be of considerable importance, and further research should be conducted to understand its significance.

See Annex 3 for details on the history of insecticide resistance in malaria vectors.

1.2.2 RESISTANCE IS WIDESPREAD AND AFFECTS ALL INSECTICIDES

Increasing number of countries are reporting insecticide resistance (Figure 6).

Figure 6: Countries with ongoing malaria transmission where insecticide resistance has been identified in at least one of their major vectors



From WHO regional entomologists in WHO Regional Offices, completed by literature review by the Global Malaria Programme.
IR, insecticide resistance

1 Includes countries with confirmed susceptibility to all insecticides used and countries where susceptibility testing is not currently conducted or results are not available.

2 The map provides no indication of how widespread resistance is within a country; therefore, a single report of resistance would be sufficient to mark a country as having resistance.

More countries are reporting insecticide resistance. Since 2009, when there was increased focus on monitoring of insecticide resistance, more and more cases of resistance have been reported, particularly in Africa. Most countries in which susceptibility tests were conducted had at least one case of resistance. The geographical pattern reflects both the scaling up of malaria vector control in the past few years and recent emphasis on testing for resistance. Resistance has been identified in 64 countries with ongoing malaria transmission, mainly to pyrethroids. Resistance to DDT is also prevalent, and there are increasing reports of resistance to organophosphates and carbamates.

Several potential causes: increased monitoring, geographical extension of resistance, and new resistance genes. Some new reports of resistance reflect first-time testing, so it is not known how long resistance has existed. In places where resistance has been monitored previously, new reports usually reflect the extension of established foci due to migration and gene flow or the appearance of a new resistance gene and focus of resistance. Susceptibility monitoring must therefore be scaled up and conducted routinely in all malaria-endemic countries that rely on insecticide-based vector control.

African Region: several areas are of critical concern because of particularly widespread resistance to pyrethroids or to multiple insecticide classes. As all these areas have a high malaria burden, a reduction in the effectiveness of vector control could have severe consequences. Countries in West and Central Africa have long been reporting high frequencies of resistance, particularly Benin, Burkina Faso, Cameroon, Côte d'Ivoire and Ghana. These countries have widespread resistance to pyrethroids and DDT; Côte d'Ivoire has also reported resistance to carbamates and organophosphates. Ethiopia has reported resistance to all four classes of insecticide, including widespread resistance to DDT and an increasing frequency of resistance to pyrethroids. Other places in East Africa with widespread pyrethroid and DDT resistance are Uganda and its borders with Kenya and the United Republic of Tanzania. The situation in southern Africa is of continuing concern. Mozambique and South Africa have reported a broad spectrum of resistance over the past decade, including metabolic resistance which provided the clearest evidence leading to control failure in KwaZulu Natal in 2000 (see section 1.2.3 for details). A high frequency of metabolic resistance to pyrethroids has now also been reported in Malawi and Zambia.

South-East Asia Region. In India, there is widespread resistance to DDT and patches of resistance to pyrethroids and organophosphates (malathion). Indonesia and Myanmar are also reporting resistance to pyrethroids; in Myanmar, there is also confirmed resistance to DDT and organophosphates.

Region of the Americas. Resistance to pyrethroids, carbamates and organophosphates has been reported in this region. In Colombia, widespread resistance in the mid-2000s was reversed in many localities by changing the insecticide and thus removing the selection pressure. Resistance, however, persists in other localities. Resistance has also been reported in Bolivia, Ecuador, Honduras and Peru (*20*).

Western Pacific Region. Resistance to pyrethroids and DDT has been reported in malaria vectors of local importance in coastal regions of Vietnam. In addition, there is resistance to pyrethroids in China and to DDT in Cambodia and Malaysia.

Eastern Mediterranean Region. Resistance to pyrethroids has been reported in several countries in this Region, notably Afghanistan, the Islamic Republic of Iran, and Oman. In addition, there is DDT resistance in Yemen. There have been reports of resistance to three of the four classes of insecticides in Afghanistan. These data need to be confirmed. Somalia and Sudan have reported resistance to all four classes of insecticide, including widespread resistance to DDT and an increasing frequency of resistance to pyrethroids.

European Region. Resistance has been reported to all four classes of insecticides in Turkey, to DDT in Azerbaijan, and to carbamates and organophosphates in Uzbekistan.

The current situation is disturbing. Yet it is likely to have been underestimated, given that many countres have yet to carry out adequate routine susceptibility testing.

Resistance is widespread, involving each insecticide class and many major malaria vectors.

Types of insecticide affected

Although resistance is being reported to all classes of insecticides, most new reports are for pyrethroids. This is worrisome, as pyrethroids are the only insecticides used on current LLINs and among the cheapest, longest-lasting insecticides for IRS. A growing number of countries are reporting resistance to all four classes of insecticide (with different resistance mechanisms affecting different classes), which will strongly restrict options for managing insecticide resistance in the short term.

Variations by species and form

Both metabolic and target-site resistance mechanisms are found throughout the world; however, different resistance mechanisms are found in different species (Figure 7). For example, only metabolic resistance has currently been reported in *An. funestus sensu stricto (s.s)*, whereas both metabolic and target-site resistance mechanisms have been found in *An. gambiae s.s.*

Figure 7: Insecticide-resistance mechanisms of selected major malaria vector species

Vector species	Pyrethroids		DDT		Organophosphates		Carbamates	
	Target-site	Metabolic	Target-site	Metabolic	Target-site	Metabolic	Target-site	Metabolic
An. gambiae s.s	✓	✓	✓	✓	✓		✓	✓
An. funestus s.s				✓				✓
An. arabiensis	✓		✓	✓	✓		✓	
An. culicifacies (C)	✓		✓					
An. culicifacies (B)	✓		✓	✓		✓		
An. stephensi	✓	✓	✓	✓		✓		
An. dirus				✓				
An. sacharovi				✓	✓	✓	✓	✓
An. albimanus		✓		✓	✓	✓	✓	

From Janet Hemingway, Liverpool School of Tropical Medicine, United Kingdom

Furthermore, resistance can vary by form[1]. In *An. gambiae*, resistance appears to be higher in the S rather than the M form. For example, in Burkina Faso, when *An. gambiae* M and S forms were tested at four sites, the S form had a greater probability of surviving the insecticide (DDT or pyrethroid)[2]. Given that the two forms have evolved separately, it is natural that evolution of resistance would vary by form.

Cross-resistance within an insecticide class and across several classes

Cross-resistance can restrict the choice of alternative insecticides. Cross-resistance often occurs between insecticide classes that have the same mode of action for killing vectors. For example, if a resistance gene creates a change in a target site in a vector, it is likely to affect any other insecticides that attack that same target site, thus conferring cross-resistance. Similarly, an alteration to an enzyme that affects susceptibility to one insecticide may result in cross-resistance to another.

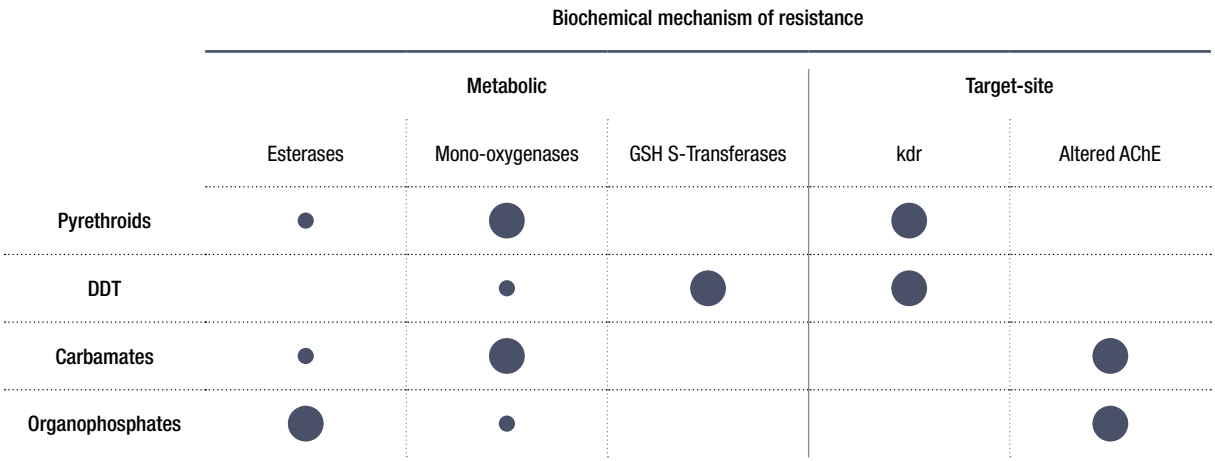
There are a number of patterns of cross-resistance (Figure 8). In target-site resistance, *kdr* mutations result in cross-resistance between pyrethroids and DDT, and acetylcholinesterase mutations result in cross-resistance between carbamates and organophosphates. In metabolic resistance, cross-resistance between pyrethroids and carbamates has also been associated with mutations in cytochrome P450 enzymes. Cross-resistance is assumed to occur between insecticides of the same class; however, cross-resistance between types of pyrethroids has been questioned; this is a potentially important topic for operational research. While switching to another pyrethroid class might result in increased local effectiveness, it is unlikely to remove selection pressure and slow the evolution of resistance. Further information is needed on cross-resistance between specific metabolic enzymes.[3]

1 'Form' refers to the different molecular varieties, within *An. gambiae*. The M and S 'forms' are now recognized as separate species and are in the process of being formally named.

2 Data from Ranson H. on survival rates for sympatric populations.

3 As there are more than 100 candidate mono-oxygenases genes for resistance, it is unlikely that exactly the same enzyme will drive resistance to several classes of insecticide; therefore cross-resistance does not always occur.

Figure 8: Cross resistance patterns of different classes of insecticide



From reference (*21*)
GSH, glutathione; AchE, acetylcholinesterase; circle size reflects relative impact of mechanism of resistance

1.2.3 OPERATIONAL IMPACT OF INSECTICIDE RESISTANCE

Most experts agree that if nothing is done to reduce selection pressure, insecticide resistance will ultimately have an operational impact that will lead to widespread control failure. Some fear that control failure may already be occurring in some places but has not yet been detected. While the high frequency of *kdr* resistance, notably in West Africa, has not been accompanied by an obvious attributable increase in the number of malaria cases, several reports indicate that resistance could have an operational impact and lead to control failure.

Insecticide resistance could have a broad range of outcomes.

With regard to operational impact, there is concern with both the degree to which insecticide resistance reduces the efficacy of an intervention and, at the extreme, the possibility that it will induce full control failure.

Reduced effectiveness of malaria control. Reduced effectiveness is when an intervention controls transmission to a certain degree, but performs less well – or for a shorter time – than in the absence of resistance. The evidence for this could include lower vector mortality, increased blood-feeding and a limited increase in malaria transmission.

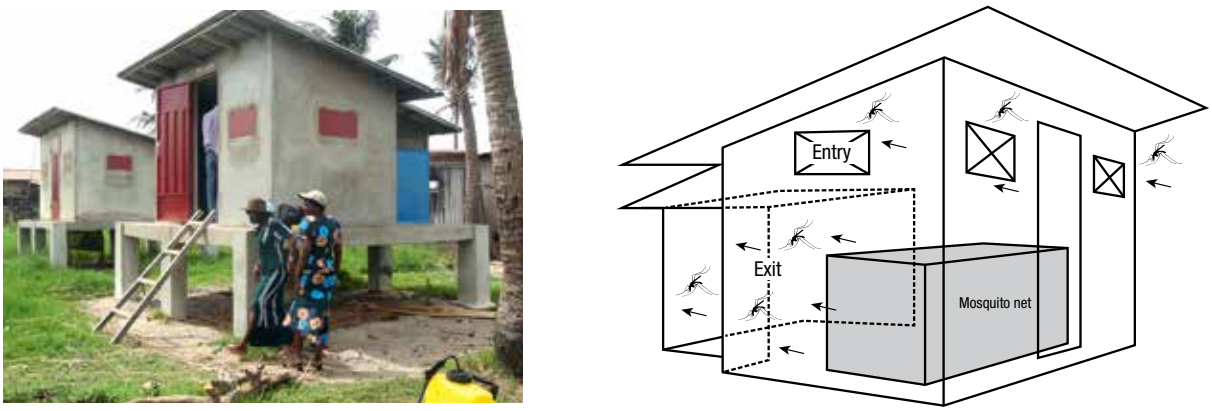
Control failure. Control failure is when an intervention has virtually no effect on transmission or fails to prevent an uncontrolled resurgence in malaria cases. Although control failure, if it occurs, will eventually be detected, this may be delayed because of weak resistance monitoring and poor epidemiological surveillance systems.

The operational impact of resistance is difficult to measure.

The impact of insecticide resistance on vector control operations should ideally be measured from an epidemiological perspective. The link to the epidemiology of malaria is, however, difficult to establish. Firstly, many confounding factors in both the implementation of vector control and factors unrelated to vector control could contribute to an increase in the number of malaria cases (see Annex 4 for more details on confounding factors). Secondly, it is not possible to design a fully rigorous experimental trial to measure the impact of resistance, as one cannot 'randomize for resistance' (allocate resistance randomly to some places and withhold it from others). Thirdly, detection of an increase in the number of malaria cases requires effective diagnosis and epidemiological monitoring and reporting, which are sometimes inadequate.

Given the obstacles to attributing an epidemiological impact to insecticide resistance, entomological outcomes have been used as a proxy, usually by measuring the relative mortality and feeding success of resistant vectors in experimental huts (see Figure 9). In one type of trial, the efficacy of the same insecticide is measured in resistant and susceptible areas. In another, the effectiveness of different insecticides is compared against a mosquito population that is resistant to one of the insecticides. While such trials have many limitations, notably that they are not linked to health (malaria) outcomes and that they are on a small scale, they are nevertheless considered to provide an important indication of the potential impact of resistance (*22*,*23*). See Annex 4 for more details regarding the challenges in linking insecticide resistance with epidemiological effect.

Figure 9: Example of experimental hut



From Mark Rowland, London School of Hygiene and Tropical Medicine

Insecticide resistance: potential for operational impact.

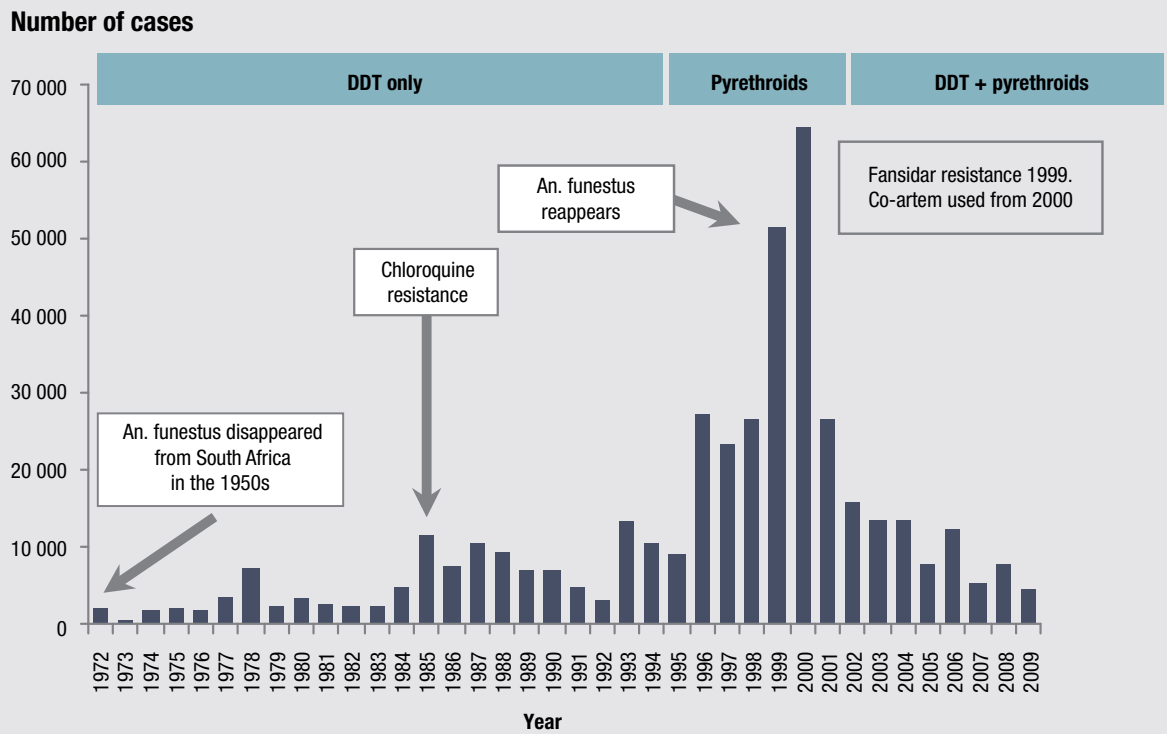
Case study 1. Example of control failure in South Africa

Context. In 1996, a national decision was made to change from DDT to pyrethroids for IRS. By 2000, however, the number of reported malaria cases had multiplied by approximately four. *An. funestus*, a vector that had been eliminated by DDT spraying in the 1950s, reappeared, and bioassays showed that the species was susceptible to DDT but resistant to pyrethroids and furthermore had a sporozoite rate of 5.4% (*25*), which is remarkably high by South-African standards.

Action and results. In November–December 1999, it was decided to revert to IRS with DDT. This was done in March and October 2000, and was followed by a prompt and substantial decrease in the number of malaria cases during the 2000-2001 transmission season (Figure 10).

Lessons learnt. As always, other trends affected the number of malaria cases. In particular, the decrease has also been attributed to the introduction of artemisinin-based combination therapies in 2000, more stringent diagnostic standards with the introduction of rapid diagnostic tests in 2001, and the start of a highly successful regional initiative (the Lubombo Spatial Development Initiative). The vast majority of experts familiar with the case are, however, convinced that insecticide resistance played a pivotal role in this example of control failure.

Figure 10: Number of malaria cases and resistance in South Africa, 1971-2009



From Maureen Coetzee, based on data from the National Department of Health, South Africa and references (24) and (25)

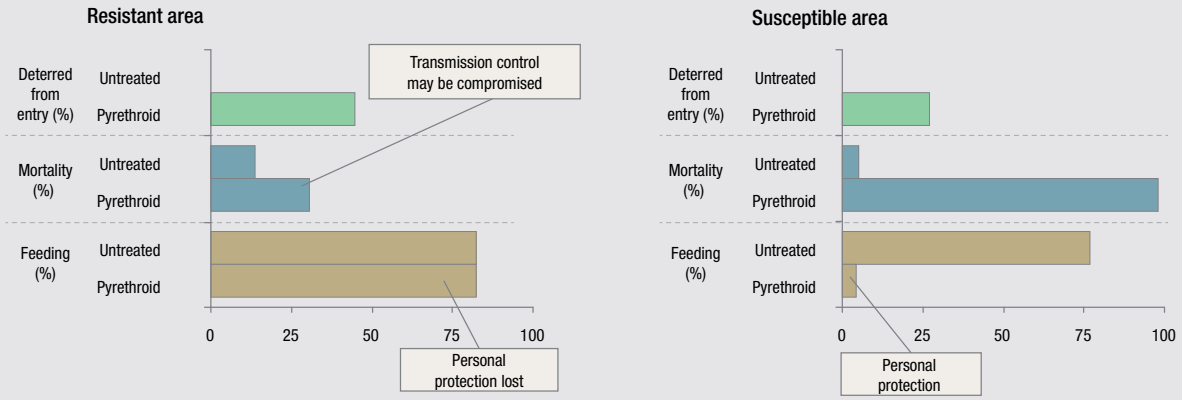
Case study 2. Experimental hut trials in Benin

Several small trials have been conducted in Benin to test the efficacy of IRS and LLINs against resistant vectors (*22, 23*).

In one trial, IRS and LLINs were tested at two sites, one with *kdr* resistance to pyrethroids (Ladji) and one with susceptibility (Malanville). Holes were made in the nets to mimic worn nets. In the huts at the site with resistance (Ladji), the efficacy of the insecticide appeared to be significantly reduced: vector mortality was lower and the level of blood feeding was the same as in huts with untreated nets (Figure 11). However, it is suspected that metabolic resistance was also present at Ladji as results from a similar experimental hut trial in northern Benin with *kdr*-resistant mosquitoes did not show a significant effect.

In another trial, the relative effectiveness of pyrethroids and chorpyrifos methyl (organophosphate formulation) was tested on an *An. gambiae* population resistant to pyrethroids. The organophosphate was significantly more effective, with vector mortality rates of only 31% with pyrethroids and 95% with organophosphates.

Figure 11: Impact of pyrethroid-impregnated insecticide-treated nets in areas of Benin with An. gambiae resistant and susceptible to pyrethroids



From references (22) and (23)

Different resistance mechanisms have different capacity to cause control failure.

It is broadly accepted that different resistance mechanisms have differing capacity to cause control failure, *kdr* tending to be less likely than metabolic resistance (or a combination of mechanisms) to cause control failure (*15*).

- Vectors with several resistance mechanisms (target-site and metabolic resistance) are likely to affect control most strongly.[1] The simultaneous occurrence of *kdr* and metabolic resistance genes has been reported in pyrethroid-resistant *An. gambiae* populations in Benin, Ghana and Nigeria (*24, 26*).[2]
- Metabolic resistance alone, particularly the mono-oxygenase resistance mechanism, might also be enough to lead to control failure. This was the case in South Africa in 2000 with *An. funestus.* Metabolic resistance has been detected in vector populations in at least eight countries of Africa (*24*).
- The 'weaker' of the two known *kdr* genes might require the presence of another resistance mechanism in order to cause control failure. No case of obvious and complete malaria control failure has been reported with *kdr* resistance alone; therefore, this scenario is not considered by most experts to be a serious problem (although this may change). As *kdr* resistance is now so widespread, however, the addition of metabolic resistance could greatly exacerbate the situation. Trials with experimental huts indicate that this may already be occurring in coastal Benin. *Kdr* and metabolic resistance mechanisms were found in the same vector populations, and the trials showed a notable reduction in the effectiveness of vector control (*22, 23*).

1.2.4 EVOLUTION AND SPREAD OF INSECTICIDE RESISTANCE

The consensus is that resistance of operational importance will eventually emerge to any insecticide that continues to be widely used. Insecticide resistance genes have clearly been spreading and will spread further, particularly in the face of continuing selection pressure. While it is not known precisely how quickly insecticide resistance will spread if nothing is done, resistance genes are capable of spreading within a vector population very rapidly. There are numerous examples of this in both public health and agriculture.

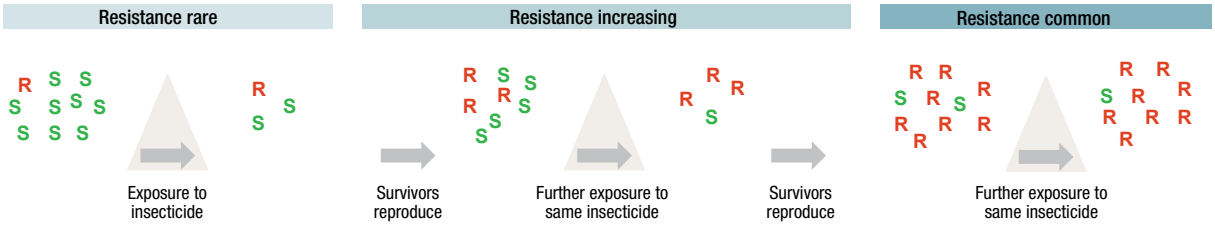
Concepts of evolution.

Most cases of resistance in the field are attributable to a few genes of major effect. Therefore, the spread of resistance throughout mosquito populations requires understanding of the evolution of those genes. A resistance gene starts as a rare gene, but, with further exposure to the same insecticide, the frequency of the gene increases until it becomes common in a population (Figure 12). Other factors being equal, resistance is likely to evolve more quickly if it is functionally dominant in field exposures. It is also likely to evolve more quickly in isolated (e.g. on islands) and uniformly exposed vector populations because there is less dilution from susceptible inward migrating vector populations.

1 'Strength of resistance' is measured as how much more insecticide is needed to kill resistant vectors than susceptible ones, usually in terms of a resistance ratio.

2 Multiple resistance mechanisms may exist in vector populations in other countries as well.

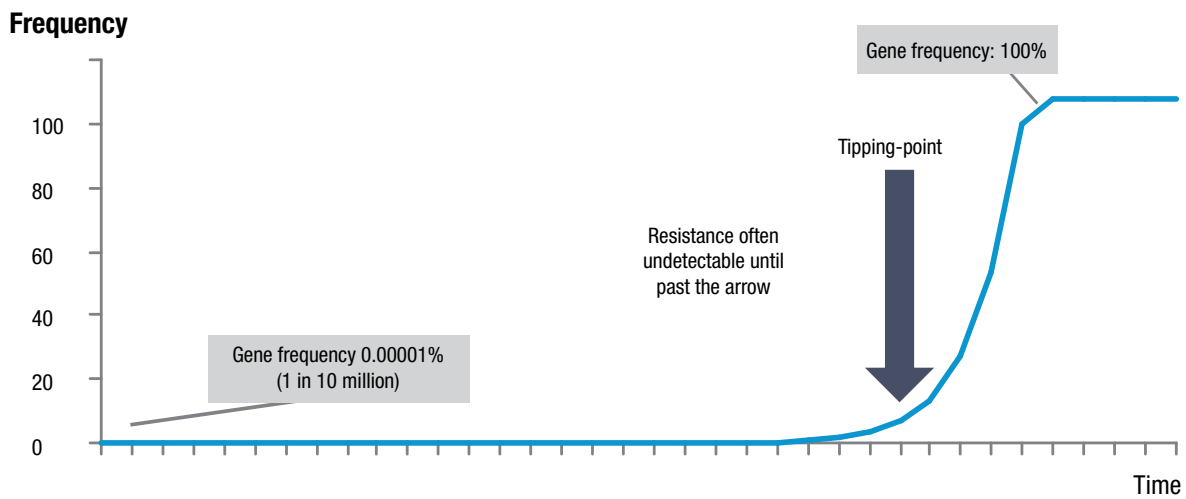
Figure 12: Genetic heritability drives increased resistance in the face of continued pressure



From reference (*15*)

Tipping-point. The concept of a 'tipping-point' (Figure 13) describes the fact that resistance can occur at low but gradually increasing frequency in the vector population for many years without being detected. When a 'tipping-point' is reached, however, resistance may increase extremely rapidly, for example a resistance gene with an initial frequency of 1 in 10 million, can double in frequency for a long time before it reaches 1% and becomes detectable within a population. At that point, theoretically, only another six generations of frequency doubling of resistant genes are needed before resistance reaches a frequency of over 50%. See Annex 5 for an illustration of the 'tipping-point' observed in resistant *Aedes* mosquitoes.

Figure 13: Concept of "tipping point"



From the Innovative Vector Control Consortium, illustration of the tipping point in Mexico trial, with adjustments from the WHO Global Malaria Programme

Fitness cost.

Resistance genes appear through random mutations occurring at very low frequency in almost all mosquito populations. It is assumed that these wild-type genes are more fit than resistance genes; otherwise the resistance genes would occur naturally at levels above the mutation rate in populations that are not under insecticide selection. As a result of this 'fitness cost', it is assumed that the resistance genes once selected will die out over time if the selection pressure is removed. Some IRM strategies (e.g. rotations) rely on the concept that removing selection pressure will reverse resistance because of the fitness cost and that it may therefore be possible at some time to reintroduce the original insecticide into vector control programmes. Insecticide management strategies must, however, be implemented before a resistance gene becomes common and stable in a population. At that point, there may be no or limited fitness cost to the vector, and therefore the resistance gene may remain even if use of the insecticide that is causing the selection pressure is discontinued.[1]

Currently, there is limited information on fitness cost in resistant malaria vectors and its implications for IRM. There are nevertheless examples of public health programmes in which an insecticide was removed as soon as resistance was detected, such that the same insecticide could be reintroduced several years later, presumably because the fitness cost of the resistance gene had resulted in its disappearance.

Example in Colombia: resistance genes disappeared from the vector population when selection pressure was removed.

A report submitted by WHO AMRO regional entomologists showed that, in 2005–2006, resistance to pyrethroids and DDT was identified in *An. darlingi*. A decision was quickly made to change to fenitrothion, an organophosphate with a different mode of action, for IRS. Rapid implementation of this alternative, which thereby removed the selection pressure, reduced the frequency of resistance. In 2010, susceptibility tests showed that the frequency of resistance genes in the vector population had dropped below the level of detection, and pyrethroids were once again introduced into the IRS programme, albeit on a more limited scale.

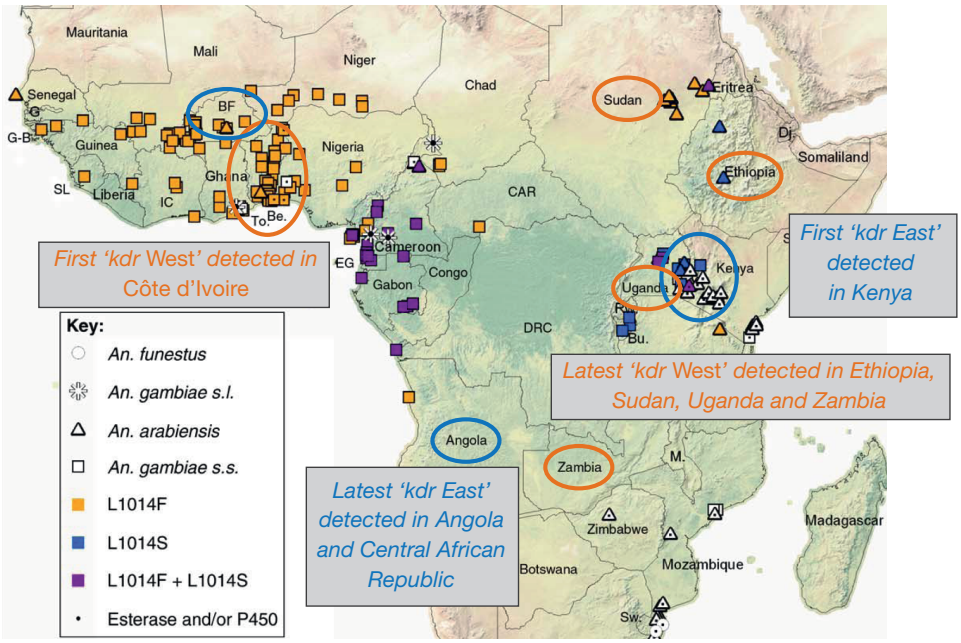
Report from Colombia submitted by WHO AMRO regional entomologists

Examples of spread of resistance genes.

There are multiple examples of insecticide resistance spreading quickly over large areas. For example, the *kdr* mutations known as 1014F and 1014S were first detected in West and East Africa, respectively (referred to as *kdr* West and *kdr* East mutations). They have now been detected on both sides of the African continent because of both the spread of the original mutations and because of new, independent origins of the same mutations (Figure 14). *kdr* West has now been detected as far East as Ethiopia, Sudan, Uganda and Zambia, while *kdr* East has been found in Angola and several countries in West and Central Africa (such as Benin, Burkina Faso and Côte d'Ivoire) (*24*).

1 As demonstrated in a study in blowflies by McKenzie and Whitten in 1982 (*3*), fitness cost is not an intrinsic property of genes; therefore, if that gene is allowed sufficient time to become common in a population, the rest of the genome will adapt to incorporate it without a significant fitness cost. At this point, even if the selection pressure is removed, the resistance gene will remain in the population.

Figure 14: kdr West and kdr East mutations are now present on both sides of Africa



From reference (24), with adjustment from the WHO Global Malaria Programme; does not show latest reports such as *kdr* East in Angola.
This map has been reproduced with the agreement of the original author. It reflects data and boundaries as of 2010 or before and should not be understood to reflect current data and boundaries.

Metabolic resistance in *An. funestus*, which has already been associated with control failure in South Africa, appears to have spread over long distances across southern Africa; resistance to pyrethroids and carbamates in the *An. funestus* population was reported in Malawi, 1500 km north of its previously known location in southern Mozambique.[1]

The rapid spread of resistance has been particularly alarming in some countries. For example, Benin has reached the point over the past 2 years at which no areas have full susceptibility.

Use of insecticides in both public health and agriculture can contribute to the evolution of resistance in malaria vectors.

Use of insecticides in both agriculture and public health contributes to the evolution of resistance in some cases by placing selection pressure on the vectors.

The role of insecticides used for public health in selecting for insecticide resistance in malaria vector has been clear since the 1940s. In some cases, however, there has been good evidence that agricultural use of pyrethroids, particularly on rice and cotton crops, has been the main factor causing insecticide resistance in malaria vector mosquitoes. For example, when cotton was a major crop in Salvador, seasonal fluctuations in resistance in malaria vectors were seen to follow the timing of the cotton-spraying (*27*). On the other hand, there have also been cases where agricultural insecticides have been suspected of being the cause of resistance in malaria vectors, but where further investigation has shown that the resistance was in fact due to anti-malaria spraying (e.g. malathion resistance in Sudan and Sri Lanka) (*28*).

In Africa, pyrethroids have been in widespread use in agriculture for decades, and in areas of intensive agriculture in West Africa, agricultural insecticides probably contributed to the initial appearance of knockdown resistance in malaria vectors. However, it is only in the last five to ten years, with massive scaling-up of malaria vector control, that we have seen these resistance genes spreading throughout the region, and reaching very high frequencies even in areas with little use of agricultural insecticides. Overall, therefore, the evidence suggests that in Africa, agriculture has been an important prompt for the initial appearance of resistance in some localities, but the massive scaling up of LLINs and IRS for malaria control has been the main factor driving the recent increases in the geographic distribution and frequency of insecticide resistance genes in malaria vectors.

Continued use of the same insecticides in both public health and agriculture will inevitably increase resistance. Effective management of insecticide resistance will therefore require activities in both public health and agriculture, and sharing of data and information.

1 As susceptibility tests mirrored the situation of *An. funestus* in Mozambique and South African populations but showed a markedly different resistant pattern to *An. funestus* populations in Uganda (which did not show cross-resistance with carbamates), it has been suggested that resistance in Malawi may have spread from South Africa during the past 10 years.

See Annex 6 for more information on selection pressure from public health and agricultural use and information on other types of selection pressure, such as hydrocarbon pollution and domestic use of insecticides.

1.2.5 STATUS OF ENTOMOLOGICAL SURVEILLANCE AND RESISTANCE MONITORING

Insecticide resistance must be monitored carefully in order to understand the current threat and evolution of insecticide resistance among malaria vectors. Until now, however, monitoring has been limited in most malaria-endemic countries.

Resistance can be monitored with three complementary methods that provide different types and depths of information.

Resistance monitoring can be undertaken with three testing methods, each of which provides a different type and depth of information (Table 1). These tests are complementary, and the choice of method depends on the information needed and on operational capability.

Table 1: Methods for monitoring resistance of malaria vectors to insecticides

Susceptibility testing	Biochemical assays	Molecular testing
Description	**Description**	**Description**
Vectors are exposed to fixed insecticide concentrations, and the level of vector mortality is subsequently recorded. The results are expressed as the percentage of vectors knocked down, alive, or dead. Susceptibility testing requires samples of at least 100 live mosquitoes per testing site *(29)*.	Biochemical assays detect the presence of a particular resistance mechanism or an increase in enzyme activity *(31)*. They require fresh mosquitoes, but much fewer than for bioassays.	Molecular tests are used on the actual gene, allowing detailed and direct analysis of resistance genes. Testing can be done with straightforward polymerase chain reaction techniques *(30)* with DNA or in more elaborate microarray tests with RNA.
Susceptibility tests are generally used for routine monitoring, as they can be used in the field. They provide standardized data that are relatively easily interpreted. Either WHO paper bioassays or CDC bottle bioassays can be used.[a] The results obtained with the two methods are not comparable. In order to observe longitudinal or temporal patterns in resistance, countries and academic institutions in all regions must therefore use the same method consistently over time.	Unlike bioassays, bio-chemical assays can identify some specific resistance mechanisms and indicate an increase in metabolic enzyme activity. Biochemical assays are normally used in conjunction with synergist[b] and molecular assays.	More advanced molecular methods can provide complex genetic information including whether the mutation is unique or has spread (*30*) . These are the most accurate tests for measuring resistance frequency in vector populations. Molecular tests must, however, be correlated with susceptibility testing.
Limitations	**Limitations**	**Limitations**
Susceptibility tests identify the existence of resistance once it is at a detectable level but do not establish the resistance mechanism involved. They may also not identify resistance if the frequency is too low. Several countries have reported shortages in the supply of testing materials and have switched between the WHO and CDC tests, making results difficult to compare. In some cases, they have limited their testing.	The method is more difficult to use in the field as it requires sophisticated equipment, and interpretation of the results requires strong technical skills *(30)*. Further, the correlation between chemical reactions in these tests and increased ability to metabolize insecticides is not yet well defined.	The method requires sophisticated equipment and entomological capacity. It can be used to detect target site resistance and a few identified metabolic mechanisms. Hence, susceptibility tests should be used to complement molecular results, as the absence of identifiable genotypic resistance does not necessarily mean that resistance does not exist.

CDC, Centers for Disease Control and Prevention

a WHO paper bioassays are the basic standard method but CDC bottle assays offer an alternative that can provide complementary information. Concern has been raised about the quality of CDC bottle bioassays when technicians coat their own bottles, but this concern can be alleviated if pre-dosed bottles are used.

b Compounds that enhance the toxicity of some insecticides, although they usually have limited toxicity themselves.

See Annex 7 for the implications of discriminating doses for the detection of insecticide resistance.

Monitoring of insecticide resistance is currently inadequate in many settings.

Frequency of insecticide resistance testing. Although a few countries have a comprehensive monitoring system, many malaria-endemic countries in which insecticide-based vector control is used do not monitor insecticide resistance or do not monitor resistance as comprehensively as required. For example, they may not cover a representative set of sentinel sites or may have no system for efficient analysis and reporting of data. In addition, insecticide resistance is rarely monitored consistently over time. In many cases, monitoring is conducted ad hoc or reactively in response to signs of insecticide resistance, rather than as part of routine surveillance. These problems result in limited time series data.

Testing methods. Current resistance monitoring is seldom fully comprehensive. Testing is often performed for a single insecticide class instead of all classes that are potentially usable for vector control. Biochemical and molecular testing are rare, even when warranted by bioassay results. Other testing methods and analyses that are critical for decision-making[1] are rarely performed.

These inadequacies have a number of causes. Firstly, routine monitoring of insecticide resistance is rarely built into vector control programmes, and monitoring of resistance has not been a condition for receiving funds for vector control. Even when funds have been allocated for resistance monitoring, they have often been used for other activities. Secondly, although significant capacity-building, often within a region, has improved the capacity for monitoring insecticide resistance in a number of countries[2] (see section 2.2.2), others still have limited local entomological, epidemiological, statistical and information technology capacity. The available capacity is often in research institutes rather than in national malaria or vector control programmes. Laboratory equipment is often lacking or of poor quality, and the capacity to collect mosquitoes appropriately is limited. Clear standardized methods for selecting sites for monitoring insecticide resistance have not been available to help countries to stratify sentinel sites. This has made routine monitoring difficult, and many countries must rely on intermittent data collection by external research institutes.

National and local decision-making for managing insecticide resistance is limited in many countries.

Achieving sound national and local decision-making for managing insecticide resistance is difficult in many countries.

Availability of data. As data are often collected by academic institutions, they may not be shared with the country until publication of the findings, sometimes resulting in delays of several years before the national malaria control programme can access the information on insecticide resistance detected in the country. Furthermore, the limited data available are not tailored for prompt policy-making on resistance management strategies.

Capacity to interpret data. Many countries need better national entomological, epidemiological, statistical and information technology capacity, and external support for analysing data and applying the WHO guidelines for decision-making on IRM. Some countries do not even have a national malaria or vector control programme structure (vector control being integrated into other health offices), which often implies even more limited resources.

Decision-making bodies. Some countries do not have well-defined or well-functioning bodies for resistance management. Decision-making for IRM requires strong cross-ministerial coordination because of the number of national stakeholders involved (e.g. ministries of health, environment and agriculture).

Although regional and global initiatives to collect data and manage insecticide resistance exist, they have several limitations.

Data are currently fragmented into several databases with different sources, format, scope and depth. The scope of the available data is limited, and large amounts of information are probably not captured anywhere. Global databases are usually based on published papers, complemented by limited data submitted directly by users. The quality of data from unpublished sources is variable, and reviewing data is difficult and resource-consuming.

Most current databases are perceived as being tailored for research purposes and not for prompt national decision-making. Many of the databases are seen as difficult to use by national programmes, presenting problems for downloading data and other issues of accessibility. Further, they are perceived as lacking key functionalities for advanced analysis of resistance mechanisms.

There has been no clear mandate for the creation of a data management system for monitoring insecticide resistance, and databases have been created with inadequate coordination among several stakeholders. For example, standardized indicators and methods are not available.

1 For example, assessments of the association between hypothesized causal factors of resistance and measures of resistance (e.g. LLIN coverage and resistance).

2 Notably through PMI-supported capacity-building projects and the Bill and Melinda Gates Foundation-funded WHO project "Malaria vector control: Filling the gap between product development and effective delivery", conducted in seven countries by the WHO African Region.

1.3 POTENTIAL EFFECT OF RESISTANCE ON THE BURDEN OF MALARIA

Given the worrying state of insecticide resistance, the malaria community must understand its potential impact on the malaria burden. If resistance to currently used insecticides leads to less effective vector control, as many experts believe, and no action is taken to address resistance, the global malaria burden will increase significantly.

The purpose of this section is to answer the question: What might be the impact on the numbers of malaria-related cases and deaths if the most commonly used insecticides were no longer usable for malaria control and no other vector control measures were put in place? As with all models, the estimates should be interpreted with caution as there is a high degree of uncertainty in the numbers upon which the estimates are based.

What has been modelled?

- *Insecticides.* The model assesses the impact of widespread failure of pyrethroids.[1]
- *Geographical scope.* The scope of the model is limited to the WHO African Region because of the availability of information and because of the high proportion of global malaria-related deaths in the Region. The evolution of insecticide resistance in other malarious regions of the world would have similar devastating consequences.
- *Interventions.* The current model takes into account the vector control interventions used in each country (LLINs or IRS) as reported by WHO in the *World Malaria Report 2010* (*31*). In order to assess the consequences for the malaria burden of no modification to countries' current vector control practices to manage insecticide resistance, the model assumes that each country would maintain the interventions they have today, even if pyrethroids failed.

If universal coverage is achieved, the failure of pyrethroids could result in about 259 000 additional deaths among children in the WHO African Region every year.

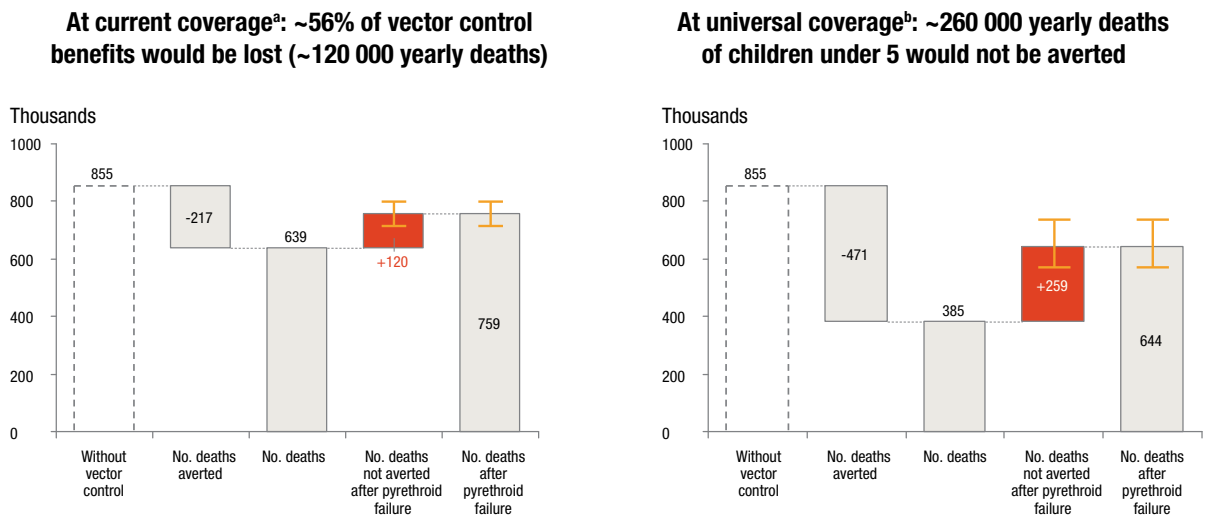
- *With current levels of LLIN and IRS coverage,* approximately 217 000 deaths among children under 5 are estimated to be averted each year in the WHO African Region due to vector control. The model suggests that, if pyrethroids failed, about 56% of the benefits resulting from vector control would be lost, resulting in about 120 000 deaths among children under 5 that would not be averted (Figure 15).
- *With universal LLIN and IRS coverage*, about 417 000 malaria-related child deaths would be averted due to vector control each year. If pyrethroids failed, the model suggests that about 259 000 deaths would no longer be averted each year.

The model shows a similar impact of insecticide resistance on the number of malaria cases: about 50% of the benefits of vector control would be lost, resulting in 26 million not averted cases with current vector control coverage and 55 million not averted cases when universal coverage is reached.

See Annex 8 for more details on the hypotheses, sources and sensitivity analyses of this model.

1 Failure of other currently available insecticides would also be a major threat to malaria control; however, additional scenarios are needed of the consequence of failure of other classes of insecticides.

Figure 15: Impact of insecticide resistance on malaria-related deaths among children under 5 years of age in the WHO African Region



a Current coverage with LLINs and IRS
b Assuming 100% coverage with LLINs and IRS, with current distribution between the two interventions maintained

Impact of additional cases on case management costs. The rise in malaria cases due to resistance to pyrethroids would lead to a considerable increase in diagnostic and treatment costs. At current coverage levels with vector control interventions, testing and treating all the additional cases would increase the cost of drugs and diagnosis by US$ 30–60 million. If universal coverage with vector control had been achieved, the cost increase would be US$ 60–130 million.[1]

Secondary costs linked to insecticide resistance. Insecticide resistance will not only increase the malaria burden and the case management costs, but could also have secondary effects. Continued pressure by currently used insecticides could affect the control of vectors other than those of malaria, and therefore increase the prevalence of other vector-borne diseases. In addition, the increase in malaria cases would result in a greater demand for antimalarial drugs, which could increase the level of drug resistance. These additional costs could have a negative impact on the gross domestic product of the affected countries.

1 Assuming that the cost for treatment with an artemisinin-based combination therapy is US$ 0.50 for 0–4-year-olds, US$ 1.20 for 5–14-year-olds and US$ 1.90 for adults, and the cost of a rapid diagnostic test is US$ 0.80 (fully loaded costs, including freight, delivery etc.)

1.4 AVAILABLE STRATEGIES FOR MANAGING RESISTANCE

1.4.1 OBJECTIVE OF IRM

IRM strategies are intended to maintain the effectiveness of vector control, despite the threat of resistance.

Resistance management is not a novel concept. IRM strategies have been used in agriculture and to address some public health situations over the past century (*2*). Several strategies have been used or proposed for managing resistance to insecticides for vector control, including rotations of insecticides, combination of interventions, mosaic spraying and use of mixtures[1]. In certain settings, non-insecticidal tools, such as non-insecticide-based larviciding and environmental management, can also be used to reduce the overall mosquito population and limit the number and size of breeding sites without selecting for resistance (*2*). Integrated vector management, by reducing reliance on chemical control, can also be considered a means of IRM.

1.4.2 AVAILABLE STRATEGIES BASED ON LLINS AND IRS

Current strategies for IRM are based primarily on indoor residual spraying; IRM strategies for LLINs are still limited and need to be further developed.

As stated above, the four main IRM strategies for malaria control (*2*) are:

- **Rotations of insecticides**. Two, or preferably more, insecticides with different modes of action are rotated from one year to the next;
- **Combination of interventions**. Two or more insecticide-based vector control interventions are used in a house (e.g. pyrethroids on nets and an insecticide of a different class on the walls), so that the same insect is likely, but not guaranteed, to come into contact with the second insecticide if it survives exposure to the first;
- **Mosaic spraying**. One compound is used in one geographic area and a different compound in neighbouring areas, the two being in different insecticide classes; further research is required on the use of mosaics;
- **Mixtures**. Two or more compounds of different insecticide classes are mixed to make a single product or formulation, so that the mosquito is guaranteed to come into contact with the two classes at the same time. Mixtures are not currently available for malaria vector control, but will become the future of IRM once they are available.

In addition, synergists, which can considerably enhance the potency of an insecticide and could be used in combinations or mixtures, should continue to be investigated and rigorously tested for their usefulness in IRM.

For IRS, three of the four suggested IRM strategies are currently available (Figure 16). Mixtures are not on the market but could be developed in the short term.

For LLINs, IRM strategies are currently more limited, with combinations of LLINs and IRS being the only current option. Individual nets with panels treated with alternative insecticides or with mixtures of insecticides could be developed, but, because pyrethroids are the only insecticide class used on currently available LLINs, an insecticide class other than pyrethroids would have to become available for use on nets. This is being investigated.

1 When they become available.

Figure 16: Potential applications of insecticide resistance management strategies for indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs)

Potential strategy	Use for IRS?	Use for LLINs?
Rotations	✓	
Combination	✓	✓
Mosaics	✓	
Mixtures	✓	✓

✓ *Currently available*
✓ *Products that could be developed*

Mosaics, use of alternative insecticides in different geographical areas

Although there are limited options for IRM with LLINs, they may retain an effect despite increased resistance to pyrethroids. Firstly, nets provide a physical barrier against biting by mosquitoes as long as they are intact (*2*). Secondly, in most vector species,[1] resistance to pyrethroids does not completely reduce the effect of the insecticide. It has also been observed that the irritancy of pyrethroids ('hyperexcitatory response') may reduce mosquito blood-feeding or encourage diversion to other hosts by certain vector species that do not feed exclusively on human hosts. This effect can vary, however, by species and geographical location.

Impact on resistant populations.

IRM strategies can have different effects on resistant vector populations.

Reduce the proportion of resistance (or delay the emergence of resistance) by removing selection pressure. This strategy is based on the assumption that owing to the 'fitness cost' (see section 1.2), resistance genes will recede from a vector population if selection pressure is removed. The strategy involves reducing the selection pressure, for example by rotations of different classes of insecticide and mosaic applications (the spatial reduction of use). These strategies aim to encourage or preserve susceptibility.

Continue to kill resistant vectors. This strategy is based on the assumption that if vectors are exposed simultaneously to multiple insecticides and are not killed by the insecticide to which they are resistant, they will be killed by the alternative insecticide. Currently, combination strategies use this approach, as will mixtures once they become available. This strategy aims to manage resistance by killing or reducing the proportion of resistance carriers by the simultaneous or near simultaneous use of alternative classes of insecticides.

See Annex 9 for more detailed descriptions of each IRM strategy, including considerations for implementation and associated costs.

1 This effect appears to vary by species and geographical area. For example, it does not apply to *An. funestus* in South Africa.

1.4.3 SUCCESSFUL IMPLEMENTATION OF IRM STRATEGIES

A number of experiences in agriculture and in the public health sector have shown IRM strategies to be successful in mitigating resistance and prolonging the efficacy of insect control tools.

Case study 1. The Onchocerciasis Control Programme

Context

A pertinent example of successful IRM in the public health sector is the Onchocerciasis Control Programme in West Africa. Before the development of ivermectin, control of onchocerciasis (river blindness) in West Africa depended completely on vector control (*32*). The Onchocerciasis Control Programme was launched in 1975 in 11 West African countries, and weekly aerial spraying of organophosphates onto the breeding sites of black flies began. Five years later, resistance of black flies to organophosphates was detected (*33*).

Action

Shortly afterwards, the Programme adopted rotational use of three chemical insecticide classes and one biological insecticide to counteract the resistance. The insecticides were chosen after careful data analysis: technicians evaluated the impact of insecticide spraying in each locality weekly, and the most appropriate insecticide for each riverside was then selected on the basis of the resistance profile, cost-effectiveness and ecological criteria (*33*).

Results

The Programme achieved full-scale rotations by the mid-1980s, which considerably reduced organophosphate resistance. It has been possible to reintroduce organophosphates in 90% of the Programme area in rotation with other insecticides, and the susceptibility of the black fly population to the other insecticide classes remained unchanged (*32*).

Lessons learnt

Firstly, large-scale IRM can be successful in reducing resistance; the Programme preserved the effectiveness of organophosphates over a large region and extended the lifespan of the vector control programme. It also showed, however, that it is almost impossible to return to a complete absence of resistant genes in a population. The aim of resistance management is to maintain the frequencies of resistant genes within the limits in which an insecticide is still effective. Secondly, early intervention with centralized, coordinated action is crucial; the IRM strategy was begun as soon as resistance was identified and quickly scaled up to cover the entire Programme area.

Case study 2. European pollen beetle control

Context

Another relevant example of IRM is in the European agricultural sector, in which IRM was recently used to sustain the control of the pollen beetle. The pollen beetle is a crop pest that attacks winter and spring oilseed rape (*34*). As there are no targeted pesticides to control it, most farmers used pyrethroids to control the beetle in the 1990s. The development of resistance was rapid; first detected in 1999 in France, resistant beetles destroyed or damaged about 230 000 ha of crops in Germany in 2006. By 2010, resistance was found in all rape-growing regions (*34*). Resistance led to a 40–100% reduction in the performance of pyrethroids against the pollen beetle in the field (*35*).

Action

To counteract the increased resistance, the Insecticide Resistance Action Committee brought together private sector and independent researchers to monitor and manage its spread. Within this initiative, a working group identified a set of effective insecticides with different modes of action (neonicotinoids, organophosphates, indoxacarb and pymetrozine) and created a 'decision management tree' to ensure proper administration of 'the right insecticide at the right time' (*36*).

Results

The basis of the action plan is that adherence to an insecticide management plan with use of non-pyrethroids will slow the development of resistance to pyrethroids and allow time for the development of new modes of action. The goal is to ensure that susceptibility to pyrethroids remains constant or increases (*36*).

Lessons learnt

To ensure the success of IRM strategies in a situation of widespread resistance, rapid, coordinated action involving the public and the private sector is needed. A clear action plan will mobilize and synchronize efforts throughout the region and among stakeholders, while providing assurance to affected communities. In addition, the use of all available insecticides—both those used in the past and compounds used in other sectors—can allow time for the development of insecticides with new modes of action.

PART 2

COLLECTIVE STRATEGY AGAINST INSECTICIDE RESISTANCE

2.1 OVERALL MALARIA COMMUNITY STRATEGY

2.1.1 INTRODUCTION TO RECOMMENDATIONS

Long-term goal and near-term objective.

Long-term goal.

The long-term goal of the malaria community is to maintain the effectiveness of malaria vector control. The susceptibility of malaria vectors to the insecticides used in vector control is a global public health good which must be preserved and which is essential for reaching the targets for reducing the malaria burden.[1] It is our collective responsibility to act immediately in a coordinated manner against insecticide resistance in order to maximize the effective lifespan of current and future malaria control tools. The strategy proposed in the Global Plan for Insecticide Resistance Management in malaria vectors goes beyond the currently available insecticides and lays the foundation of sound IRM practices beyond the 'pyrethroid era'.

Near-term objective.

Given the limited number of alternatives to pyrethroids and the current situation of resistance, it will not be possible to maintain susceptibility to pyrethroids forever; therefore, in the near term, all efforts should be focused on preserving the susceptibility of major malaria vectors to pyrethroids and other classes of insecticides, at least until new insecticides have become available for wide-scale vector control.

Achieving this near-term objective will be subject to several requirements. Firstly, IRM strategies should not prevent the implementation and scaling up of vector control; instead, they should support plans for increasing coverage with vector control. Secondly, resistance must be integrated into the cost-effectiveness equation that forms the basis for deciding on vector control interventions at all levels. Thirdly, sustaining the susceptibility of vectors to insecticides will require routine monitoring of the effectiveness of IRM and vector control programmes. It will also be important to monitor potential threats and consider ways to mitigate them. Fourth, success will depend on securing sufficient funding for capacity-building and implementation of IRM strategies. Finally, developing an adequate range of new insecticide classes will require accelerating the research and development of new products and active ingredients.

Three overarching principles of the GPIRM.

IRM will be country-driven, with inter-country, regional and global coordination. As for all vector control programmes, the main decisions in IRM will be taken by countries.[2] All countries should understand that susceptibility to insecticides is a shared finite resource; it is a kind of international public health good that is exhaustible. Countries must recognize their shared responsibility for preserving this resource for as long as possible. This means that each country must take responsibility for assessing the status of insecticide resistance within its borders and prepare appropriate management strategies. It is recognized that capacity and expertise are constrained at country level and therefore that considerable external support will be required. Inter-country coordination is crucial to the success of IRM strategies, both in terms of information sharing and planning at the subregional level. Poor cooperation between neighbouring countries could undermine collective efforts, as insecticide resistance does not respect country boundaries. Support for regional and subregional coordination will be important to ensure such cooperation.

1 These targets are both the malaria Millennium Development Goal (to reach a situation in which malaria is no longer a major cause of mortality and no longer a barrier to social and economic development and growth anywhere in the world) and the Global Malaria Action Plan targets for 2015 and beyond (to achieve universal coverage and near-zero global and national mortality related to malaria).

2 At national or in some cases district (or equivalent) level.

Every country should have a strategy, even though there are other immediate priorities in a resource-constrained environment. Every country is important to the success of the global strategy: each should perform a situation analysis of insecticide resistance to assess the threat and define an appropriate IRM strategy. The strategy may be a deliberate decision to continue with the current vector control programme or may result in modification of the current programme. In the short term, urgent, decisive action should be taken in geographical areas of high priority, where there is:

- evidence of an increase in the number of malaria cases suspected to be attributable to resistance;
- significant resistance to pyrethroids (e.g. metabolic resistance, especially oxidases, or high *kdr* frequency);
- a high malaria burden and intensive use of pyrethroid-based vector control (where control failure would have devastating consequences); or
- the status of resistance is unknown.

Pre-emptive action is required as soon as possible. IRM strategies should be built into every vector control programme[1] from the outset in order to minimize the evolution of resistance. IRM strategies should be pre-emptive rather than responsive to the identification of resistance, because the basic methods of IRM are far more effective when resistance is still rare and are less effective or ineffective when it has reached moderate or high frequency in the vector population, in particular after resistance has reached the tipping-point (see section 1.2.4).

India: Different degrees of success in IRM depending on the speed of response to insecticide resistance (37)

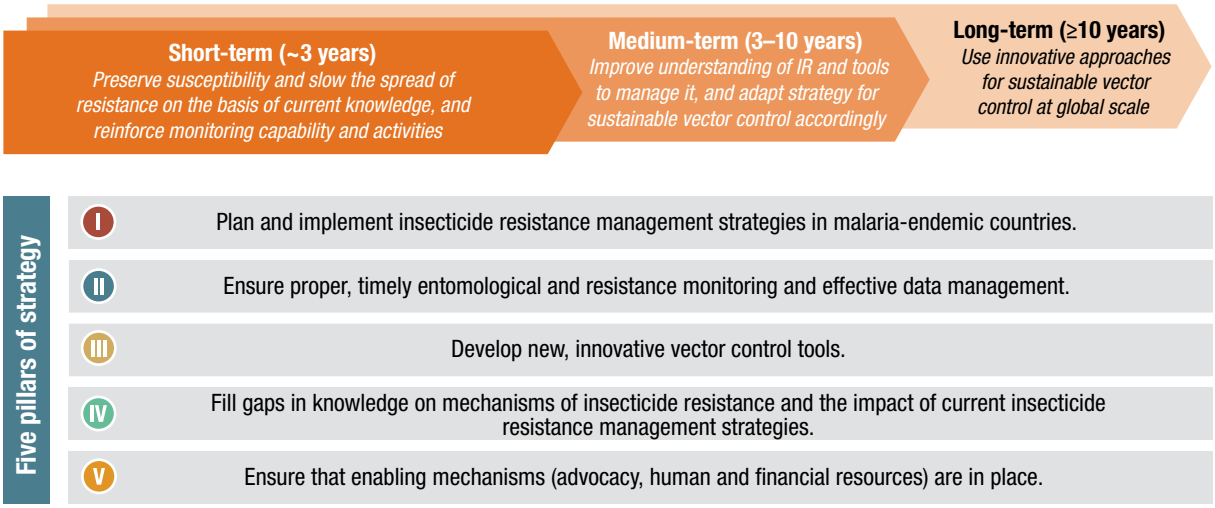
When low levels of pyrethoid resistance were identified in *An. culicifacies* in Surat district in 2001, pyrethroids were promptly withdrawn from IRS in the villages in 2002. This withdrawal of selection pressure, while resistance was still at a low frequency, resulted in reversal of resistance within 2–3 years (to 98% susceptibility).

In contrast, resistance to DDT and malathion persist in Surat, despite withdrawal of these insecticides from IRS for 30 and 9 years, respectively. Delayed action after the identification of resistance (for example, resistance to malathion was first reported in 1973 but its use continued until the 1990s) meant that resistance genes became stable in the vector population. Reversal of resistance to DDT and malathion now appears impossible.

1 Or equivalent body responsible for vector control

Overview of the strategy against insecticide resistance.

Figure 17: Five pillars of the Global Plan for Insecticide Resistance Management in malaria vectors



The GPIRM strategy has five pillars (see Figure 17): designing a resistance management strategy; preparing monitoring plans; developing new vector control tools; continuing research into insecticide resistance; and ensuring that the appropriate enabling mechanisms are in place to implement the strategy. These five elements have different priorities, in the short-term (~3 years), medium term (3–10 years) and long term (≥ 10 years), and are described below.

The framework sets out the activities required from the malaria community as a whole, including national malaria control programmes, country partners, WHO, research institutions, donors and other multilateral organizations. The implications and roles of each stakeholder group are explained in section 4.1. Given the complexity of insecticide resistance, a combined effort will be needed to successfully implement the strategy.

Provide advisory services to countries on IRM strategies.

National malaria control programmes, in line with WHO recommendations, should develop capacity in a variety of fields (including entomology, statistics and epidemiology) in order to analyse data on insecticide resistance and make decisions on IRM. Given the complexity of resistance and the need for specialized understanding of a wide range of cases, advisory services should be available to help countries in reviewing and interpreting entomological and epidemiological data, and linking the results of the analysis with the latest scientific knowledge on insecticide resistance, including from other countries and regions. In addition, advice should be available on the choice of vector control interventions and appropriate IRM strategies on the basis of a review of the data.

Giving technical advice is one of WHO's core functions. It can be delivered at the global, regional and country levels of the WHO system. Countries are encouraged to ask WHO for advice in engaging the expertise of partners, for both malaria vector control generally and insecticide resistance specifically. However, it is important that there be sufficient capacity and an appropriate platform at national level through which expert input can be channelled.

Advice can also be sought from other partners with entomological and insecticide resistance expertise, such as experts in the agricultural sector and in other public health sectors. WHO can facilitate coordination with these experts at global, regional and country levels.

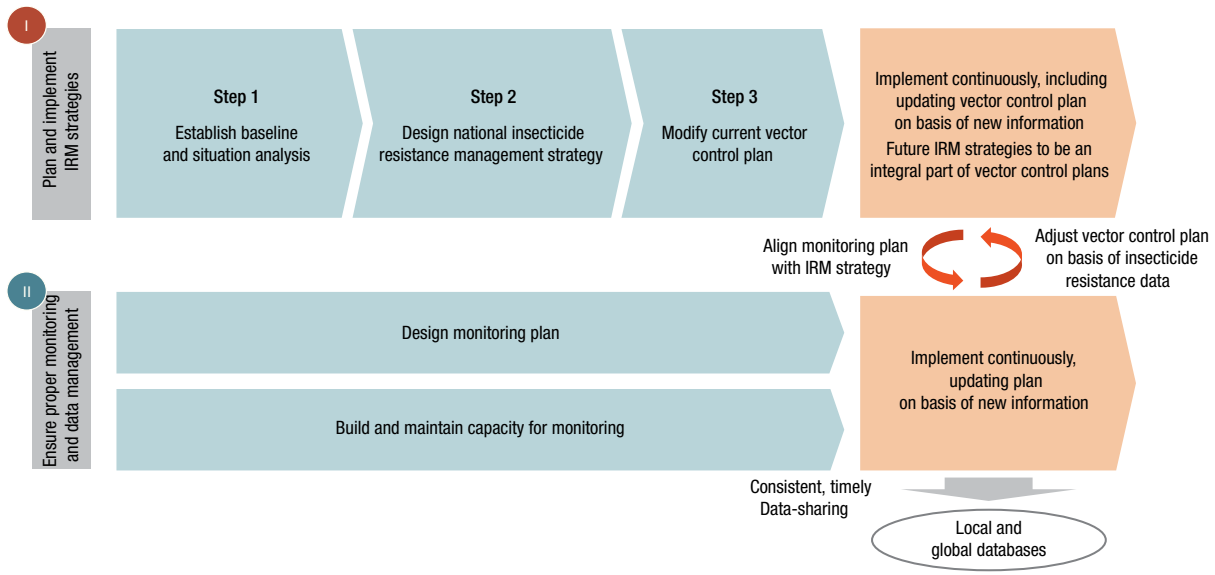
Review and analyse new research and scientific knowledge on insecticide resistance and update WHO policies accordingly.

Decision-making in insecticide resistance in malaria vector control must be based on the latest scientific developments. Therefore, WHO should convene relevant experts to review new science on insecticide resistance, including: evidence on subregional and regional trends in the spread of resistance in locally important vector species; new knowledge on resistance mechanisms; the impact of resistance on malaria control; and new evidence on IRM methods. The group would prepare an annual situation update on insecticide resistance in which recommendations would be revised on the basis of the latest scientific information on the effectiveness of strategies and products. Epidemiological information should also be available to allow the group to understand the malaria situation as a whole.

2.2 COUNTRY ACTIVITIES

Overview of recommendations at country level (pillars I and II of the GPIRM strategy).

Figure 18: Recommendations at country level: two parallel activities



IRM, insecticide resistance management

Plan and implement IRM strategies. The first element of these parallel efforts is for countries to identify how to modify their current vector control programmes to address insecticide resistance (see section 2.2.1). The starting point is to establish and analyse the current situation of insecticide resistance. This will require comprehensive collection of the available data, including information from neighbouring countries. To fill any gaps in the data, additional susceptibility tests will be necessary in most countries to identify the state of resistance.[1]

The next step is to design a national IRM strategy, on the basis of analysis and interpretation of the data. Support from national, regional and global experts should be sought, as required. Current vector control plans should then be modified to incorporate the strategy.

Ensure proper, timely monitoring and data management. The second element to be implemented at country level is to increase monitoring (see section 2.2.2). For this, countries should undertake two activities simultaneously: design a monitoring plan, which should include entomological monitoring, monitoring insecticide resistance, and monitoring the quality of vector control interventions; and, particularly in sub-Saharan Africa, build capacity and expertise in handling and interpreting entomological and resistance data. This includes the design of routine data collection, hypothesis generation and situation analysis, as well as practical skills for sampling mosquitoes in the field by a variety of methods.

Countries should not wait until they have established monitoring capacity before analysing their resistance situation and taking action. Capacity-building will take time and investment, possibly over several years in some countries. In the meantime, countries should quickly identify their resistance situation, use support networks and institutions for technical advice and capacity, as required, and adjust their vector control programmes accordingly.

Ongoing implementation (orange boxes in Figure 18). In the longer term, implementation and updating of vector control programmes and monitoring should be closely aligned and based on new information. Groups monitoring insecticide resistance must ensure consistent, timely sharing of data, especially at subregional level and across sectors. Local and global insecticide resistance databases should be set up and the new information added.

1 Unless there are comprehensive recent data (within the past 12 months) on insecticide resistance and on the resistance mechanisms at an appropriate number of sentinel sites.

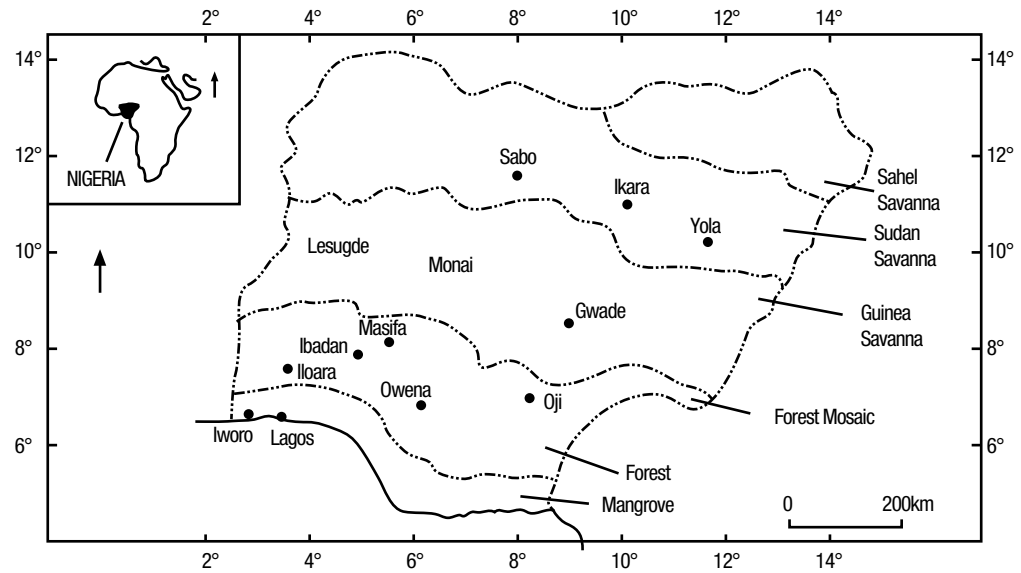
2.2.1 PILLAR I. PLAN AND IMPLEMENT INSECTICIDE RESISTANCE MANAGEMENT STRATEGIES IN MALARIA-ENDEMIC COUNTRIES.

Step 1. Establish baseline, and conduct situation analysis of insecticide resistance.

Data to be gathered on the basis of country stratification.

In deciding which malaria vector control measures are appropriate in different areas, most malaria-endemic countries have set up a system of eco-epidemiological stratification to divide a country into a few zones that are functionally different for vector control purposes. For this purpose, WHO recommends that a range of factors be considered, including eco-climatic zones, demographic zones, local malaria patterns (such as endemicity, interactions with agriculture, altitude), vector species and accessibility (*38*). An example is given in Figure 19.

Figure 19: Eco-epidemiological stratification of Nigeria for vector control



From reference (*39*)
Mosquitoes were collected from localities in five ecological zones.

In some countries, the current system of stratification might have to be refined to ensure that it is appropriate for insecticide resistance and takes into account known variations in susceptibility, even within a previously defined eco-epidemiological setting. Additional factors that should be considered with regard to stratification for resistance monitoring include: the history of insecticide use in different areas (for both public health and agriculture); the distribution of vector species; and the results of susceptibility tests (*40*). Existing strata may have to be subdivided into susceptible and resistant areas.

Within these strata, there must be sufficient numbers of sentinel sites. The WHO Regional Office for Africa (*40*) and PMI (*14*) have proposed, as an approximate guide, that there should be at least one sentinel site per every 500 000 nets distributed or 200 000 houses sprayed. This is equivalent to about one site per 1 million people protected, although the exact number would depend on the country. There might, however, be large variations in resistance frequency within small areas, which must not be ignored in planning and implementing IRM. Priority sites should therefore be those in which the threat of resistance appears to be greatest, for example, those with the greatest malaria burden and where insecticides are used in large quantities for both public health and agriculture. In addition, if there is a newly identified focus of resistance in a vector population, a further detailed study should be conducted in the area to establish the geographical extent of resistance.

Data for IRM decisions should cover the broad context of resistance.

In collecting data as background for decision-making on IRM, both susceptibility data and factors that relate to the broader resistance context should be reviewed, as detailed below.

Data on susceptibility should be recent (within the past 12 months).

Data on susceptibility from appropriate sentinel sites are of paramount importance. Depending on whether a country has recently (within the past 12 months) carried out comprehensive susceptibility testing, this will involve consolidation of existing data or collection of new data. If resistance has been identified, further testing should be conducted to identify the mechanisms,[1] which provide some indication of severity (see section 1.2.1).

Background information to be taken into account in assessing the significance and implications of insecticide resistance (41).

- *Factors related to the evolution of resistance:* In assessing information on insecticide resistance, the factors considered should include vector species (major malaria vectors and their typical behaviour) and insecticide pressure (presence of other possible causes of selection pressure, such as agriculture). In order to further understand the potential threat of resistance, consideration must also be given to the status and trends of resistance in neighbouring countries, the resistance genes identified, and the patterns of cross-resistance (on the basis of the observed or expected resistance mechanism). This information should provide a good understanding of the potential resistance to be mitigated.
- *Information on operational factors:* Of particular importance are the intensity, quality and completeness of vector control (whether interventions have been implemented correctly, with sufficient follow-up), the length of the malaria transmission season and which areas are sprayed at different times. A good operational indicator of possible resistance is the presence of surviving mosquitoes in properly treated houses.
- *Epidemiological information:* The ability to detect promptly an increase in malaria cases is important. Consideration should be given to the capacity of the local health system to detect an upsurge of malaria cases. While an increase might occur for many reasons, insecticide resistance should always be considered a potential cause, especially in Africa. If high levels of resistance are identified in areas with a surge in malaria cases, immediate action should be taken, in line with the recommendations set out later in this section. In addition, consideration should be given to the severity of the probable consequences of vector control failure. For example, if the area is one in which transmission is naturally intense but has been suppressed to low levels for several years, the local population might have lost much of its immunity; therefore, control failure could lead to a severe epidemic, with substantial loss of life.

1 According to the *Test procedures for insecticide resistance monitoring in malaria vector mosquitoes* (*29*).

The initial analysis should be based on existing information.

Up-to-date information on vector susceptibility status is essential for preparing an IRM strategy. Most national malaria control programmes will have – or have access to – at least some knowledge about each of the factors mentioned above. The probable exception is data on resistance elsewhere in the region, which should be available through subregional channels. Even with information gaps, programmes will already have sufficient knowledge to start planning IRM. At the same time, gaps in knowledge on contextual factors can be identified and plans made to fill the gaps.

Initial collection of baseline data should be completed as quickly as possible. Although a comprehensive plan for monitoring insecticide resistance is essential, this will take longer to establish and implement. What is needed immediately is an overview of the current situation.

Step 2: Design an IRM strategy.

Principles for an IRM strategy.

In 2010, WHO convened a group of malaria experts to define the technical principles for addressing insecticide resistance (*2*). The report contains the proposed initial policy framework, of which the GPIRM is the continuation. That document set out the technical principles upon which the action plan is based. Like all technical aspects of malaria control, insecticide resistance policies must be continuously updated to include new information, new tools and new recommendations when appropriate.

The main messages of the document are:

- Insecticides should be used with care and deliberation in order to reduce unnecessary selection pressure. Countries should consider whether they are using insecticides judiciously, carefully and with discrimination, and if there is a clear epidemiological benefit.
- Vector control programmes should avoid using a single class of insecticide everywhere and every year; instead, they should use rotations, mosaics, combinations of interventions, and mixtures (when they become available).
- Wherever possible, vector control programmes should diversify from pyrethroids in order to preserve their effectiveness. Although pyrethroids will continue to be used for LLINs in the near term, they should not generally be used for IRS where there is high LLIN coverage.
- IRM principles and methods should be incorporated into all vector control programmes, not as an option, but as a core component of programme design.
- The agricultural sector should try to avoid using classes of insecticide that are widely used for public health and should collaborate with vector control authorities in an intersectoral approach.
- Routine monitoring of insecticide resistance is essential to sustain the effectiveness of vector control interventions.
- The short-term additional costs of IRM should be balanced against the potential long-term public health impact and potential costs of insecticide resistance.

IRM is essential not only for malaria control but also for elimination. Managing insecticide resistance is essential in countries in which malaria is controlled (scaling-up or sustained control). IRM should nevertheless continue to be incorporated into every vector control programme, even in countries in pre-elimination and elimination phases, which may use vector control more focally. All malaria control and elimination programmes should recognize the threat of resistance and implement strategies to delay its emergence and spread. In the event of a malaria outbreak at any phase of a vector control programme, data on resistance should be part of the outbreak response plan.

IRM strategies should be adapted locally. IRM recommendations apply to all areas in which malaria vector control is based on the use of insecticides. They should, however, be adapted to local circumstances. One of the strengths of LLINs and IRS in comparison with other vector control tools is their suitability for scaling-up to universal coverage in different eco-epidemiological settings. Insecticide resistance will 'change the rules of the game': delaying resistance but continuing to have cost-effective interventions will require solutions that are more local and depend on interpretation and use of local data.

IRM strategies as part of integrated vector management. Resistance management strategies should be implemented in the broader context of integrated vector management, which is intended to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of disease vector control in a multi-disease approach. Integrated vector management is based on six principles: cost-effectiveness; intersectoral action; regulatory and operational measures; subsidiarity; decision-making, and sustainability. On the basis of evidence-based decision-making, the use of human and financial resources for the control of vector-borne disease is rationalized, and the engagement of communities and other sectors is emphasized to ensure sustainability. Although the focus of the GPIRM is malaria vector control, strategies for managing resistance in malaria vectors may have implications for other vector-borne diseases, and these interactions should be reviewed at country level. This will be particularly important in Latin America and Asia, where malaria is a secondary priority; therefore, IRM strategies for malaria vectors should support vector control for other diseases, such as dengue. As the control of other vector-borne diseases is the remit of other sectors, national mechanisms for intersectoral coordination should be strengthened.

Recommendations for an IRM strategy in various eco-epidemiological settings

The strategies for specific geographical areas depend on the vector control interventions already in use, the state of resistance and the epidemiological context.

Ultimately, new active ingredients are needed for both LLINs and IRS in order to manage insecticide resistance in the medium to longer term. This is of particular importance for LLINs. As soon as they become available, nets with non-pyrethroid active ingredients should be used (if possible, such new active ingredients could be used in a mixture with a pyrethroid) to delay the spread of resistance to the new insecticide.

In the meantime, the GPIRM presents the framework for a pragmatic approach to managing insecticide resistance with the tools that are currently available. For IRS, the recommendation is for pre-emptive and responsive use of rotations. For LLINs, the options are more limited, and IRM strategies will require consideration case by case. Where warranted and operationally feasible, countries should introduce focal IRS in resistance 'hot spots' where LLINs are the currently employed vector control method.

The detailed recommendations for various settings are presented in Part 3, *Technical recommendations for countries*.

Step 3. Modify the vector control plan.

Many elements of current vector control plans will have to be updated to incorporate an IRM strategy. The main elements to be revised are described below.

Overall implementation planning.

- *Support required*: Identify the resources and capabilities required to implement IRM strategies.
- *Detailed workplan*: Define a detailed workplan at the appropriate administrative level to implement the strategy, and communicate the workplan to local authorities.
- *Risks and mitigation*: Identify the risks to implementing the strategy effectively, and consider ways to mitigate them.

Specific operational elements.

- *Training*: Identify the areas in which staff will have to be trained, such as for collecting mosquitoes, conducting susceptibility tests, delivering vector control with new insecticides and maintaining equipment.
- *Procurement*: Work with suppliers procuring new insecticides. For IRS, the timing of procurement is particularly important. Bottlenecks can mean that IRS is started too late to interrupt transmission.
- *Regulatory pressures*: Identify which additional insecticides should be registered in the country, even as a precautionary measure, and identify the necessary steps in authorization, including an environmental assessment. This usually takes a long time, so it is important to start early.

Funding.

- *Budget and funding*: Update the budget for malaria and vector control to incorporate the costs of the IRM strategy, and identify potential sources of additional funding, including government, donors and reallocation in the current malaria budget.

2.2.2 PILLAR II. ENSURE PROPER, TIMELY ENTOMOLOGICAL AND RESISTANCE MONITORING AND EFFECTIVE DATA MANAGEMENT

Monitoring insecticide resistance has been limited in most countries. As a result, they have had incomplete information on the significance of the threat of resistance. This has affected their ability to manage insecticide resistance.

IRM should be seen in the context of integrated vector management and be part of the coordinated vector surveillance system. As stated in section 1.2.5, countries must address their monitoring inadequacies and ensure proper, timely entomological and resistance monitoring, as well as effective data management. Four recommendations are given below for establishing effective monitoring of insecticide resistance (Figure 20):

- Design a resistance monitoring plan;
- Build and maintain capacity to collect and interpret data on resistance;
- Interpret the data to make decisions at country level;
- Aggregate the data to guide global action.

Figure 20: Recommendations for monitoring resistance to insecticides

A — Design plan for monitoring resistance

- All countries should have a plan for routine entomological surveillance and monitoring of insecticide resistance. The plan should also take account of monitoring quality, effectiveness of interventions and coverage.
- Funding of large-scale vector control should be conditional on development and implementation of an adequate entomological and insecticide resistance monitoring plan

B — Build and maintain capacity to collect and interpret data on resistance

- The national malaria control programme or an equivalent office should be responsible for collecting data.
- National capacity in entomology, epidemiology, statistics and information technology should be increased for efficient data collection and correct interpretation of data.
- Capacity for field and laboratory testing should be improved. Each country should have at least one senior entomologist and field staff for collecting mosquitoes.
- Data on all insecticide classes that might be used for malaria control should be collected regularly at a representative number of sentinel sites and according to WHO guidelines.

C — Interpret data to make decisions at country level

- Data should be sent rapidly to national malaria control programmes to allow proper decision-making.
- Countries should have a functioning decision-making body for insecticide resistance management.
- On the basis of the available data, countries should follow WHO guidelines on insecticide resistance management for malaria.
- National malaria and vector control programmes should have access to technical support (from WHO and partners) for interpretation and decision-making.
- When possible, data on resistance should be compared with epidemiological data.

D — Aggregate data to provide global direction

- An aggregated global database should be built to provide global direction. The data should be available to all stakeholders.
- WHO should manage the database on behalf of malaria-endemic countries, although the database could be housed by another operator (e.g. an academic institution).
- Data should be added frequently (< 3 months after collection). Respect for confidentiality will facilitate data input.

A. Design a resistance monitoring plan.

Each country should design a comprehensive annual plan, including a budget, for routine monitoring of entomological parameters, including insecticide resistance and the quality of vector control interventions. The plan should be prepared in the context of the overall annual malaria operational plan.

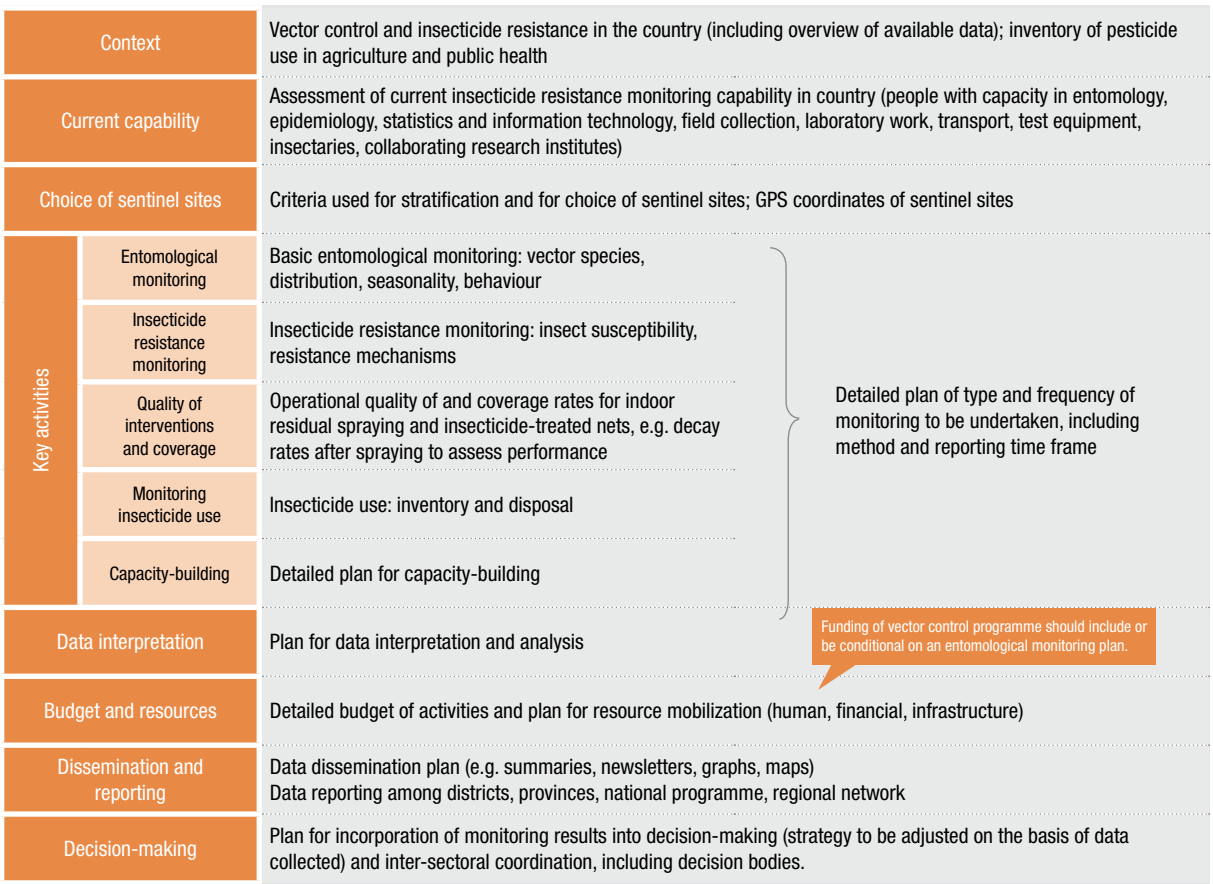
Not only entomological data but also the quality of interventions should be monitored.

The first step in achieving effective vector control is to ensure the quality of the interventions. Therefore, the quality of interventions must be included in the monitoring plan, with entomological monitoring and monitoring of insecticide resistance. Many countries have problems with bednets (e.g. due to weak fabrics that quickly develop holes) and low residual efficacy of insecticides due to substandard or counterfeit products or to the quality of spraying operations (e.g. inadequate spray quality or the washing, replastering or painting of sprayed walls by inhabitants). These factors may eventually result in control failure if quality is not systematically monitored and followed up. With regard to substandard vector control products (LLINs and insecticides), independent quality control should be requested during procurement.

The monitoring plan will depend on the country situation.

The exact format of the plan will depend on the country situation, but routine entomological and insecticide resistance surveillance and monitoring the quality of interventions should be covered. Figure 21 is an illustrative checklist of features to be included in monitoring insecticide resistance plans. The plan is for data collection and focuses on entomological and resistance indicators. For decision-making, a larger data set, including epidemiology data, will be needed.

Figure 21: Features that could be included in insecticide resistance monitoring plans



From the WHO Global Malaria Programme, based on reference (14), Global Fund tool for strengthening monitoring and evaluation systems and on interviews.
Other indicators should be part of a broader plan for monitoring and evaluating malaria control but will also be used for IRM decision-making.

Link vector control funding to the design and implementation of the monitoring insecticide resistance plan.

To ensure successful monitoring of insecticide resistance, funding of wide-scale vector control should be conditional on a plan for such monitoring.

B. Build and maintain national capacity to collect and interpret data on resistance.

Enable national malaria and vector control programmes to guide monitoring.

In order to ensure routine monitoring in a country, the national malaria and vector control programmes or the relevant national authority must be responsible for and guide IRM activities.

In order to assume responsibility for monitoring insecticide resistance, national malaria and vector control programmes or another authority must acquire the capability to oversee data collection efficiently, including adequate entomological, epidemiological, statistical and information technology capability. For example, all programmes must have at least one chief entomologist and ideally one entomologist in each region or province of large countries. The entomologists will work with a team of trained technicians and auxiliary staff, who can be employed internally or by partners (e.g. research institutes) to collect data on insecticide resistance in the field.

Examples of regional entomological capacity-building.

Entomological capacity for the collection and interpretation of data must be built in order for national malaria control programmes to take appropriate decisions on IRM. Each country has a different situation, which must be addressed differently. Entomological capacity-building has been approached in two main ways by countries and regions: strengthening the capacity of the national malaria control programme; and forming partnerships with academic and research institutions. Both strategies have been successful. Ideally, capacity should be built for entomological surveillance broadly; however, when such capacity is nonexistent, building capacity for monitoring insecticide resistance could be an important entry point.

National capacity-building can be supported by regional coordination networks. For example, Roll Back Malaria vector control working groups can be used, in addition to regional and subregional networks. Donors can also support capacity and infrastructure to monitor insecticide resistance. For example, the PMI and the Bill and Melinda Gates Foundation (through the 'Filling the gap' project as described below) support capacity-building for monitoring insecticide resistance in several countries.

Partnerships with research institutions.

Partnerships with national research institutions can be mutually beneficial for developing entomological capacity. In the WHO African Region, each of the seven countries that are part of the 'Filling the gap' project have formed partnerships with national research institutions. As a result the cost and logistical challenges of building entomological capacity were significantly reduced for national malaria control programmes, as the research institutions already had experts and facilities. This capability was supplemented by the procurement of adequate equipment and laboratory supplies for molecular differentiation of vector species, identification of insecticide resistance mechanisms and testing tools.

Strengthening the capacity of national malaria control programmes.

Although strengthening the capacity of a national malaria control programme requires more investment and consideration than partnering with research institutions, it can yield beneficial results.

In sub-Saharan Africa, the African Network for Vector Resistance to Insecticides has played a role in capacity-building. It has prepared frameworks and protocols for resistance surveillance and management for its member countries and has supported them in collecting and publishing information on insecticide resistance in Africa. It has also fostered collaboration between control programmes and research institutes at national and international levels and, with WHO, has organized training in entomology in many countries.

The WHO Eastern Mediterranean Region has invested heavily in building entomological capacity to support national malaria control programmes, following a Regional Committee resolution[1] to establish a Regional MSc course in entomology and vector control. Investment in the MSc course, established in collaboration with the Blue Nile Institute, Gezira University (Sudan), the London School of Hygiene and Tropical Medicine, the Liverpool School of Tropical Medicine (United Kingdom) and Witwatersrand University (South Africa), has produced a large cadre of vector control programme staff (80 people have been trained over the past 3 years), who can be relied upon to collect and interpret data on resistance in their respective countries to assist decision-making in vector control. Similarly, in the WHO African Region, about 300 national technicians have been trained, although to a more basic level than through the MSc course in the WHO Eastern Mediterranean Region.

Many other training and diploma courses have been conducted in the WHO Eastern Mediterranean Region. In the WHO Western Pacific Region, training and diploma courses in integrated vector management have been organized for insecticide resistance monitoring in the context of both dengue and malaria. As the recommendations of the GPIRM for IRM strategies are implemented, capacity in entomology and vector control and its flexibility in all the WHO regions will be a key asset.

Example of capacity-building in Sudan (5).

Having invested in capacity-building in entomology and vector control, Sudan has established a strong entomological surveillance system. The system includes monitoring for insecticide resistance at 74 functional sentinel sites in 12 of the 15 provinces of the country once or twice a year. There are at least two entomologists in each province, supported by a core team of 14 entomologists at central level to guide vector control decisions. Although this capacity building required a significant investment, it rapidly yielded benefits. Monitoring revealed insecticide resistance in many provinces, leading local decision-makers to modify their vector control plans to introduce insecticide rotations to manage emerging resistance.

Key considerations in strengthening national capacity.

- When establishing courses, institutions must develop a unique curriculum, which is tailored to the needs of vector control programmes, and which has a practical, field-based component. Admission criteria should take into account practical experience in control programmes as well as academic background.
- Monitoring and reporting of insecticide resistance must be systematic and organized so that the data can be used most effectively (e.g. to identify 'hot spots' of resistance).
- Any capacity-building initiative should include a mechanism for engaging WHO and the national ministry of health in follow-ups with district teams to monitor progress, share practical experience and best practices.

1 Fifty-second Session of the Regional Committee for the Eastern Mediterranean (2005), Resolution EM/RC52/R.6 on Integrated vector management

Ensure that countries have access to all testing methods (susceptibility testing, biochemical assays, molecular testing).

The different methods available for testing insecticide resistance (biochemical and molecular susceptibility tests) are complementary. Countries must have access to all these methods, with field testing facilities as well as basic and molecular laboratory capability at national and regional levels.

For routine susceptibility monitoring, data should be collected by trained field technicians with supervisors who hold an MSc degree in entomology (or equivalent). Routine testing can usually be performed nationally. For advanced molecular testing, countries can either use their own facilities, if the capability exists, or they can use external resources via collaboration with regional or subregional research institutes.

If collection and testing capacity is built outside the national malaria or vector control programme, the national programme should form close relationships with the organizations that are conducting the testing and ensure frequent reporting of results (preferably fewer than 3 months after collection).

Build infrastructure for all types of testing.

Infrastructure should be built within the national malaria or vector control programme or in national or regional research institutes to cover all types of testing. Field equipment (e.g. mosquito traps and test kits), laboratory equipment (e.g. dissection microscopes), insectaries, and transport are required for field sampling and testing, and more advanced laboratory equipment (e.g. deep freezers, plate readers, microcentrifuges) is needed for molecular or biochemical testing.

Countries should also have access to the necessary 'consumables'. As significant scaling-up of monitoring is recommended and there are already problems with the supply of consumables, the production of insecticide-impregnated papers for WHO susceptibility tests should be significantly scaled up, and quality control and quality assurance of these operations should be strengthened.

Please refer to the WHO guidelines on *Test procedures for insecticide resistance monitoring in malaria vector mosquitoes* for more details (*42*).

C. Ensure correct interpretation of data and effective decision-making for IRM at country level.

As mentioned above, decisions on insecticide resistance are difficult to make in many countries because of limited resources for monitoring. Several measures would help to improve national decision-making and accelerate countries' response capacity for managing insecticide resistance.

Ensure availability and timeliness of data.

Countries need good, timely data, tailored for prompt decision-making. This should be achieved mainly by facilitating data collection by the national malaria control programme. A number of activities can persuade academic institutions to submit data to national malaria programmes in a timely manner. For example, granting the confidentiality of data submitted (e.g. by aggregating data before use, appointing a focal person to guide data collection and data sharing, and making timely data sharing a condition for conducting research in the country.

Build national capacity to interpret data.

Many countries need to build capacity to interpret data, including statistical resources and entomological and epidemiological expertise. Actions should be coordinated to ensure that all available human resource capacity is fully used.

This type of capacity has been built in a number of African countries[1] with the support of WHO, the Bill & Melinda Gates Foundation, and the African Network on Vector Resistance to Insecticides, in two targeted ways. Firstly, the countries identified all current national resources and, where possible, reallocated them to the national malaria or vector control programme or to the relevant research institutes. Secondly, the national programmes increased training and capacity-building (by technical experts, often from WHO).

Ensure that countries have access to entomological advisory services.

Given the complexity of insecticide resistance and its consequences, countries need access to technical support for interpreting data and taking decisions on IRM strategies. Entomological advisory services should therefore be available, for example, from WHO's global, regional and country experts, from selected partners and through international collaboration.

1 *WHO project funded by the Bill and Melinda Gates Foundation, 'Filling the gap', in seven African countries — Cameroon, Kenya, Madagascar, Mali, Mozambique, Senegal, and the United Republic of Tanzania — coordinated and supported by the African Network on Vector Resistance to Insecticides.*

Establish a strong intersectoral body to decide on IRM.

Decisions on IRM affect not only the national malaria strategy but also insecticide registration and agricultural and environmental policies. To ensure effective decision-making, countries should have a strong intersectoral decision-making body (such as a technical advisory committee) for IRM. The body could include representatives of ministries of health, agriculture, and environment and experts from WHO and academic institutions, as well as other appropriate partners (e.g. donors, nongovernmental organizations and representatives of the private sector). Countries should decide on the most appropriate composition of the group. Most countries with an integrated vector management plan have an intersectoral coordination mechanism, which could be adapted for insecticide resistance decisions (Figures 22 and 23).

Ensure international coordination and data-sharing for effective national decision-making.

Insecticide resistance is an international problem, necessitating coordination and data sharing across borders. Regional networks can coordinate action and resistance management across borders.

Figure 22: A strong intersectoral steering committee for vector control used for insecticide resistance management decisions in Sudan

Committee objectives	The Intersectoral Steering Committee for Vector Control provides the Sudanese Government with policy and operational recommendations on vector control. This committee was established in the context of integrated vector management.		
Membership	Broad inter-sectoral membership with national vector control stakeholders		
	Public	Ministry of Health (Chair) National Vector Control Programme Regional malaria coordinators	Ministry of Agriculture: irrigation and pesticide council Ministry of Environment Ministry of Industry Higher Council for Environment and Natural Resources
	Other	Research and academic institutions WHO technical advisory staff	Other relevant external experts (e.g. experts on insecticide resistance) invited to discuss specific topics
Meetings and decisions	The Committee has quarterly meetings to discuss and decide on vector control interventions. Full participation is the general rule but varies somewhat depending on the topics discussed. Data on insecticide resistance discussed once a year in the context of decisions on a vector control strategy. Discussion on insecticide resistance scheduled at annual operational planning meetings to ensure sufficient time to make changes.		
Lessons learnt	Data on insecticide resistance should be collected routinely and used as the basis for decisions on vector control (discussed once a year by the steering committee). Intersectoral organization ensures involvement in and rapid implementation of decisions; e.g. a representative of the regulatory system can give interim approval for insecticides that are not yet registered. The presence of relevant experts on insecticide resistance at committee meetings ensures the necessary capacity for sound decision-making.		

Figure 23: A technical working group for vector control and insecticide resistance management with a public-private collaboration in Kenya

Group's objectives	The Technical Working Group for Vector Control takes decisions on national vector control policy and operations.		
Membership	Broad intersectoral membership involves both the public and the private sector.		
	Public	National Malaria Control Programme (Chair), vector control unit within National Malaria Control Programme	Ministry of Health Ministry of Agriculture, insecticide regulations Ministry of Environment
	Other	Research and academic institutions WHO technical advisory staff UNICEF	United States Agency for International Development, President's Malaria Initiative Umbrella organization for Kenyan nongovernmental organizations Distributors and manufacturers of insecticides and long-lasting insecticidal nets
Meetings and decisions	The group meets at least quarterly to discuss and decide on vector control interventions. Full participation is the general rule. The group decides on a vector control strategy on the basis of data on resistance and cost-effectiveness. Data on insecticide resistance are generally discussed at the same time as the report on monitoring for insecticide resistance.		
Lessons learnt	Intersectoral nature of technical working group ensures strong involvement and flexible decision-making. All stakeholders are involved in deciding on insecticide resistance management. The existence of one body responsible for resolving all questions on vector control provides a comprehensive understanding of all issues and their potential links to decision makers. Insecticide resistance management is thus placed in the broader context of vector control.		

D. Aggregate national data at global level to guide global policy and direction.

As detailed in section 1.2.5, the data on insecticide resistance are scattered in several databases, and many data are not captured. In order to guide global policy and direction on IRM in malaria control and to improve access of countries to subregional data, a comprehensive global resistance database should be developed. The database should be based on data in current regional and global databases and thereafter collect data from all country programmes and other partners. A number of prerequisites must be filled in order to achieve this.

Strong national data management steered by the national malaria or vector control programme.

National databases should be the responsibility of the national malaria or vector control programme or the relevant national authority. The databases should be managed by national personnel with sufficient capability in information technology and statistics, as informatics and bioinformatics are critical for effective data management.

Strong call from the community for a global database.

The global database should serve the needs of malaria-endemic countries and relevant partners (including researchers). WHO, representing the interests of its Member States, would oversee the database.

Efficient management of a global database.

The WHO Global Malaria Programme would consult with countries, Regional Offices and partners to identify a reputable institution to host the database, to be overseen by WHO on behalf of Member States. The WHO Global Malaria Programme should ensure the flow of data on insecticide resistance from countries to the hosting institution. The host organization should set up the database and work with WHO to design an input template for countries. WHO would manage data requests from partners in consultation with countries.

Standardized data format and timely input.

Data should be submitted to national and global databases in a standardized format, which should be prepared by the manager of the global database. In order that the database is relevant for decision-making, data must be submitted in a timely fashion. Country programmes and partners, including academia, should send data as soon as they become available or at the latest 3 months after collection.

In other sectors,[1] academic institutions and major funders have agreed on written public policy statements for full data sharing. In a similar manner, funding of insecticide resistance monitoring and research could be conditional on the requirement for full data sharing. Regional networks can also play an important role in data collection and sharing.

Ease of use of the database.

The basic functionalities of the database must be easy to use and accessible. In particular, the database must be easy to use by country programme managers.

1 For example, for genome data, as explained by genome database managers

2.3 RESEARCH AGENDA

2.3.1 PILLAR III. DEVELOP NEW, INNOVATIVE VECTOR CONTROL TOOLS

Sustained investment is needed in the development of new active ingredients for insecticides with different modes of action. This is due to the current reliance on insecticide based strategies for vector control, and to the inevitability of insecticide resistance if selection pressure is maintained. The IRM strategies detailed in this document are intended to delay the spread of resistance and preserve susceptibility to insecticides - at least until new classes or molecules become available. This is especially important for LLINs, as pyrethroids are currently the only class of insecticides used for these.

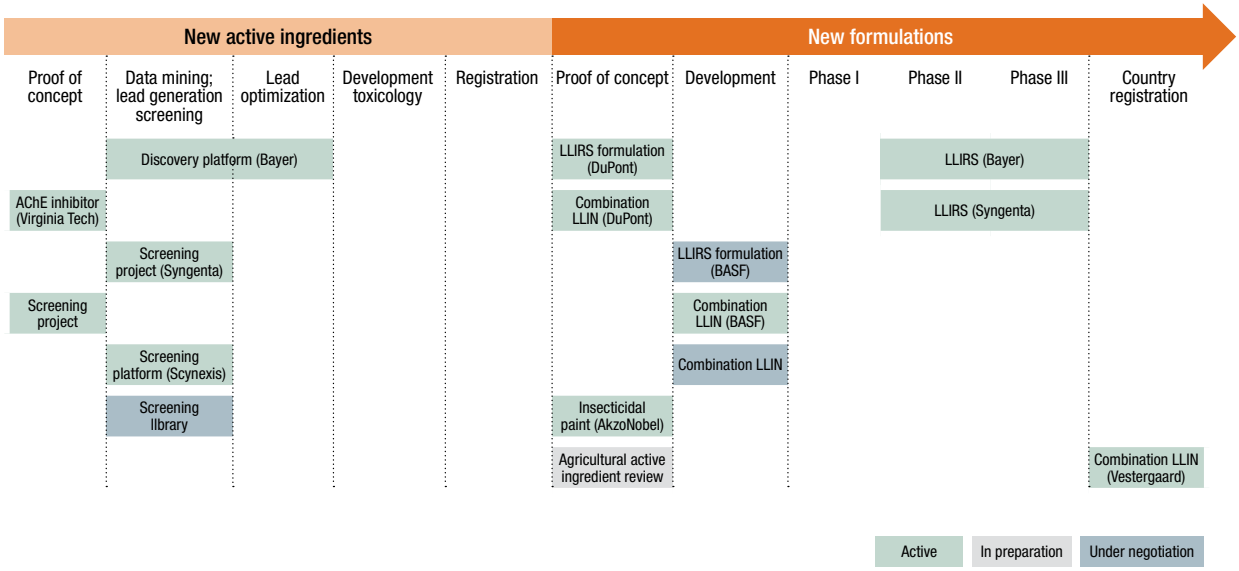
New, non-insecticide-based vector control tools may also be important in the long term to reduce the reliance on insecticides in controlling malaria transmission.

Research and development: reformulations and active ingredients.

The current pipeline is promising; however, more attention and investment are required, given the urgency.

As shown in the Innovative Vector Control Consortium pipeline (Figure 24), several reformulations are in late stages of development, and these could be used as a temporary option in the next few years. These include longer-lasting IRS, non-pyrethroid LLINs and LLINs treated with two insecticides. In addition, the Consortium is developing at least three new active ingredients. These include one ingredient with a different mode of action and with no evidence of cross-resistance with any insecticides currently used for vector control. This new ingredient could potentially be used on LLINs. However, the new active ingredients are in the early stages of assessing proof of principle[1] and will not be on the market for 7–10 years.

Figure 24: Innovative Vector Control Consortium portfolio for public health insecticides for indoor residual spraying and long-lasting insecticide-impregnated nets[2]



From the Innovative Vector Control Consortium
AChE, acetylcholinesterase; LLIRS, long-lasting indoor residual spraying; LLIN, long-lasting insecticidal net
Other industry projects on reformulations are under way.

1 A proof of principle assessment determines whether a new product or tool is effective for a defined public health purpose under a defined set of circumstances, will be useful to and feasible for its intended user and has an epidemiological impact.

2 It should be noted that there are other industry projects also being carried out in relation to reformulations.

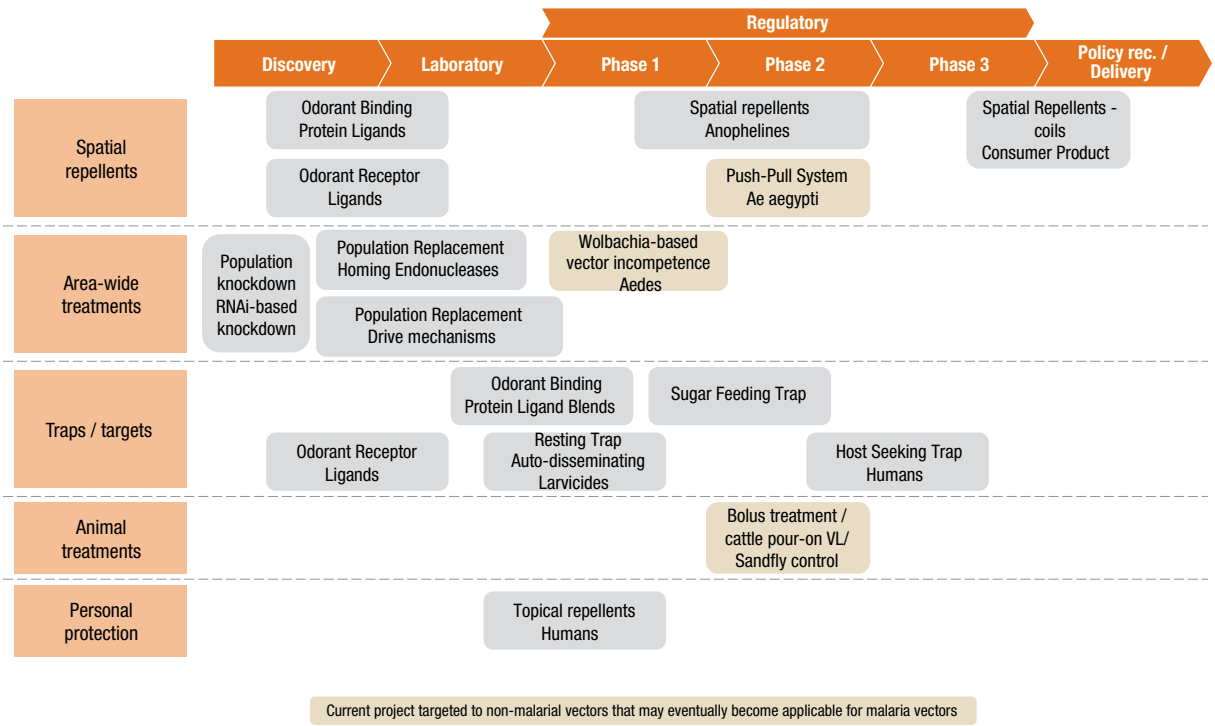
New products to supplement IRM strategies that may be available in the near term include:

- *Pirimiphos-methyl-CS*, which is a reformulated pirimiphos-methyl compound (organophosphate) in a longer-lasting capsule suspension format developed as part of an initiative of the Innovative Vector Control Consortium. When used for IRS, this reformulated version is expected to have a residual effect of more than 6 months, whereas other organophosphates are generally effective for 2–3 months. The product is in phase II of WHOPES evaluation, with a decision expected in early 2013.[1]
- *Chlorfenapyr* is a halogenated pyrrole that inhibits production of coenzyme adenosine triphosphate and causes cellular death and mortality of insect vectors. Cross-resistance between chlorfenapyr and existing insecticide classes used for vector control has not yet been reported. The active ingredient is used in non-malaria control applications; however, Chlorfenapyr SC is currently under testing and evaluation by WHOPES for IRS.

Research and development: new tools and paradigms.

Considerable work is under way to develop innovative vector control tools and paradigms, including a durable wall lining to complement IRS. Solid epidemiological evidence is needed, however, before durable wall linings can be recommended for wide-scale implementation. The current durable wall linings are pyrethroid-based and are therefore likely to have a limited role for IRM. Other paradigms require further research and testing. New paradigms, particularly those that do not depend on insecticides, could be helpful in future IRM strategies (Figure 25).

Figure 25: The pipeline of the Bill and Melinda Gates Foundation represents many of the new paradigms being developed for vector control



From the Bill and Melinda Gates Foundation
This is not a fully comprehensive list of new paradigms; while it encompasses products developed by multiple partners, it omits projects receiving funding from other sources

1 Estimates based on interviews with stakeholders

The new paradigms under development fall into four main categories:

- *Spatial repellents*: Repellents cause vectors to move away from the treated space and therefore prevent blood feeding;
- *Area-wide treatments*: These treatments alter genes in a broad vector population to change their traits;
- *Traps and targets*: Baited traps attract vectors to sites that expose them to insecticides;
- *Animal treatments*: Animals in frequent contact with vectors, such as cattle, are treated with an agent that is not harmful to them but inhibits vector survival.

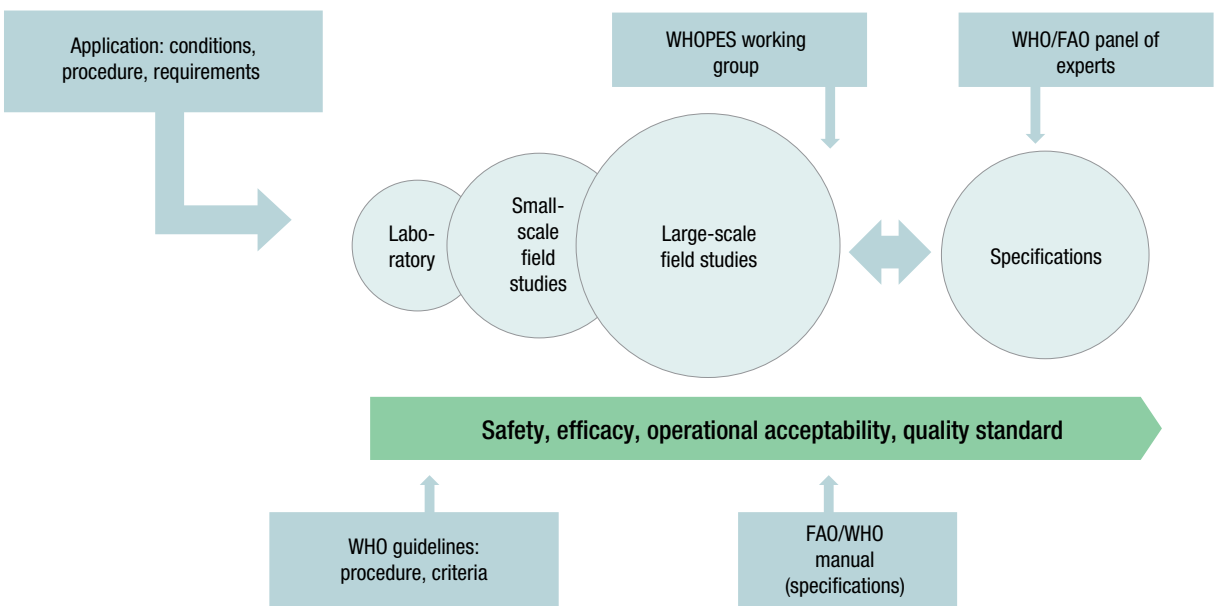
Strengthen capacity for faster flow of new products.

There is not currently a defined system for evaluating the evidence for new forms of vector control. Therefore, WHO has proposed the creation of a 'vector control advisory group' (VCAG) to make initial recommendations regarding new vector control tools for public health purposes. This would apply to the development of vector control tools for both malaria and other vector-borne diseases. The group would consist of experts from a range of entomological and vector control disciplines. It would help the development of new and innovative vector control tools by clarifying and accelerating the process by which these are recommended for, and adopted in, public health practice. One of its roles would be to consider 'proof of principle', i.e. whether the new intervention is effective for some defined public health purpose and, under defined circumstances, will be useful and feasible for its intended user. Once 'proof of principle' has been established by the group, the responsibility for specific product assessment would pass to WHOPES.

If the new tool is destined for malaria control purposes, policy recommendations would be made by the Malaria Policy Advisory Committee (MPAC) convened by the WHO Global Malaria Programme. If, however, the new tool has been developed for application in the control of other vector-borne diseases, policy recommendations would be made by the Department of Control of Neglected Tropical Diseases (NTD) and its Strategic and Technical Advisory Group (STAG) for vector-borne neglected and tropical diseases.

WHOPES was established in 1960 to promote and coordinate the testing and evaluation of pesticides for public health. Its global objectives are to facilitate the search for alternative pesticides and application methods that are safe and cost-effective and to design and promote policies, strategies and guidelines for the selective, judicious application of pesticides for public health. In addition, it assists and monitors their implementation by Member States. Its testing and evaluation programme is illustrated in Figure 26.

Figure 26: Four-phase testing and evaluation programme of the WHO Pesticide Evaluation Scheme (WHOPES)

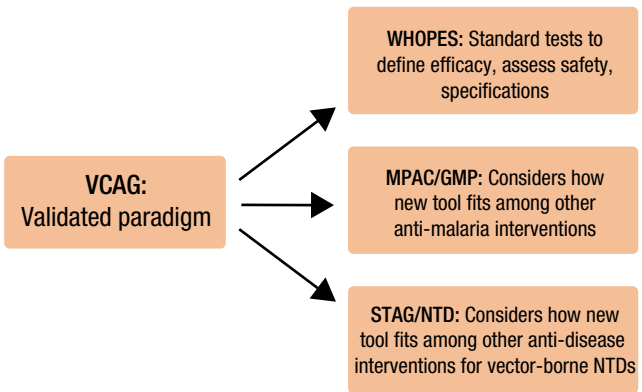


From the WHO Pesticide Evaluation Scheme (WHOPES)

Currently, WHOPES addresses only products for existing vector control interventions (IRS, LLINs, larvicides, space spray products and pesticide products for personal protection). If a new vector control tool is recommended by the vector control advisory group, WHOPES will: establish relevant testing guidelines for safety and efficacy; make recommendations on use after their safety and efficacy assessment; and develop specifications for their quality control and international trade.

The Malaria Policy Advisory Committee (MPAC) and the NTD STAG will in parallel establish the role of the new vector control tool in the context of malaria and of vector-borne NTD control and in relation to other interventions, respectively. For example, the MPAC would determine the circumstances in which the new tool might be used with or instead of another form of malaria vector control. The relations among these four groups are shown in Figure 27.

Figure 27: Roles of proposed vector control advisory group (VCAG), the WHO Pesticide Evaluation Scheme (WHOPES), and the Malaria Policy Advisory Committee (MPAC)



GMP, Global Malaria Programme; STAG/NTD, Strategic and Technical Advisory Group for the Control of Neglected Tropical Diseases.
The roles and interactions of these groups should be further clarified.

WHOPES' ability to respond to a growing number and new types of products is critical to the success of the accelerated vector control pipeline. This will require increasing the capacity of WHOPES by ensuring sufficient human and financial resources are made available. Capacity must be increased not only within WHOPES but also throughout the network of collaborating centres and institutions that conduct assessments on its behalf. Success will further depend on partnerships and dialogue among WHOPES, technical policy setting bodies within WHO, manufacturers, local regulatory authorities, and implementing partners.

2.3.2 PILLAR IV. FILL GAPS IN KNOWLEDGE ON MECHANISMS OF INSECTICIDE RESISTANCE AND ON THE IMPACT OF CURRENT IRM STRATEGIES

Current understanding of insecticide resistance is sufficient to justify immediate action to preserve the susceptibility of malaria vectors to pyrethroids and other insecticide classes. Furthermore, scientific theory and agricultural experience provide enough information on currently available IRM strategies to guide development of IRM strategies for malaria vectors.

Nevertheless, there are large gaps in our knowledge about both insecticide resistance and resistance management methods, and additional information is needed to deliver IRM strategies effectively. For example, there is limited understanding of how to measure the impact of resistance on the effectiveness of vector control and on how to assess the relative effectiveness of resistance management strategies in delaying the emergence of resistance and in killing resistant vectors in small-scale trials. Tackling these questions is hampered by a number of factors, including a lack of clear genetic markers for some important oxidase-mediated forms of resistance to pyrethroids. The answers to such questions would facilitate the preparation of better IRM strategies as well as an evidence-based assessment of their success.

Operational impact: better field research for designing tactics.

Background: Limited evidence is available on the operational impact of resistance, partly because of methodological constraints. Methods are needed to measure the impact rigorously. Countries should not, however, wait for evidence regarding the impact of insecticide resistance before taking action to manage it.

Research agenda: A study is being conducted in four countries in Africa and in India to investigate the potential link between resistance and control failure.[1] In general, increasing the number of such studies would provide additional data points and would reveal distribution patterns related to the impact of insecticide resistance. They would also show differences in impact between target-site and metabolic resistance. Efforts to understand the link between insecticide resistance and control failure could be strengthened both by using experimental huts to test possible IRM strategies and by increasing epidemiological surveillance for confirmed malaria cases. See Annex 4 for more details of the challenges in associating insecticide resistance with epidemiological effect.

When new foci of resistance are identified, it is useful to investigate when, where and why they appeared (for example, selection by public health, agricultural or domestic insecticides, and cross resistance mechanisms). This improves understanding of how best to avoid the future emergence of resistance. In addition, when further cases of control failure occur in apparent association with insecticide resistance, studies should be conducted to identify other possible causes[2] and to gather evidence about the relative importance of these factors in causing resurgence of malaria.

Assessment of IRM strategies.

Background: IRM should be undertaken now on the basis of encouraging results with recommended IRM strategies, including successful practices in both agriculture and public health. With limited experience in IRM specifically for malaria, and the fact that this is the first global IRM malaria strategy, further information is needed on the use of tools to manage resistance most effectively in the context of malaria control.

Research agenda: Many questions remain on the efficacy, feasibility and applicability of different strategies for managing insecticide resistance under different circumstances. In addition, relevant indicators of effectiveness are needed to measure the success of different IRM strategies.

The efficacy of potential IRM strategies must be assessed further, including:

- *Overall*: Do current IRM strategies maintain susceptibility to insecticides?
- *Rotations*: Can resistance be both slowed and reversed by yearly rotation between two insecticides? What is the relative efficacy of rotations with insecticides having two and three modes of action?
- *Combinations*: Can resistance be both slowed and reversed by combinations? What additional benefit does a combination strategy (LLINs plus IRS) offer for reducing morbidity and mortality from malaria, including cost-effectiveness over time?
- *Mixtures*: Will mixtures, once developed, induce linkage disequilibrium under field conditions if there is already resistance to one compound i.e., will an insecticide in a mixture accelerate development of resistance to the other insecticide?
- *Synergists*: What is the role of synergists in IRM?

1 Bill and Melinda Gates Foundation-funded WHO project "Implications of insecticide resistance on malaria vector control", conducted in four countries in Africa and in India.

2 For example: gaps in coverage; changes in other interventions; loss of immunity in the human population; or unusual weather, human movement or behaviour.

The practical issues in implementation of IRM strategies require further investigation, for example:

- *Overall*: What additional challenges are involved – and what additional activities are needed – to change from one vector control intervention to another and to change insecticides for IRS (including political acceptance, donor flexibility, training and supervision, and community education)?
- *Rotations*: What are the challenges to timely procurement of multiple insecticides, and how can they be overcome?
- *Mixtures*: In what conditions could insecticide formulations be mixed, in the factory or during applications, as in agriculture? What would be the implications for cost, registration, training and chemical safety? Some argue that insecticides for use in public health must be properly formulated at the factory, and not mixed during application. Can mixture formulations be devised so that different components decay over time at exactly the same rate?

Further understanding is required regarding the applicability of different IRM strategies under varying circumstances, as well as the decision criteria used to select among different options. Specialized technical support should be provided on the selection of alternative IRM strategies.

Many of these questions cannot be evaluated before the interventions are implemented on a large scale. More empirical evidence is needed to strengthen confidence that the IRM strategy of using combinations, synergists, or mixtures can work. More evidence can be accumulated on a smaller scale, by testing these IRM strategies in experimental huts and monitoring the effect on mosquitoes entering and leaving the huts. Evidence for the efficacy of rotations can be accumulated only by testing on a larger scale, in a village or several villages.

Trends: Resistance should be monitored over time to identify trends in its evolution, with the aim of providing guidance on when to respond to resistance

Metabolic resistance.

Background: The understanding of metabolic resistance is relatively limited. This is a concern, given the increasing reports of metabolic resistance and the widely accepted hypothesis that it is a stronger resistance mechanism, and that it could potentially have greater operational impact.

Research agenda: The research agenda should focus on three elements. Firstly, the genetic mutations responsible for metabolic resistance to pyrethroids in different geographical settings need to be identified, and their relative importance should be studied. The task is more challenging than for most resistance mechanisms in mosquitoes, because the cytochrome-oxidase enzymes are coded by a large gene family scattered throughout the genome. In addition, the mutations associated with resistance appear to be located in promoter or regulator sequences that are not necessarily genetically linked to the resistance gene itself and are much harder to locate.

Secondly, identification of these resistance genes, preferably with high-throughput DNA-based methods, will be essential for understanding the fundamental genetic processes of the spread of resistance, for developing new methods to assess the impact of resistance on malaria transmission, and as proxy indicators of selection for resistance. Experts hope that such methods will be available within 3 years. High-throughput methods are already available for *kdr* resistance, which has allowed researchers to study its spread more closely and understand its importance and impact more clearly. The current inability to track metabolic resistance in this way is a significant obstacle to the design of rational, evidence-based resistance management strategies.

Thirdly, a range of vector strains resistant to different insecticides should be colonized in different locations in order to understand their resistance mechanisms and to determine the probable effectiveness of new resistance management products and active ingredients as they appear.

Genetics.

Background: With limited genetic information on resistance genes, it is difficult to track and anticipate the course of resistance, and understand which IRM strategies would be most effective. The evolution of resistance and the possibility of reducing and even reversing resistance cannot be predicted because of limited information on factors such as baseline frequency (mutation rates), fitness cost, genetic mode of inheritance and the selection pressure due to different uses of insecticides in agriculture and public health. Inability to track resistance genetically makes the consequences of insecticide resistance more difficult to anticipate; it is also difficult to measure the efficacy of IRM strategies.

Research agenda: The genes that confer metabolic resistance must be identified in order to answer several important research questions. Outputs from this research agenda would have immediate practical implications for decisions on resistance management taken in national malaria control programmes. The topics for research should include genetic dominance, fitness cost, cross-resistance, linkage disequilibrium, drivers of selection pressure and behavioural resistance. See Annex 10 for more details of the genetic research agenda.

2.4 ENABLING MECHANISMS

2.4.1 PILLAR V. ENSURE THAT KEY ENABLING MECHANISMS (ADVOCACY, HUMAN AND FINANCIAL RESOURCES) ARE IN PLACE

IRM is a shared global responsibility. Successful implementation of IRM strategies requires motivating stakeholders at global, regional and national levels. Many stakeholder groups are inter-dependent, particularly with regard to funding, capacity-building and coordinating responses among countries and sectors. Partners should be aware of their roles and responsibilities and ensure a sufficient allocation of capacity and funds for IRM. The proposed roles of stakeholder groups are described in this section

Advocacy is necessary to engage all decision-makers early in the design of IRM strategies.

The political profile of insecticide resistance must be raised to focus allocation of resources for IRM. All stakeholders should be aware that preserving susceptibility to insecticide classes is in the public interest. National malaria control programmes, WHO and the Roll Back Malaria Partnership should work together to advocate for IRM strategies.

It is particularly important to engage governments and donors, as their endorsement will help to secure funding. Moreover, the engagement of these stakeholders will communicate the importance of insecticide resistance to the community. It will also facilitate intersectoral mobilization, especially between agriculture and public health, and may help to convince the private sector that there is a market for new public health products. In addition, it will help national malaria control programmes to focus on IRM and facilitate implementation of such strategies. This is important to deflect criticism that funding and capacity used for IRM could be better used elsewhere. Finally, support from some governments and donors may put 'peer pressure' on others that are more reluctant to take the threat of insecticide resistance seriously.

Sudan: example of government engagement

Support directly from the Sudanese Government enabled rapid implementation of an IRM strategy after resistance was identified. The Government understood the importance of IRM for both public health and the economy and decided to lead the strategy in order to encourage other governments in Africa to do the same. In 2006, the national malaria control programme changed from pyrethroids to bendiocarb for IRS. In the areas in which bendiocarb was introduced, the frequency of resistance genes was reduced.

See Figure 22 on page 61 for a more detailed description of the Sudanese programme

Modelling insecticide resistance to inform countries and donors about the human and financial costs.

Current estimates in the GPIRM provide a preliminary indication of the financial and epidemiological impacts of insecticide resistance. The estimates are based on 'high-level' assumptions and scenarios (made on the basis of general principles, providing rough estimates only), such as 'complete failure of pyrethroids'. (See section 1.3 for malaria burden modelling and section 2.5 for financial cost modelling.) While these estimates give an indication of the potential human and financial burdens, partners (in particular endemic countries and donors) require more details about the health and financial impacts of insecticide resistance in order to plan the most efficient and cost-effective IRM strategies.

Modelling the impact of insecticide resistance on malaria burden. Epidemiological models for malaria should be revised to include insecticide resistance if they are to inform decision-making at national and global levels. A model is needed of the epidemiological impact of potential IRM strategies in order to inform possible options. Additional modelling of the dynamics of insecticide resistance (in particular the link with the size of the vector populations, biting and resting behaviour, transmission levels, morbidity and mortality) should also be undertaken.

Modelling the impact of insecticide resistance on financial costs. The initial cost modelling conducted for the GPIRM should be revised and refined to provide greater granularity. Cost modelling has three aims. Firstly, it should provide estimates on a country-by-country basis of the costs of all IRM strategies, not only rotations. Secondly, the cumulative costs and benefits of IRM strategies over time should be used to define the conditions under which increased short-term costs are repaid by longer-term savings due to extended use of less expensive insecticides. Thirdly, the costs of new vector control tools should be integrated into the model.

Adequate, sustainable human and financial resources must be available for global and local IRM strategies.

Human and technical capacity: Capacity-building is required both in malaria-endemic countries and for partner organizations to ensure that they can support countries.

Requirements within countries. Entomological capacity and other specialized skills, such as epidemiology, statistics and expertise in insecticide resistance, are required to design monitoring plans, interpret data and make decisions about the IRM strategy. (See section 1.4.2) Capacity to implement IRM strategies should go beyond the selection of a strategy and alternative insecticides to the planning and implementation of strategies; for example, training staff to do rotations or mosaics.

Requirements within partner organizations. Organizations must have sufficient capacity to provide support to countries. The areas in which capacity-building is required are:

- *Advisory services*: Advisory services should be available to countries, particularly for analysis of data and decision-making on IRM strategies. WHO, together with relevant partners, will be important in this capacity.
- *Support for planning*: All partners with experience in vector control planning should make resources available to countries for preparing IRM plans and monitoring insecticide resistance.
- *Research and evidence*: WHO should convene a group of experts that can review new science and evidence and revise recommendations accordingly. Countries rely on WHO to consolidate information and provide up-to-date guidelines on IRM.
- *Dissemination of IRM strategy*: Implementing agencies and partners should ensure that they have capacity to disseminate IRM strategies within countries.
- *WHOPES*: The capacity of WHOPES and collaborating centres should be strengthened to ensure a timely response to new vector control tools.

Financial resources for increased costs associated with IRM.

Funding is required for insecticide resistance both for countries to implement IRM strategies and monitor insecticide resistance, and for research into insecticide resistance, and research and development of new insecticides and vector control tools.

Insecticide resistance monitoring. Costs are associated with increasing entomological capacity, the equipment for testing (including susceptibility test kits, use of laboratories for molecular testing, paying for the support of research institutions), and training of staff to collect and test vectors.

IRM strategies. Integration of IRM strategies into vector control programmes may increase costs for non-pyrethroid insecticides (the alternatives, besides DDT, are significantly more expensive at current prices), training staff for different vector control strategies, such as rotations and mosaics, and other programme costs.

In order to maintain vector control coverage, near-term funding will have to increase to cover the costs associated with monitoring insecticide resistance and implementing IRM strategies.

Potential sources of funding. All potential sources of funding should be considered by countries, although domestic governments and donors will naturally play an important role. Donors should stress the long-term importance of monitoring insecticide resistance by making a monitoring programme a condition of any large grant for vector control. Ideally, they should also provide additional funding for this activity. National malaria control programmes should consider re-allocating a portion of their vector control budgets to conduct monitoring or implement urgently needed IRM strategies.

Accelerated funding. The idea of acceleration has been suggested so that action can start immediately after the launch of the GPIRM. WHO will work with partners to discuss the options, which include a catalytic fund to initiate entomological monitoring and strategic support for IRM strategies in countries considered by the group to be of high priority.

Research. Although research on insecticide resistance is already taking place, continued funding for this is needed. One of the first tasks in implementing the GPIRM will be to establish research priorities.

2.5 FINANCIAL COST

2.5.1 CONTEXT OF MODELLING

Implementation of the recommended IRM strategies (section 2.2) is essential to delay the evolution of resistance and prolong the use of current insecticides. In some cases, susceptibility might even be reversed to undetectable levels, but this will require action before the resistance gene becomes stable in the population. Action will have associated financial costs, such as for more expensive insecticides (e.g. carbamates and organophosphates), additional training, new equipment or additional spraying rounds for IRS, and systematic monitoring of insecticide resistance.

These supplementary costs should be compared with the additional cost that would be incurred, if no pre-emptive action were taken, of implementing IRM strategies after the failure of the most commonly used, affordable insecticides (e.g. pyrethroids and DDT).

Additional modelling will be needed. To estimate the effects of insecticide resistance on financial costs, a 'scenario-based' model based on simple assumptions has been developed, not to estimate the exact cost of an IRS rotations programme in a specific country but to provide orders of magnitude and illustrations of the impact of insecticide resistance on control failure.[1]

Further modelling will be needed to refine the analyses outlined in the GPIRM. The research necessary for adequate decision-making at country and global level is described in section 2.4.1.

This section addresses the following questions:

- What might be the cost implications of implementing pre-emptive measures to delay resistance?
- What might be the cost implications of waiting until current insecticides fail to implement IRM?
- What are the projected costs of monitoring insecticide resistance?

2.5.2 FINANCIAL COST OF MANAGING INSECTICIDE RESISTANCE

Financial cost for geographical areas in which IRS is the primary tool for vector control.

What has been modelled?

- *Pre-emptive rotations.* The model compares the estimated cost of IRS with pyrethroids alone to pre-emptive rotations with three different insecticides: pyrethroids, carbamates and organophosphates.
- *Rotations after failure of pyrethroids.* The model compares the estimated cost of IRS with pyrethroids alone with that of rotations without pyrethroids (i.e. rotations of carbamates and organophosphates).

Implementing IRS rotations pre-emptively would increase the cost by 20–47%.

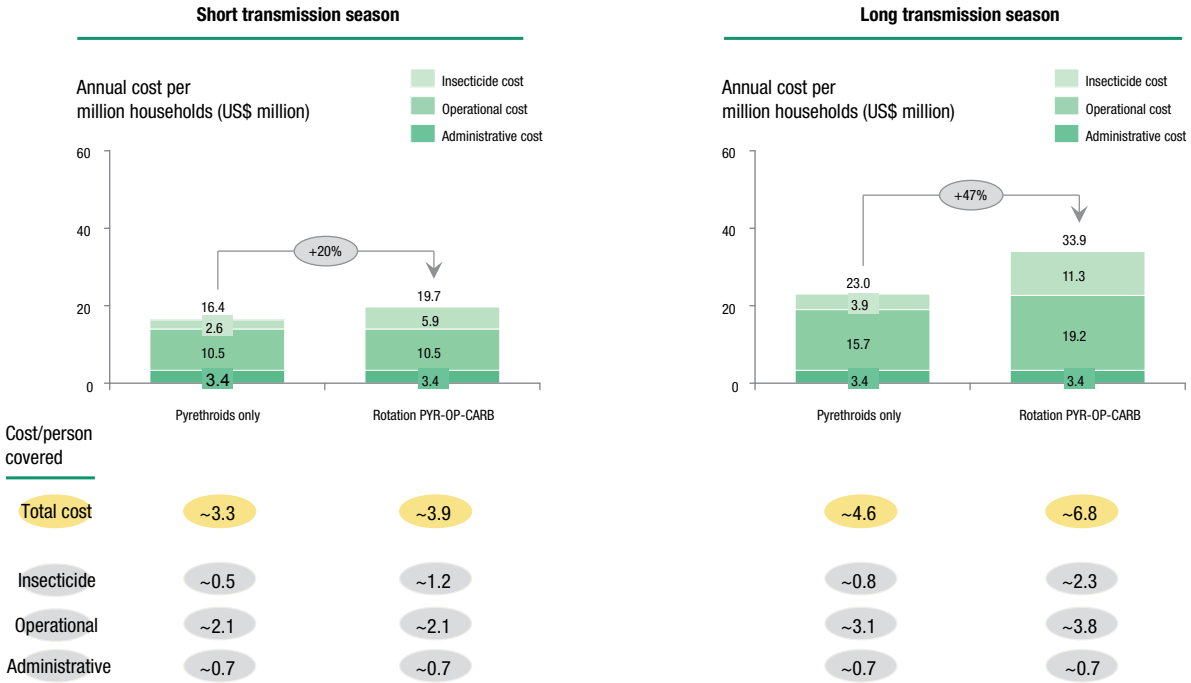
- *Short transmission season.* The model suggests that replacing IRS with pyrethroids alone by 3-year rotations of pyrethroids, carbamates and organophosphates would increase the cost in areas with short malaria transmission seasons by approximately 20%, corresponding to an increase in the cost per person from US$ 3.30 to US$ 3.90.
- *Long transmission season*. This same model suggests that in areas with long transmission seasons, IRS rotations would increase costs by approximately 47%, the corresponding costs per person increasing from US$ 4.60 to US$ 6.80.

See Figure 28.

1 As explained in section 1.2, most experts consider that metabolic resistance or simultaneous metabolic and kdr resistance are more likely than other mechanisms to lead to control failure than kdr alone.

The overall cost increase is due to both the higher cost of the alternative insecticides and increased operational programme costs for the additional spraying rounds required for carbamates and organophosphates, which generally have shorter residual efficacy than pyrethroids.

Figure 28: Cost implications of implementing indoor residual spraying rotations pre-emptively



PYR, pyrethroids; OP, organophosphates; CARB, carbamates

Costs estimated for 1 million households each with five people and 150 m^2 sprayable surface.

Operational costs: Planning and logistics; environmental compliance, including soak pit or evaporation tank construction; training; information, education and communications; warehousing; short-term labour; transport; medical costs; mop-up operations; post-spray meetings; monitoring and evaluation; shipping; spray equipment; and personal protective equipment.

Administrative costs: National labour; local office leases, utilities and maintenance; office equipment and supplies; office services; and management transport. Considered to be a yearly fixed cost (occurring once regardless of number of spray rounds).

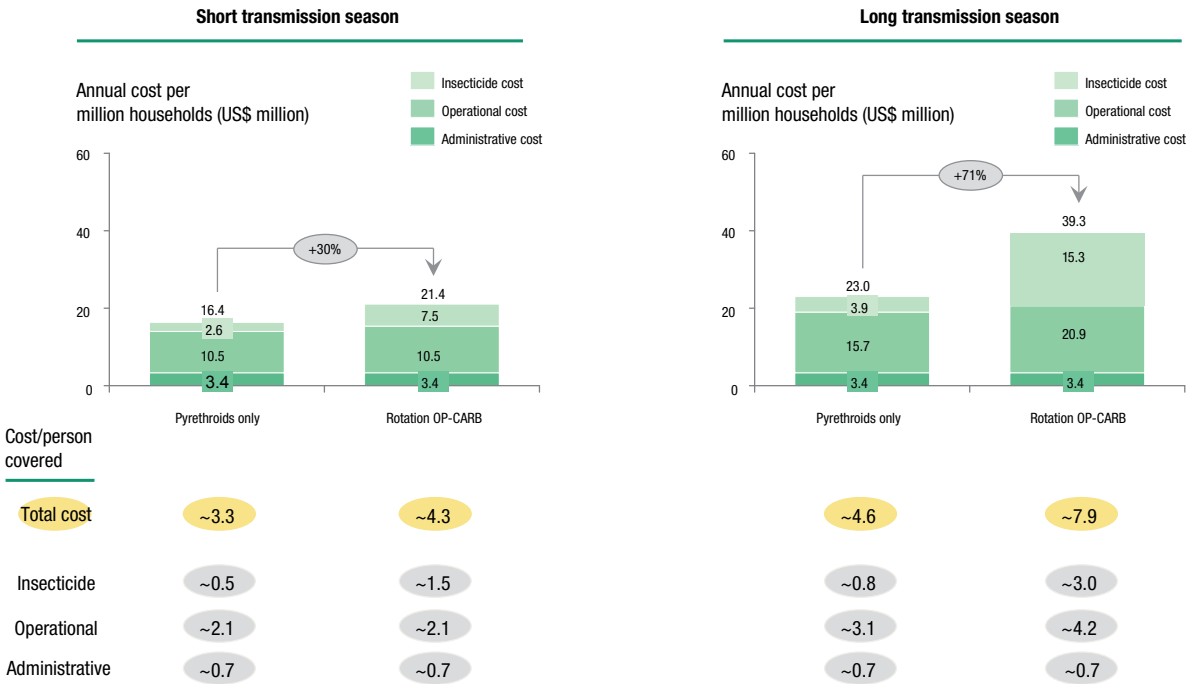
These results do not take into account potential use of DDT. If IRS with pyrethroids only were replaced by 4-year rotations of pyrethroids, carbamates, organophosphates and DDT, the cost would increase by about 17% in areas with short transmission seasons and 30% in those with long transmission seasons. As DDT costs less than carbamates and organophosphates, using DDT in rotations could lower the overall cost and therefore be a useful option in certain settings. DDT should be used only under the conditions described in the WHO position statement (*10*), and countries should closely monitor cross-resistance with pyrethroids.

Implementing rotations after failure of pyrethroids would increase the cost of IRS by 30–71%. If pre-emptive IRM strategies are not implemented, the efficacy of the current insecticides might be lost. Implementing rotations after failure would be significantly more expensive than implementing them pre-emptively because pyrethroids would likely be excluded from the rotations (Figure 29):

- *Short transmission season.* The model suggests that the approximate 20% increase in cost for IRS rotations would increase to 30% if implementation was delayed until pyrethroids were no longer usable.
- *Long transmission season.* In areas with long malaria transmission seasons, the cost of IRS would increase by approximately 71%, instead of 47% with pre-emptive rotations.

See Annex 11 for more details on the hypotheses and sources used for this model of the financial impact of insecticide resistance.

Figure 29: Cost implications of implementing IRS after failure of pyrethroids



Costs estimated for 1 million households each with five people and 150 m^2 sprayable surface.
Operational costs: Planning and logistics; environmental compliance, including soak pit or evaporation tank construction; training; information, education and communications; warehousing; short-term labour; transport; medical costs; mop-up operations; post-spray meetings; monitoring and evaluation; shipping; spray equipment; and personal protective equipment.
Administrative costs: National labour; local office leases, utilities and maintenance; office equipment and supplies; office services; and management transport. Considered to be a yearly fixed cost (occurring once regardless of number of spray rounds).

Financial cost for geographical areas in which LLINs are the primary tool for vector control.

Although continued use of LLINs is recommended, even in areas of resistance, focal non-pyrethroid-based IRS might have to be introduced in addition to LLINs in areas where resistance is of particular concern, under the conditions described in Part 3.

What has been modelled?

The model compares the cost of an LLIN to the cost of a combination of LLINs and IRS rotations of organophosphates and carbamates.

Adding focal IRS in areas primarily covered by LLINs could multiply the cost per person protected by three to six times, and therefore should be highly targeted.

- *Short transmission season.* The model suggests that adding IRS rotations without pyrethroids to LLINs would increase the cost per person protected by approximately three times (from US$ 1.40 to US$ 5.00).
- *Long transmission season.* In areas with long malaria transmission seasons, the cost per person protected would increase by about six times (from US$ 1.40 to US$ 8.60).

This combination strategy is recommended for highly focal IRM, until nets with non-pyrethroid active ingredients or mixtures become available. The vector control costs at country level would therefore be affected to only a limited extent in most cases.

2.5.3 FINANCIAL COST OF MONITORING INSECTICIDE RESISTANCE

As discussed in section 2.2, all countries in which insecticide-based vector control is used should monitor insecticide resistance regularly for appropriate decision-making. At a minimum, they should:

- design a monitoring plan;
- build national capacity for monitoring;
- conduct routine susceptibility testing to identify resistance; and
- conduct testing to identify resistance mechanisms.

Although some countries already monitor resistance, implementing the recommendations of the GPIRM will probably entail additional costs. Regular entomological monitoring is also recommended by WHO, but this is beyond the scope of the GPIRM and is not covered.

Summary of costs for monitoring insecticide resistance. Table 2 indicates the possible total cost of monitoring insecticide resistance at country level. It assumes that the main recommendations of the GPIRM are followed and that insecticide resistance is monitored annually. For illustrative purposes, it was assumed that resistance mechanisms would be tested once a year at all sentinel sites in a country. In reality, most countries will not identify resistance at all sentinel sites, and the overall cost may be lower. If resistance is detected, however, more intense, reactive monitoring might be conducted. (See Annex 11 for more details on the cost of each category.)

Table 2: Indicative costs of monitoring insecticide resistance

Activity	No. of sentinel sites in country		
	10	**20**	**30**
Design monitoring plan	US$ 15 000	US$ 15 000	US$ 15 000
Capacity-building for basic field entomology and bioassays	US$ 33 000	US$ 33 000	US$ 33 000
Bioassys for susceptibility	US$ 50 000	US$ 100 000	US$ 150 000
Molecular and biochemical[a] testing for resistance mechanisms	US$ 18 700	US$ 36 400	US$ 54 100
Total cost to country	US$ 116 700	US$ 184 400	US$ 252 100
Cost per sentinel site	US$ 11 670	US$ 9 220	US$ 8 400

From the national malaria control programmes of Senegal and Zambia, the National Institute for Medical Research of the United Republic of Tanzania, and the Liverpool School of Tropical Medicine (United Kingdom). Some economies of scale in insecticide resistance testing are probable. As limited data are available, they are not taken into account in this analysis.

a Biochemical equipment assumed to be amortized after 5 years; training costs for biochemical testing are not included.

Monitoring insecticide resistance costs less than US$ 0.01 per person protected per year. The cost of monitoring insecticide resistance is a small fraction of that of vector control. For instance, if a country at risk with a population of 20 million people sets up one sentinel site per 1 million people protected with vector control, it would have 20 sentinel sites. If two people sleep under a net, the cost per person protected by an LLIN is about US$ 1.40 per year.[1] Monitoring insecticide resistance would cost less than US$ 0.01 per person protected, corresponding to less than 1% of the cost of an LLIN.

1 The cost per treated-net year of protection is assumed to be US$ 2.70 on the basis of a review of costs published by Roll Back Malaria (*43*).

2.5.4 OVERALL COST OF IMPLEMENTING THE GLOBAL PLAN FOR INSECTICIDE RESISTANCE MANAGEMENT IN MALARIA VECTORS

Table 3 shows the overall cost of implementing all the recommendations in the GPIRM. The calculations take into account the main costs incurred for each element of the strategy, which would be additional to those currently estimated for global malaria vector control. The overall cost is based on implementation of IRM strategies and building monitoring capacity in all malaria-endemic countries, as well as global and regional support costs for technical expertise and research.

The total costs amount to approximately US$ 200 million. This estimate is a 'fully loaded' annual cost at its peak, if all countries and partners were able to implement all GPIRM recommendations: on IRM, insecticide resistance monitoring, capacity building and global activities.

It should be noted that this 'peak cost' represents only a limited fraction of the global cost of vector control. The total implementation cost of GPIRM represents only 5% of the approximately US$ 3.9 billion needed for vector control in 2010, as estimated in the RBM Global Malaria Action Plan (*44*).

See Annex 11 for details of the assumptions used for deriving the figures in Table 3.

The actual cost will be lower than the total cost of US$ 200 million due to the combined effect of two factors; the phased implementation of recommendations, and the price decrease in alternative insecticides that could follow. There will be no 'shock effect' of the cost of situation analysis, improved monitoring, operational research, and capacity building, since the costs linked to these activities are very small. Hopefully, prices will decrease over time due to scaling up of IRM measures, as was the case for Artemisinin based Combination Therapies (ACTs).

Table 3: Overall cost of implementing the Global Plan for Insecticide Resistance Management in Malaria vectors

Cost elements	First year (US M$)	Subsequent years (US M$)
Pillar I: Implementation of insecticide resistance management strategies		
• Comprehensive situation analysis	10.0	0
• Implementation of insecticide resistance management strategies	144.0	144.0
Pillar II: Implementation of monitoring		
• Routine susceptibility testing	5.0	5.0
• General laboratory equipment and materials	3.5	3.5
• External molecular testing	1.2	1.2
• Building capacity for molecular testing	4.5	0.5
• National database	2.0	1.0
• Global database	1.5	1.5
Pillar III: New vector control tools		
• Acceleration of product development	5.5	5.5
Pillar IV: Fill knowledge gaps on insecticide resistance		
• Operational research on insecticide resistance	30.0	30.0
Pillar V: Enabling mechanisms		
• Functional national technical advisory committee	1.5	1.5
• Human resource capacity	7.5	7.5
• International experts and technical support to countries	3.0	3.0
• Coordination: meetings, advocacy, and resource mobilization	0.4	0.4
Total cost of implementing the GPIRM strategy	**219.6**	**204.6**

Obvious parallels can be drawn between insecticide and drug resistance. Combating antimalarial drug resistance involved pre-emptive development and use of artemisinin-based combination therapies. The transition to these drugs involved the adoption of innovative treatment policies at global and country levels and the rapid development and adoption of new combination products. There was fear of a massive increase in unit costs, with consequent supply and coverage problems.

Ultimately, the increase in price and the supply bottlenecks were not as large as had been predicted because of efficient procurement negotiations and economies of scale.[1] Hence, artemisinin-based combination therapies quickly became accepted as the standard of care and an essential step in preserving the susceptibility of *P. falciparum* to our most valuable anti-malarial drugs.

1 For example, Novartis has lowered the price of Coartem by 50% since 2001.

PART 3

TECHNICAL RECOMMENDATIONS FOR COUNTRIES

Introduction to the recommendations.

The following recommendations are initial working proposals for IRM strategies. They are valid as of May 2012 and will be revised as more evidence and research results become available.

Updated versions of these recommendations are available at http://www.who.int/malaria.

IRM strategies for specific countries should be planned in discussion with technical experts, either in-country or with external support. WHO is responsible for making policy recommendations and for giving advice on the implementation of malaria prevention and control activities by countries and their partners, following national policies.

In order to produce the recommendations outlined below, a number of different insecticide resistance scenarios were conceived. The interpretation of these, together with the design of appropriate responses, was used to develop strategies that are likely to be applicable to current conditions in different situations. In some cases, countries may request additional detailed advice that is more closely adapted to local situations. WHO, together with partners, will endeavour to provide such technical support and, whenever necessary, will convene experts to assist in this.

In most cases, the methods of resistance management that would, in the long run, be most appropriate and effective for a given scenario, will not be adopted immediately because the new insecticide products that would be necessary to do this are not yet available. In such situations, countries may be forced to use those methods that are available, regardless of their limitations. The recommendations that follow are specific to both of these situations - detailing both interim methods of IRM for immediate implementation, and preferred methods that can be implemented in the future once new tools become available.

Thresholds for susceptibility and resistance

WHO has recently updated the *Test procedures for monitoring susceptibility of mosquitoes to insecticides (42)*. Please refer to these guidelines for more details (referred to as the 'WHO test procedures' in the following sections). The document is available at http://www.who.int/malaria.

WHO defines susceptibility and resistance to insecticides on the basis of testing for the mortality rates of vectors exposed to a discriminating dose:

- *Susceptibility*: An observation of more than or equal to 98% mortality rate among vectors tested for resistance with WHO methods provides evidence of clear susceptibility.
- *Possible resistance*: An initial observation of less than 98% vector mortality in bioassays conducted with WHO methods indicates possible resistance. Once this observation has been made, further testing is required to confirm resistance. Additional tests should be conducted to determine whether the vector mortality rate is consistently lower than 98% and to understand the extent of resistance. The mosquito sample size should be extended; the number of bioassays increased and the geographical scope widened. On the basis of these additional tests, resistance will either be confirmed or not, and its geographical distribution will be clarified. Those additional tests have to be conducted soon after resistance is suspected.

Once resistance has been confirmed based on bioassays, the mechanisms of resistance should ideally be investigated by biochemical and molecular testing. The results of additional tests to understand the underlying mechanisms of resistance provides valuable information to further guide the choice of tools for IRM. Nevertheless, action should not be delayed in situations where such testing is not possible. Countries that are not in a position to conduct biochemical and molecular tests in the short term will have to make decisions on the basis of bio-assays only.

3.1 GEOGRAPHICAL AREAS WITH UNKNOWN LEVELS OF RESISTANCE

Where the current status of resistance is unknown, the first form of pre-emptive action is to conduct susceptibility tests, including identification of resistance mechanisms. All countries should do this, drawing on research institutes, WHO, and other partners for expertise and assistance as required.

3.2 GEOGRAPHICAL AREAS IN WHICH INDOOR RESIDUAL SPRAYING IS THE MAIN FORM OF VECTOR CONTROL

Pre-emptive action: rotations of insecticides available today, and mixtures or rotations including new active ingredients when they become available.

Today, in order to preclude the emergence of resistance, insecticides of different classes should be sprayed in rotation, ideally in an annual cycle. This is best practice and should be implemented wherever possible, even before resistance has been identified.

In the future, new active ingredients may provide additional resistance management opportunities (for example for use in rotations). The current pipeline for new active ingredients for IRS looks promising, and two or more of these products may be brought to market in the next 7–10 years (*44*, *45*).

Susceptibility to insecticides will define further action.

A pragmatic approach is proposed for the management of insecticide resistance with the tools currently available. The solutions depend on the transmission ecology of local malaria vectors, especially their susceptibility or resistance to the insecticides being used for IRS (Table 4).

Table 4. Recommendations for areas in which vectors are controlled primarily by indoor residual spraying (IRS)

Status	Scenarios and responses
Susceptibility	**Scenario:** no foci of possible resistance identified, according to WHO test procedures **Interpretation:** resistance is not an immediate threat, vector control is still effective. **Monitoring action:** • conduct frequent[a] monitoring of vector susceptibility through susceptibility tests to confirm that there is no resistance emerging **Vector control action:** • implement pre-emptive rotations, preferably on an annual basis**.** While full susceptibility is consistently confirmed, rotations can include the insecticide which is currently being used
Resistance	**Scenario:** resistance has been confirmed based on bioassays according to WHO test procedures, or genotypic data show rapid increase in resistance **Interpretation:** resistance is an immediate threat and action should be taken **Monitoring action:** • conduct frequent susceptibility tests in a range of locations to monitor any increase in resistance or return to full susceptibility • investigate resistance mechanisms using bio-chemical and molecular testing methods • check and if necessary reinforce epidemiological surveillance **Vector control action:** • in geographic areas with confirmed resistance, switch away from the current insecticide that is being used as quickly as practicable; the aim is that by promptly removing the selection pressure, the spread of resistance to the initial insecticide will be reduced or even reversed; in some cases, such reversal may allow for future reintroduction of the initial insecticide • use new insecticide in annual rotation

a At least once a year and preferably once every six months

Additional rationale and detailed recommendations.

What if rotations must be introduced in stages because of financial constraints?

Rotations should ideally be implemented pre-emptively in all settings in which IRS is used as a way to preserve susceptibility to current insecticides. In places where this policy is to be implemented in stages, areas of identified resistance are the first priority for introduction of rotations, as are areas in which the potential public health consequences of the loss of vector control are greatest.

Why is it important to implement rotations if the insecticide to which there is resistance is being changed?

To prevent early development of resistance to a new insecticide, it should be used in an annual rotations scheme with other insecticide classes. It may be possible to reintroduce the original insecticide into this rotations scheme later, if resistance has reversed. Susceptibility tests should be carried out routinely to identify any return to full vector susceptibility. If this kind of reversion is not seen, the rotations scheme should not include the original insecticide. Definition of resistance mechanisms using biochemical and genetic methods will help to refine options available for IRM.

3.3 GEOGRAPHICAL AREAS IN WHICH LLINS ARE THE MAIN FORM OF VECTOR CONTROL

Pre-emptive action: use non-pyrethroid LLINs when they become available.

As soon as they become available, nets with non-pyrethroid active ingredients should be used. Guidelines are needed for incorporating LLINs treated with non-pyrethroids into existing LLIN programmes.[1] The current pipeline indicates that non-pyrethroid and bi-treated LLINs may become available in the shorter term (the next 3–5 years) and LLINs with new active ingredients in the longer term (the next 7–10 years) (*44*, *45*). Research on novel tools and products is described in section 3.5.

In the meantime, until new products become available for vector control, programmes should continue to use pyrethroid-based LLINs and assess susceptibility status to define additional actions.

A pragmatic approach for managing insecticide resistance with the tools currently available is proposed. The solutions depend on the susceptibility status of major malaria vectors to pyrethroids in the target areas (see section 2.3 for an overview of research on new vector control tools).

An IRM strategy for areas in which LLINs are the main form of vector control should be aligned with the perceived level of threat from resistance, which depends on:

- the nature and strength of the resistance mechanism/s and the frequency of the mechanism/s in the vector population; and
- whether the number of confirmed malaria cases has increased. If countries do not have a surveillance system that can promptly detect an increase, this capacity must be established as a matter of urgency. Several potential resistance scenarios are summarized in Table 5, with recommendations for action.

It should be noted that combination strategies are not designed to make up for poor implementation of either intervention. When executed, both LLINs and IRS must be implemented well and fully.

1 For example, guidelines will address whether new active ingredients should be used in mixtures to delay as much as possible the spread of resistance to them, and whether it is feasible to deploy LLINs treated with pyrethroids and LLINs treated with non-pyrethroids in a mosaic in communities.

Table 5. Recommendations for areas in which vectors are controlled primarily by use of long-lasting insecticidal nets LLINs

Status	No increase in confirmed malaria cases	Increase in confirmed malaria cases
Susceptbility	**Scenario:** no foci of possible resistance identified, according to WHO test procedures [a] **Interpretation:** resistance is not an immediate threat; vector control is still effective **Monitoring action:** • conduct frequent [b] monitoring of vector mortality rates through susceptibility tests to determine that there is no resistance emerging **Vector control action:** • no change	**Scenario:** no reports of resistance but evidence of an increase in the number of malaria cases and no other clear cause **Interpretation:** insecticide resistance is not an immediate threat and is probably not the cause of the increase in the number of cases **Monitoring action:** • conduct frequent monitoring of vector mortality rates through susceptibility tests to confirm that there is no resistance emerging • monitor closely the quality and coverage of vector control interventions, which could be responsible for the increase in malaria cases **Vector control action:** • ensure system for timely replacement of worn-out nets and assure the quality and extent of LLIN coverage
***Kdr* resistance only**	**Scenario:** *kdr* resistance reported but no evidence of increase in malaria cases **Interpretation:** vector control working well despite *kdr-based* resistance **Monitoring action:** • conduct frequent and extensive susceptibility tests to monitor any increase and spread in resistance • check for metabolic resistance using bio-chemical and molecular testing methods • check and if necessary reinforce epidemiological surveillance **Vector control action:** • continue to promote the use of LLINs • ensure system for timely replacement of worn-out nets and assure the quality and extent of LLIN coverage	**Scenario:** resistance has been confirmed based on bioassays according to WHO test procedures, or genotypic data show rapid increase in resistance, with confirmation of *kdr* only; also evidence of an increase in the number of malaria cases and no other clear cause. **Interpretation:** resistance is an immediate threat and might already be contributing to the increase in malaria cases making it a serious and current public health problem **Monitoring action:** • conduct frequent and extensive susceptibility tests to monitor any increase in resistance • check whether metabolic resistance is present using bio-chemical and molecular testing methods **Vector control action:** • continue to promote the use of LLINs • introduce, in addition, focal IRS with a non-pyrethroid insecticide, preferably on annual rotations . Best practice is to do this in all areas of resistance, good practice is to do it at least in the areas of greatest concern [c]

<table>
<tr><th>Status</th><th>No increase in confirmed malaria cases</th><th>Increase in confirmed malaria cases</th></tr>
<tr><td>Metabolic resistance
(either with or without kdr also present in the same vector species)</td><td colspan="2">Scenario: resistance has been confirmed according to WHO test procedures and metabolic resistance is known to be present

Interpretation: resistance is an immediate threat ; if there is also evidence of an increase in malaria cases and no other clear causality, resistance could already be contributing to an increase in transmission making it a serious and current public health problem

Monitoring action:
• conduct frequent monitoring of vector mortality rates through susceptibility tests to monitor any increase in resistance
• monitor for any increase in operationally significant metabolic resistance
• check for the possible appearance or increase in the frequency of kdr genes
• check and if necessary reinforce epidemiological surveillance

Vector control action:
• continue to promote the use of LLINs
• introduce, in addition, focal IRS with a non-pyrethroid insecticide, preferably on annual rotations. Best practice is to do this in all areas of resistance; good practice is to do it at least in the areas of greatest concern</td></tr>
<tr><td>Resistance but unknown mechanism/s</td><td>Scenario: resistance has been confirmed according to WHO test procedures but mechanism/s have not been tested for or identified

Interpretation: resistance is an immediate threat and could at some point bring about an increase in malaria cases

Monitoring action:
• investigate resistance mechanisms[d]
• conduct frequent monitoring of vector mortality rates through susceptibility tests to monitor any increase in resistance
• check and if necessary reinforce epidemiological surveillance

Vector control action:
• continue to promote the use of LLINs
• introduce, in addition, focal IRS with a non-pyrethroid insecticide, preferably on annual rotations. Best practice is to do this in all areas of resistance; good practice is to do it at least in the areas of greatest concern
• Review and revise IRM strategy once resistance mechanism/s are known</td><td>Situation: resistance has been confirmed according to WHO test procedures but mechanism/s are unknown; also evidence of an increase in malaria cases and no other clear causality

Interpretation: resistance is an immediate threat and could already be contributing to the increase in malaria making it a serious and current public health problem

Monitoring action:
• investigate resistance mechanisms[d]
• conduct frequent monitoring of vector mortality rates through susceptibility tests to monitor any increase in resistance

Vector control action:
• continue to promote the use of LLINs
• introduce, in addition, focal IRS with a non-pyrethroid insecticide, preferably on annual rotations. Best practice is to do this in all areas of resistance; good practice is to do it at least in the areas of greatest concern
• Review and revise IRM strategy once resistance mechanism/s are known</td></tr>
</table>

a As pyrethroids are the only class currently used on LLINs, the recommendations address the resistance mechanisms that affect the pyrethroids: metabolic resistance and *kdr* resistance.
b At least once a year and preferably once every 6 months
c 'Areas of greatest concern' are defined in the following section *Additional rationale for recommendations.*
d Full characterization of a new resistance mechanism requires specialized research methods, but the critical basic information can be obtained without sophisticated equipment using synergists and careful bioassay methods. However, interpretation of synergist data is complex and expert advice is needed before concrete conclusions are drawn.

It should be noted that combination strategies are not designed to make up for poor implementation of either intervention. When executed, both LLINs and IRS need to be implemented well and fully.

Additional rationale for recommendations.

Why is a distinction made between kdr and metabolic resistance mechanisms for LLINs?

Given the magnitude, both operationally and financially, of adding IRS rotations in areas in which vector control is currently managed with LLINs, IRS should be implemented first and foremost where the threat of resistance is greatest. This is perceived by most experts to be when operationally significant metabolic resistance is present. This is because metabolic resistance is stronger than *kdr* resistance and because there is evidence that metabolic resistance is linked to control failure (for example in South Africa, see section 1.2.3 for details).[1]

Why should LLINs continue to be used in all cases?

Countries should continue to scale-up or maintain coverage with LLINs both because they act as a physical barrier and because the sub-lethal irritant effects of the pyrethroids may still contribute to malaria control. It is assumed that the irritant effect of pyrethroids persists, at least to some extent, even when there are resistant vectors in the *Anopheles* population. As continued use of LLINs is likely to contribute to selection pressure, resistance and any associated operational impact must be monitored closely. Thus, resistance must be tested at least once a year and preferably every 6 months. This recommendation may be revised when non-pyrethroid LLINs become available.

How should areas of resistance be chosen for the introduction of focal IRS with a non-pyrethroid insecticide?

Best practice is to introduce focal IRS with a non-pyrethroid active ingredient in all areas in which operationally significant metabolic resistance has been identified, and all areas in which there is *kdr* resistance and an increase in the number of malaria cases (with no other clear cause). It may be financially and logistically difficult to introduce IRS in all areas with reported resistance. However, it may be possible to identify the foci where the frequency of resistance is highest or where the threat of control failure is greatest. In such areas, it is essential to target those areas for IRS. In national malaria control programmes with limited entomological capacity, collaboration with research and academic institutions may help in identifying such resistance foci.

A newly identified focus of insecticide resistance may be localized, and it may therefore be possible to eliminate it. However, resistance can remain at low frequency for many years before it becomes detectable. As such, in some places it is likely to have already spread across a wide geographical area before it is identified. In this case, spraying should focus on those areas in which the epidemiological risk of malaria is greatest. If budget constraints prevent countries from adding IRS in all the areas where there is resistance, and in the event of a sustained outbreak of malaria, the final option (less preferable), is to prepare an emergency response plan with IRS.[2]

Will these recommendations entail a general switch from LLINs to IRS?

It is incorrect to assume that resistance to pyrethroids will require a general change to IRS from LLINs. Both LLINs and IRS are expected to continue to be core elements of vector control in the short, medium and longer term. A general switch would probably be counter-productive. Firstly some forms of pyrethroid resistance may have no impact on the effectiveness of LLINs. Secondly, annual spraying is still not feasible in many places, for logistical reasons, and LLINs are the only practical form of effective vector control. Hence, the goal of universal coverage cannot be achieved and sustained with IRS alone but also requires the use of LLINs. Thirdly, as IRS is a more expensive form of vector control, switching solely to IRS to control malaria would substantially increase costs and have implications for the level of coverage and the proportion of the population protected. The cost of the insecticide represents a relatively large proportion of the total cost of IRS, but only a small fraction of the cost of LLINs. Therefore, a switch to mixture products, with new and more expensive active ingredients, can be expected to result in a larger increase in the cost of IRS than with LLINs.

1 Some experts consider that *kdr* does weaken the impact of pyrethroid-based vector control and would argue for less distinction between *kdr* and metabolic resistance in determining IRM strategies. This distinction may be revised as new evidence becomes available.

2 It should be noted, however, that an emergency response plan is likely to be effective only if there is adequate surveillance to predict or spot the onset of an outbreak very early.

3.4 GEOGRAPHICAL AREAS IN WHICH LLINS AND IRS ARE ALREADY USED IN COMBINATION

Pre-emptive action: Stop using pyrethroids for IRS and continue to use nets.

Before resistance has been confirmed, the LLIN strategy should not be changed, but two pre-emptive actions are needed. Firstly, in areas of high coverage with LLINs, pyrethroids should not be used for IRS, as this will contribute to selection pressure. IRS should therefore be done with alternative, non-pyrethroid insecticides. The alternative insecticides should preferably be used in a rotations scheme to avoid the development of resistance to any one of them. The key, however, is to use a non-pyrethroid[1]. Secondly, as continuing use of LLINs is likely to contribute significantly to selection pressure, countries should ensure frequent entomological monitoring, at least once a year and preferably every 6 months.

Where there is full susceptibility of vectors to pyrethroids.

As described in the section on pre-emptive action with combinations, even when the local vectors are fully susceptible to pyrethroids, it is important to stop the use of pyrethroids in areas of high coverage with LLINs and to continue to monitor for resistance, at least once a year and preferably every 6 months. In addition, to avoid the emergence of resistance, pre-emptive action should be taken by implementing IRS rotations (without pyrethroids[1]), preferably annually.

Where there is confirmed resistance to pyrethroids.

Continue with LLINs, including scaling-up, as an insecticide-treated bednet is always better than no protection, even in an area with insecticide resistance. Use of LLINs is, however, likely to contribute significantly to selection pressure; therefore, it is essential to monitor whether the effectiveness of LLINs is reduced. As a minimum this means monitoring insecticide resistance at least once a year and preferably every 6 months.

Make sure that all areas have changed from pyrethroid-based IRS to rotations without pyrethroids.

1 There might be very specific circumstances in which alternative insecticides are not available, e.g. in some parts of West Africa where there is confirmed evidence of AChE resistance. If such circumstances are evidenced, endemic countries and partners are invited to seek WHO's assistance to analyze the situation and define the most appropriate IRM strategy.

3.5 CHOOSING ALTERNATIVE INSECTICIDES

When choosing alternative insecticides, it is important to consider factors related to cross resistance, efficacy and costs. These factors should be taken into account: when introducing alternative insecticides in an IRS rotation (which may or may not include the current insecticide, depending on the resistance status); when introducing non-pyrethroid based IRS in areas with high coverage with LLINs; or when changing from an insecticide to which resistance has developed.

Firstly, the possibility of cross-resistance to other insecticides should be considered. Information about which insecticides may confer cross-resistance can be obtained either by identifying the resistance mechanisms and examining the known cross-resistance patterns or by conducting susceptibility tests for each of the other insecticides.

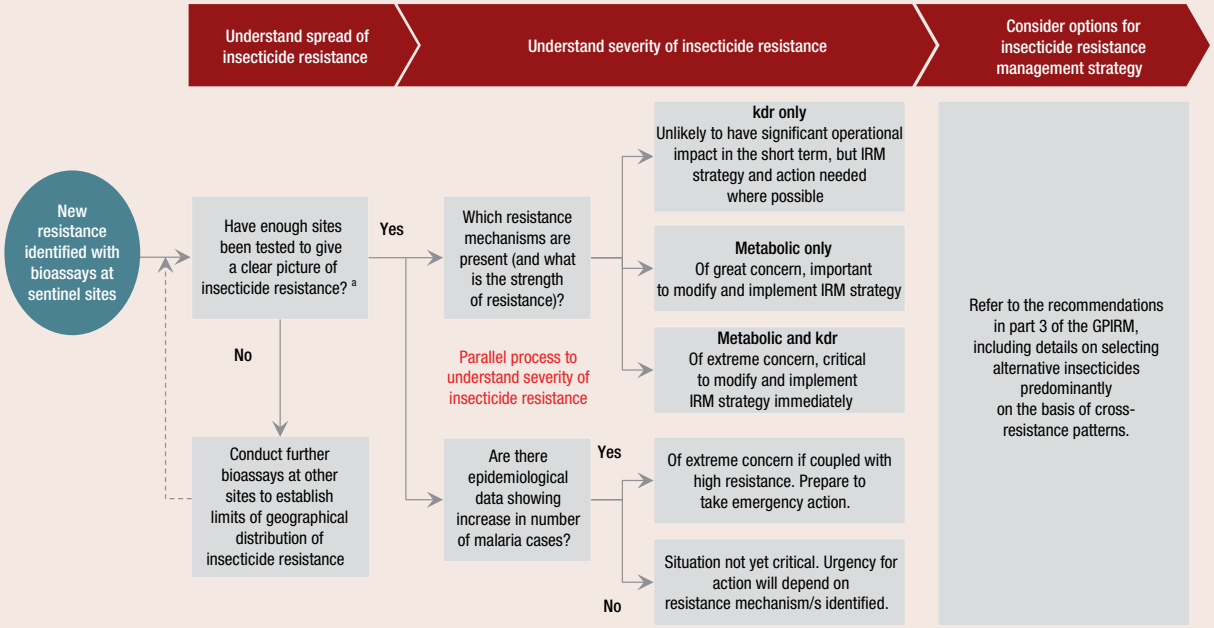
Secondly, testing should be conducted to determine the insecticides to which there is currently resistance and avoid using these insecticides in IRM if necessary. In the event of resistance to all four classes of insecticide, vector control programmes should rotate annually through as many classes as possible and should start rotations with the insecticides to which there is the lowest frequency of resistance. In an area in which LLINs are also used, pyrethroids should be avoided.

Thirdly, the country's policy on DDT should be confirmed. If DDT is registered and its use permitted, and where vectors are susceptible to it, countries should, in line with WHO guidelines, consider it as an alternative insecticide for IRS (*10*). Where DDT is not registered locally, ways of speeding up its registration should be considered. Many countries may find themselves with a very short list of available insecticides for IRS rotations, and DDT could make a significant difference, for example, allowing a three-class rotation (having removed the insecticide to which there is resistance) rather than only a two-class rotation. As DDT is less expensive than organophosphates and carbamates, the cost implications are potentially significant.

The duration of the efficacy of each insecticide used in a rotation should also be considered, together with the length of the transmission season, as this will have implications for the number of spray rounds required, and will therefore have a potential effect on total cost.

The three factors that should be assessed when a new focus of insecticide resistance is identified are illustrated in Figure 30.

Figure 30: Three factors to be assessed when a new focus of insecticide resistance is identified



a 'Enough' sites tested means at least enough sentinel sites to cover a minimum of 200 000 houses or 500 000 nets. Resistance ratios (strength of resistance) should be investigated with WHO resistance test kits or CDC bottle bioassays.

Other forms of vector control.

IRS and LLINs are the core malaria vector control techniques, because they are not only more effective than other forms of control against mosquitoes that preferentially enter houses for biting and resting, but they also consist of a uniform set of methods that do not require significant adaptation to local situations. Other methods of malaria vector control have specific roles and are effective only in selected settings and circumstances. Within these settings, such methods require local entomological studies and careful adaptation to suit local conditions. Implementation of such interventions in an inappropriate setting may lead to wastage of public health resources, and could lead to a risk of malaria control failure. See Annex 2 for information on larviciding and environmental management.

If resistance to all insecticide classes is identified in a given setting, and particularly if resistance is resulting in control failure, the appropriateness of other forms of vector control should be considered. In the right circumstances, they could provide an additional, urgently needed, degree of vector protection.

Space sprays, are not currently recommended because of their limited effect in malaria control.

PART 4

NEAR-TERM ACTION PLAN

4.1 ROLE OF EACH STAKEHOLDER GROUP

4.1.1 INSECTICIDE RESISTANCE MANAGEMENT IS A SHARED RESPONSIBILITY FOR ALL RELEVANT STAKEHOLDERS

Figure 31: Overview of the main roles and responsibilities of each stakeholder group

	Global norms and guidelines	Designing IRM strategies	Implementation	Evaluating IRM strategy	Monitoring	Coordination of action / info	IR research	R&D	Resource mobilization	Advocacy
NMCPs and other VBD programmes	✓	✓	✓	✓	✓	✓	✓		✓	✓
Senior government officials			✓			✓			✓	✓
Other health programmes and agricultural sector					✓	✓	✓			
Implementation agencies / NGOs		✓	✓	✓	✓	✓			✓	✓
WHO GMP	✓	✓	✓	✓	✓	✓	✓		✓	✓
WHO regional and country offices	✓	✓	✓	✓	✓	✓			✓	✓
Multilateral agencies		✓	✓						✓	✓
Funding agencies and bilateral donors					✓		✓	✓	✓	✓
WHOPES	✓			✓			✓	✓	✓	✓
Research Institutes and academia		✓		✓	✓		✓			✓
Manufacturers of VC products / PDPs				✓				✓	✓	✓

✓ Primary role ✓ Secondary role: support

Every stakeholder group in the community must fulfil its responsibilities in managing resistance of malaria vectors to insecticides, as outlined in the GPIRM. The roles listed in Figure 31 are described in more detail on the following pages and will be refined over time. The description may not be exhaustive, and some stakeholder groups might have additional roles.

While this section addresses the role of each stakeholder group, section 4.2 describes concrete, immediate steps to be taken in the community to support IRM.

Roles of national malaria control programmes.

- Design and implement appropriate IRM strategies, in line with policy and guidelines set by WHO (and seek support as necessary).
- Increase monitoring in order to understand the current situation, and implement routine monitoring of insecticide resistance.
- If required, seek help from research and academic institutions to conduct such monitoring activities.
- Assess the effect of IRM strategies on: slowing down or reducing the frequency of insecticide resistance; decreasing malaria transmission (if implemented as a result of control failure); and entomological and epidemiological effectiveness of vector control.
- Participate in coordination at regional level to ensure sharing of data and best practices.
- Coordinate IRM strategy with other relevant sectors, including agriculture, environment, and finance, as well as with municipalities and local governments.
- Work with local academic and research institutes to ensure that relevant research is conducted in-country (e.g. on links to control failure) and data are shared.
- Identify and mobilize human and financial resources for monitoring insecticide resistance and IRM plans.
- Consider whether current budgets could be reallocated to provide funds for monitoring insecticide resistance and management activities.
- Engage high level government support, particularly from ministries of health, finance and agriculture, by raising the profile of insecticide resistance.
- Provide feedback, where relevant, to help WHO to refine policies on vector control in general and monitoring and management of insecticide resistance in particular.

Role of senior government officials.

- Make funds available for monitoring insecticide resistance and IRM strategies.
- Encourage neighbouring governments and donors that are reluctant to take the threat of insecticide resistance seriously.

Role of the agriculture sector.

- Try to use classes of insecticides that are not available for public health use.
- Conduct research on insecticide resistance in agriculture, and share the results with the malaria control community.
- Share information on insecticide resistance with vector control advisors, national malaria control programmes and, when necessary, prepare an intersectoral IRM strategy.

Role of implementation partners and nongovernmental organizations.

- Where appropriate, support national malaria control programmes in the design and implementation of IRM strategies, in line with policy and guidelines set by WHO.
- Support national malaria control programmes in monitoring insecticide resistance, and ensure that monitoring is conducted as a routine component of every malaria vector control programme.
- With national malaria control programmes and local research institutions, assess the impact of IRM strategies, particularly: on slowing down or reducing the frequency of insecticide resistance; on decreasing malaria transmission; and on the entomological and epidemiological effectiveness of vector control.
- Coordinate with and provide technical assistance to national malaria control programmes, and make sure that information is shared with them.
- Identify and mobilize human and financial resources for monitoring insecticide resistance and for IRM strategies.
- Advocate for the inclusion of insecticide resistance as a priority in global malaria control and resource mobilization.

Role of the WHO Global Malaria Programme.

- Refine and update global policies and guidelines for monitoring and managing insecticide resistance on the basis of new evidence and information.
- Provide leadership, oversight and coordination of activities triggered by the GPIRM. This includes increasing awareness about the urgency of the threat, and advocating for increased funding for IRM strategies and research.
- Coordinate support for countries in the design and implementation of IRM strategies; in particular, convene international experts on insecticide resistance.

- Convene experts to review new science on insecticide resistance, including evidence on subregional and regional spread of resistance, on resistance mechanisms, on the impact of resistance on malaria control and on IRM methods. These evidence reviews will be the basis for policy refinement and revision.
- Coordinate support for countries in building capacity and training staff to collect data for monitoring insecticide resistance – including their analysis and interpretation for global policy and direction.
- Consult with countries, Regional Offices and partners to identify a reputable institution to host a global database, to be overseen by WHO on behalf of member states; ensure the flow of data on insecticide resistance from countries to the hosting institution.
- Advocate for sufficient capacity at global, regional and country levels of WHO to support countries in implementing the recommendations contained in the GPIRM.

Role of WHO regional and country offices.

- Provide regular opportunities for sharing information on insecticide resistance and best practices at regional level, between countries and across public health and other relevant sectors (e.g. agriculture).
- Advocate for inclusion of insecticide resistance priorities in malaria control and research agendas at country level.
- Support national malaria control programmes in increasing awareness, and obtain support at national and regional levels; advocate for increased funding for IRM strategies and research.
- Promote intersectoral interaction and coordination for the implementation of IRM at country level.
- Coordinate and support countries in the design and implementation of monitoring plans for IRM.
- Coordinate support for countries in building capacity and training staff to collect data (susceptibility tests and advanced testing methods).
- Advocate for sufficient capacity at WHO regional and country offices to support countries in their IRM efforts.

Role of other multilateral organizations (depending on their focus).

- Advocate for inclusion of insecticide resistance priorities in global malaria control and research agendas.
- Support national malaria control programmes in increasing awareness, and obtain support at national and regional levels.
- Advocate for increased funding for IRM strategies and research.
- Commit funding for IRM and encourage other multilateral organizations and funding agencies to do the same, if appropriate.
- Coordinate with WHO to offer technical support to countries for the design and implementation of IRM strategies.

Role of funding agencies and bilateral donors.

- Encourage the establishment of insecticide resistance monitoring for all vector control programme grants, in coordination with WHO.
- Support countries in meeting the conditions of grants.
- Make resources available for the academic research (operational and laboratory research) required to improve understanding of insecticide resistance and effective IRM strategies.
- Invest in the development of new products and vector control tools.
- Commit funding to support the financial costs of IRM strategies and capacity-building for monitoring, in coordination with WHO.

Role of WHOPES.

- Prepare guidelines for safety and efficacy assessment of new public health pesticides.
- Conduct independent assessment of new vector control pesticides, through its networks of collaborating centres.
- Develop specifications for quality control and international trade of public health pesticides.
- Support Member States in life-cycle management of public health pesticides.
- Monitor and publish information on use of pesticides for vector-borne disease control.
- Increase WHOPES capacity at global level and in collaborating centres to enable timely response to the growing number of new vector control products in the development pipeline.

Role of research and academic institutions.

- When needed, support national malaria control programmes in interpreting data and making decisions on an IRM strategy.
- With the national malaria control programmes, conduct trials and research to assess the effectiveness of IRM strategies for both maintaining effective vector control and reducing insecticide resistance.
- When needed, support national malaria control programmes in collecting data on and testing for insecticide resistance (particularly biochemical and molecular testing).
- Seek funding to conduct research on identified priorities and undertake this research together with national malaria control programmes.

Role of manufacturers of vector control products.

- Invest in development and in bringing to market new products and vector control tools to support IRM.
- Work with partners to find ways to reduce the cost of insecticides and other vector control products to make IRM strategies more affordable.

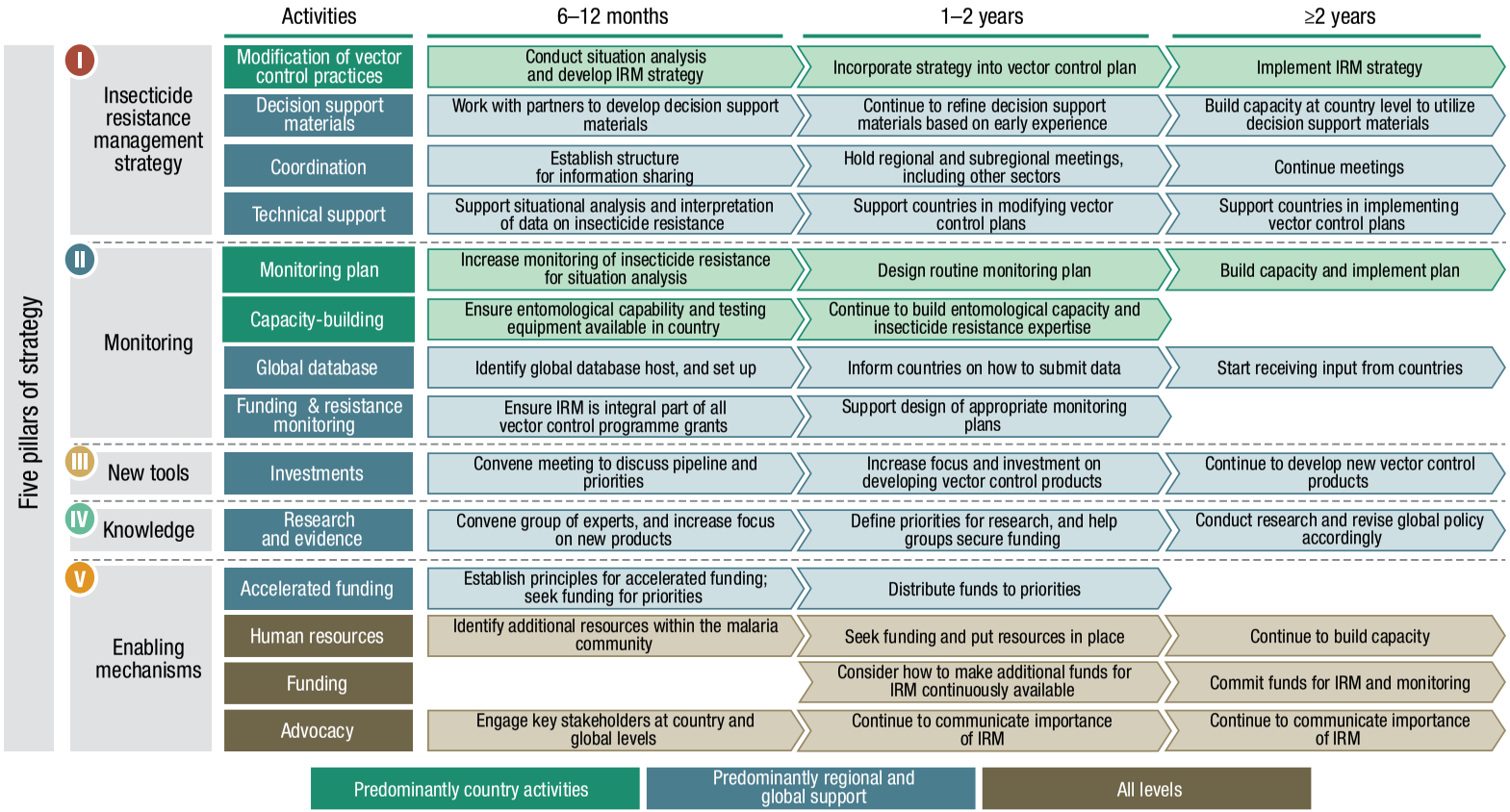
Given that most of these constituencies are part of the RBM Partnership, RBM has a critical role in implementing the GPIRM, especially with regard to advocacy, resource mobilization, and harmonization of partner efforts.

4.2 ACTION PLAN

A near-term action plan has been prepared to clarify priorities, particularly for the next 12 months. These activities are important prerequisites for proper implementation of the recommendations of the GPIRM. The activities are aligned with the five pillars of the strategy (see section 2.1). The timelines for each activity will serve as indicators to monitor progress in implementation of the recommendations.

In Figure 32 and in the rest of this section, three colours are used: activities in green should be implemented in malaria-endemic countries, usually by the national malaria control programme; activities in blue represent regional or global activities to support countries; and activities in brown are to be implemented at all levels: country, region and global.

Figure 32: What should we do over the next 12 months and beyond?
Overview of the key activities required to implement GPIRM in the near future



4.2.1 PILLAR I: INSECTICIDE RESISTANCE MANAGEMENT STRATEGIES

Within 6–12 months.

Modification of vector control practices

- **National malaria control programmes** should consolidate recent data on insecticide resistance (less than 12 months old), conduct additional susceptibility tests and, where insecticide resistance has been detected, identify the mechanisms (see section 2.2).
- **National malaria control programmes** should compile existing information on other factors in order to put resistance data in a broader context (see section 2.2).
- **National malaria control programmes** should then analyse the data and prepare appropriate IRM strategies, with the support of partners as detailed below.
- **National malaria control programmes** may have to seek external technical expertise and should contact WHO country offices to coordinate support from regional and global level.

Decision support materials

- **WHO will work with partners** to develop decision support materials for interpreting data on insecticide resistance.

Coordination among endemic countries and between partners

- **Networks for regional coordination (national malaria control programmes, multilateral organizations, implementing agencies, local nongovernmental organizations)** should devise a formal process for sharing information and coordinating strategies for national malaria control programmes, other implementing agencies (including nongovernmental organizations), the public health and agriculture sectors (e.g. in quarterly meetings).

Technical support to countries

- **Experts in insecticide resistance** should support countries in interpreting data on insecticide resistance. WHO, at country, regional, and global levels can provide this technical support and coordinate additional support from relevant malaria control partners.

Within 1–2 years.

Modification of vector control practices

- **National malaria control programmes** should review and, when relevant, modify all components of their vector control plan to incorporate an IRM strategy, with the support of external technical experts, if needed.
- **National malaria control programmes** should pursue procurement options for different insecticides and other vector control tools, in line with WHO guidelines and recommendations.

Decision support materials

- **Continue to refine the decision support materials** based on early experience.

Coordination among endemic countries and between partners

- **Regional and country partners** (in both public health and agriculture sectors) should be convened to share information on the insecticide resistance situation and IRM strategies.

Technical support to countries

- **Partners with experience in vector control planning** should support overall revision of the IRM plan and the subsequent budget.
- **Representatives of government ministries** should support national malaria control programmes with regulatory procedures allowing implementation of IRM strategies.

2 years and beyond.

Modification of vector control practices

- **National malaria control programmes** should implement their revised or reoriented vector control plans, taking into account insecticide resistance. This will require additional training and capacity building.

Decision support materials

- **WHO and partners** should build capacity at country level to utilize decision support materials.

Coordination among endemic countries and between partners

- **Regional coordination** should continue between neighbouring countries, including other sectors such as agriculture.

Technical support to countries

- **WHO regional and country offices, together with nongovernmental organizations and implementing agencies** should support national malaria control programmes in implementing reoriented vector control plans, for example by offering advice, expertise and resources, as needed.

4.2.2 PILLAR II. MONITORING ACTIVITIES

Within 6–12 months.

Monitoring plan

- **National malaria control programmes** should consolidate all existing data on insecticide resistance, and conduct additional testing if the data are more than 12 months old, to form the basis for a situation analysis of insecticide resistance in the country (see Pillar I).

Capacity-building

- **National malaria control programmes** should identify the human and infrastructural capacity required for monitoring and investigate ways to build the capacity.
- **Regional initiatives** should continue to develop monitoring capacity.
- **Implementing agencies and donors** should continue to implement and fund capacity-building for monitoring.

Global database

- **The WHO Global Malaria Programme** should consult with countries, Regional Offices and partners to identify a reputable institution to host the database, to be overseen by WHO on behalf of Member States.
- **The WHO Global Malaria Programme** should ensure the flow of data on insecticide resistance from countries to the institution hosting the global database.
- **The host organization** should set up the database and work with WHO to design an input template for countries. WHO would manage data requests from partners in consultation with countries.

Funding and IR monitoring

- **Donor agencies** should ensure that insecticide resistance monitoring is an integral part of all vector control programme grants.

Within 1–2 years.

Monitoring plan

- **National malaria control programmes** should, after conducting an initial situation analysis, prepare a plan for routine monitoring of insecticide resistance (see section 2.2).
- **National malaria control programmes** should raise funds (by mobilizing national and external resources) as required to build monitoring capacity and procure the necessary equipment.

Capacity-building

- **National malaria control programmes** should continue to build expertise in entomology and insecticide resistance; partnerships should be formed with local and regional research institutes.

Global database

- **The WHO Global Malaria Programme**, through the WHO Regional Offices, should contact national malaria control programmes, implementing agencies and research institutes to explain the data that are needed and how they are intended to be used.

Funding and IR monitoring

- **Donor agencies and multilateral organizations** should support countries in preparing appropriate monitoring plans for the implementation of large vector control grants.

2 years and beyond.

Monitoring plan

- **National malaria control programmes** should implement routine monitoring plans.

Global database

- **Malaria-endemic countries** should submit data on insecticide resistance for inclusion in the database.
- **WHO, at global, regional, and country level** should conduct further discussions with countries and with research and academic institutions as required to encourage submission of data.

4.2.3 PILLAR III. NEW TOOLS

Within 6–12 months.

Investment

- **Partners in innovative vector control** should continue to meet to discuss the current pipeline and urgent needs, with a view to increasing the focus on products with IRM properties.

Within 1–2 years and 2 years and beyond.

Investment

- **Partners in innovative vector control** should increase their focus on new products for IRM.

4.2.4 PILLAR IV. KNOWLEDGE

Within 6–12 months.

Research and evidence

- **The WHO Global Malaria Programme** should convene a group of experts focusing on knowledge needs in insecticide resistance, after consultation with the Malaria Policy Advisory Committee.
- **Partners from research institutes and academia with national malaria control programmes** should continue current trials and studies on insecticide resistance.

Within 1–2 years.

Research and evidence

- **The experts** should finalize the research agenda and communicate the highest priorities to the malaria community.
- **Partners in research institutes and academia** should apply to donors, with support from experts, to secure funding for the research priorities.

2 years and beyond.

Research and evidence

- **Partners in research and academic institutions with national malaria control programmes** should initiate additional high-priority research.
- **The experts** should review new evidence (in coordination with the global database and national malaria control programmes) and prepare an annual report on insecticide resistance.
- **The experts** should consider whether global policies should be revised in the light of new evidence.

4.2.5 PILLAR V. MECHANISMS

Within 6–12 months.

Accelerated funding

- **A group of donors, multilateral organizations and other relevant partners** (e.g. from the private sector) should convene to investigate the possibility of accelerating funding to allow urgent action in countries in which the situation of insecticide resistance is critical. For instance, the creation of a 'catalytic fund' has been proposed to initiate monitoring or implementation of IRM strategies in defined high-priority geographical areas.
- **This group** should define the principles and mechanisms for such 'accelerated funding', identify priorities and seek funding commitments.

Human resources

- **Malaria-endemic countries, implementing agencies and other partners** should identify the human resources needed to implement the recommendations of the GPIRM.
- **WHO at global, regional and country levels** should identify the technical capacity needed for the design and implementation of plans for monitoring and managing insecticide resistance.
- **WHOPES** should identify additional capacity at global level and collaborating centres to respond to the growing number of IRM products in the pipeline.

Advocacy

- **WHO** should provide leadership, oversight and coordination of the GPIRM, including advocacy to increase awareness of the urgency of the threat of insecticide resistance and funding for implementation of IRM strategies. The World Health Assembly and WHO regional committee meetings should be used to solicit support from Member States and partners.
- **National malaria control programmes** should seek government support, particularly from ministries of health and agriculture, by raising the profile of insecticide resistance.
- **Government officials** should encourage other governments and donors that appear reluctant to react seriously to the threat of insecticide resistance.
- **Stakeholders in the Roll Back Malaria Partnership and specialists in advocacy and communication** should take opportunities to communicate the importance of insecticide resistance, advocate for IRM and raise appropriate funds.

Within 1–2 years.

Accelerated funding

- **Accelerated funding, when identified,** should be allocated to areas with high insecticide resistance.

Human resources

- **Endemic countries, implementing agencies, other partners, the WHO Global Malaria Programme, WHOPES and WHO regional offices** should seek funding where necessary for building additional entomological capacity and ensure that resources are allocated as soon as possible after they have been received.
- **WHO** should continue to identify and build capacity.

Funding

- **National malaria control programmes** should review options for funding IRM strategies and monitoring, including grant proposals, requests to national governments and reallocation of their current vector control budgets when appropriate.
- **Donor agencies** should discuss internally and with the malaria community how to commit sufficient funds to malaria vector control to meet the increased costs associated with insecticide resistance.
- **Fund-raising entities** should add IRM to their list of priorities.

Advocacy

- **All stakeholders** should continue to communicate the importance of insecticide resistance and use the GPIRM to advocate for political commitment and for resource mobilization.
- **WHO** should make sure that insecticide resistance is an integral part of reports on malaria.

2 years and beyond.

Human resources

- **Endemic countries, implementing agencies, other partners, the WHO Global Malaria Programme, WHOPES and WHO regional offices** should continue to build capacity.

Funding

- **Donor agencies and governments** should commit funding to allow additional countries to implement IRM strategies and monitoring plans.

Advocacy

- **All stakeholders in the Roll Back Malaria Partnership** should continue to communicate the importance of insecticide resistance.
- **WHO** should coordinate with other partners to ensure that insecticide resistance is an integral part of reports on malaria control.

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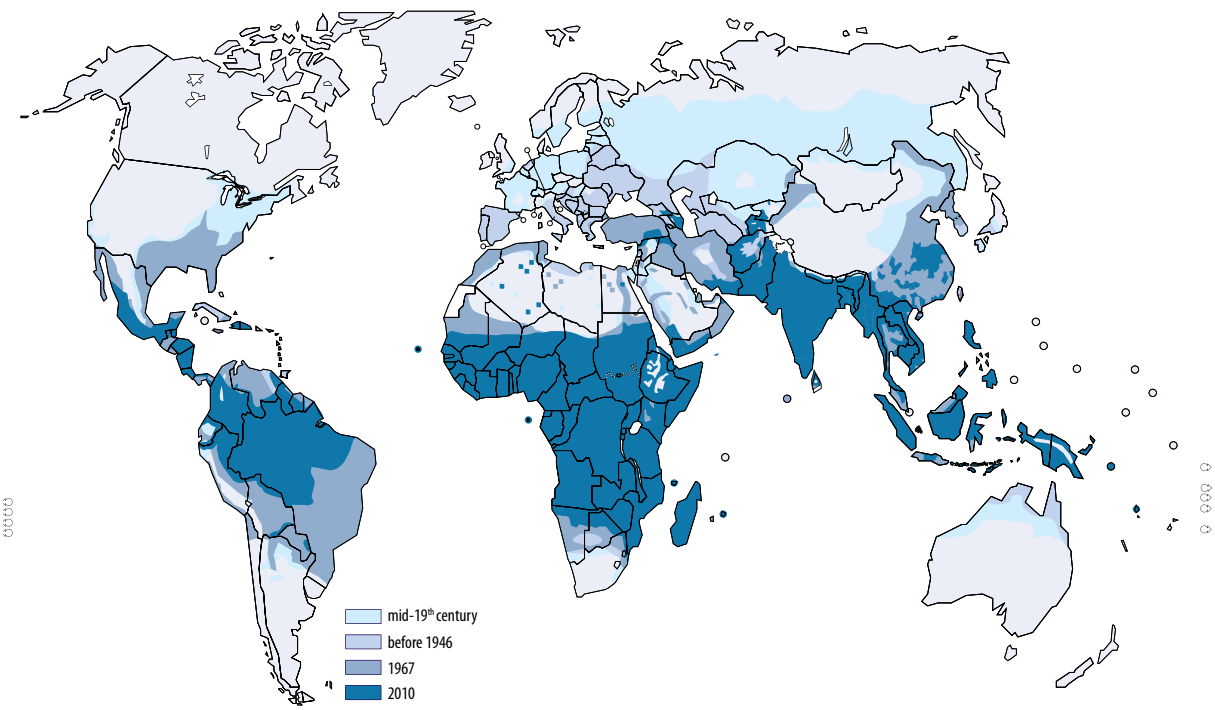
ANNEX 1 PAST USE OF MALARIA VECTOR CONTROL TOOLS

In the mid-nineteenth century, malaria was endemic in most countries and territories of the world, affecting about 90% of the world's population and stretching as far north as the Arctic Circle (*1*). Strategies for malaria vector control, namely environmental management and larviciding, were initiated at the beginning of the twentieth century. Since widespread introduction of indoor residual spraying (IRS) with dichlorodiphenyltrichloroethane (DDT) in the 1950s, vector control has played a major role in malaria control. Vector control interventions are highly effective, and scaling-up of interventions has been associated with a reduction of malaria-related deaths (Figure A1.1).

Figure A1.1: World distribution of malaria, mid-ninetieth century to 2010: areas at risk for malaria have diminished dramatically



From references (*2*) and (*3*)
The map reflects data and boundaries as of 2010 or before and should not be understood to reflect current data and boundaries.

First steps in malaria vector control.

Malaria transmission was first linked to mosquito vectors in the late 1890s.[1] Subsequently, the theory and practice of malaria control were developed, involving general and selective removal of specific vector populations in line with the concept of 'mosquito species sanitation' (*5*). The basis of this concept is that *Anopheles*, obligatory vectors for malaria, have species-specific breeding sites; when these sites are sanitized, malaria is deprived of its ecological preconditions (*6*). On the basis of the species sanitation theory, malaria vector control was introduced, together with the use of quinine for populations at risk. Vector control relies on the principle that the prevention of malaria transmission saves lives and reduces spending on antimalarial drugs and treatment as well as the societal costs of illness and lost productivity. The early vector control measures were source reduction (i.e. eliminating breeding sites), water management, environmental sanitation, larviciding and individual protective measures. These interventions succeeded in eliminating malaria from the extreme margins of its distribution, in particular between the first and second world wars (*7*). These types of vector control were used until the mid-twentieth century, but usually on a small scale because of limitations of the methods and their use, which was often restricted to affluent areas.

Vector control became a founding pillar of the Global Malaria Eradication Programme.

At the beginning of the twentieth century, several attempts were made to use IRS with the insecticide pyrethrin to control malaria vectors;[2] however, the method required weekly sprayings to preserve the effectiveness of the insecticide and was therefore costly and labour-intensive. In 1939, the insecticidal properties of DDT were discovered, and DDT was quickly perceived as superior to the existing insecticides, given its long residual activity of 6–12 months and its low cost (*4*). As a result, IRS with DDT was adopted on a global scale from the 1950s, although the level of implementation varied among regions (*8*).

The efficacy of DDT in reducing malaria-related mortality was seen almost immediately, and IRS was embraced by the international community as a remarkably efficient tool for combating malaria (*7*). To explain the theoretical background of the success of IRS, George MacDonald translated the empirical effectiveness of IRS into theory through mathematical models (*9*), further increasing the acceptance of, and advocacy for, IRS.

The success of DDT (*4*) led to the launch of the global malaria eradication campaign by the World Health Assembly in 1955 (*8*). This campaign accelerated efforts for malaria eradication in all countries except those in sub-Saharan Africa and Madagascar, which were in the pre-eradication phase. This area had been included in the objective of full eradication during planning of the eradication programme, but because of the high transmission levels in the region, coupled with logistic and administrative challenges to implementing a large-scale elimination programme (*8*), this objective was changed to 'malaria control' until suitable, economically feasible methods became available for complete eradication of the disease (*7*).

The eradication campaign accelerated use of IRS vector control operations in the following decades and led to elimination of malaria in many countries. In all, 37 of the 143 countries that were endemic in 1950 were freed from malaria by 1978; 27 of these were in Europe and the Americas. In many other countries, major gains were made in decreasing the burdens of disease and death (see Figure A1.1).

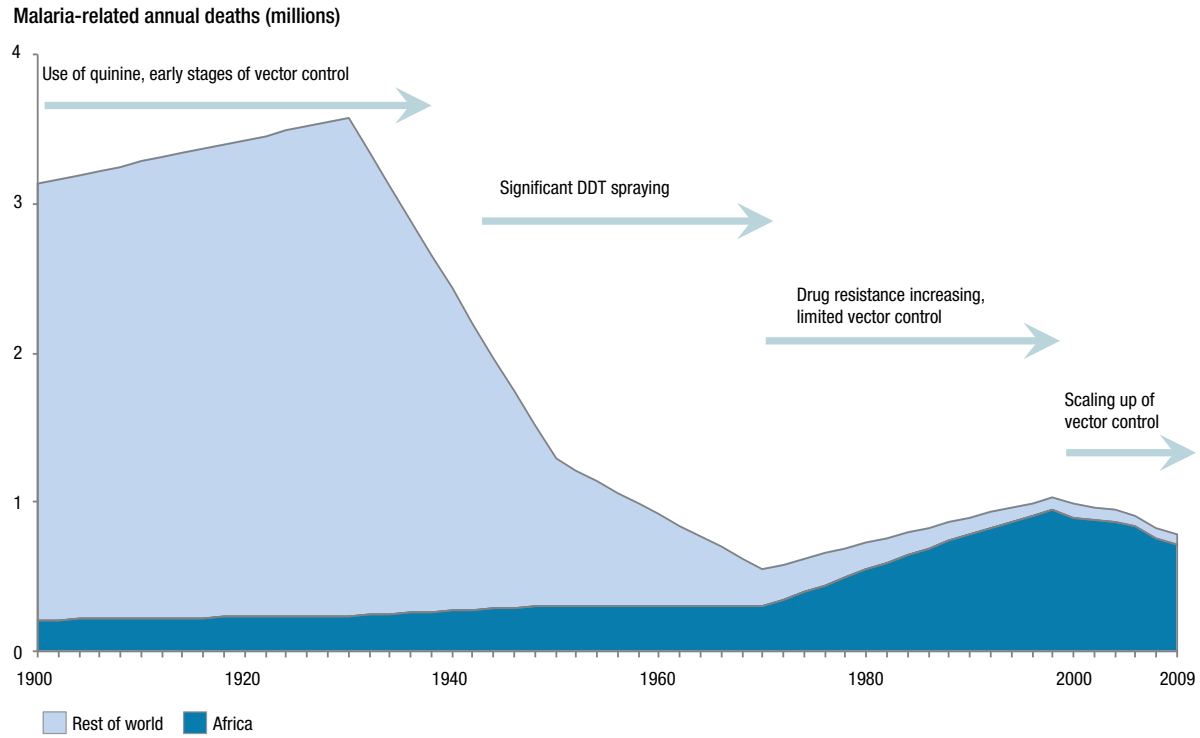
Disillusionment and decreased funding for malaria prevention.

In the 1970s, decreasing global commitment and resource allocation brought the eradication efforts of the previous decades to a halt. The causes of this situation included reports of limited progress in controlling malaria (or even resurgence of the disease), rising political and public concern about the safety of DDT, growing evidence of vector resistance to DDT, and parasite resistance to antimalarial drugs. Concern was also raised about whether malaria control should continue to be conducted as vertical campaigns or, instead, be integrated into national health systems. In 1978, WHO reoriented its policy from 'eradication and elimination of malaria' to 'control of malaria' (*10*). Although global policy changed from eradication to control, the guidelines were limited, and many malaria programmes that had been set up as 'one-off' eradication campaigns were difficult to integrate into national health systems (*11*). In this context, malaria-related deaths in sub-Saharan Africa tripled during the ensuing two decades, although the cumulative number of deaths elsewhere continued to fall (Figure A1.2).

1 By Manson in 1877, by Ross in 1895 and by Grassi, Bignami and Bastianelli in 1898 (the parasite cycle in vectors) (*4*)

2 For example, in Brazil, Egypt, the Netherlands, Panama and South Africa

Figure A1.2: World distribution of deaths from malaria, early twentieth century to 2010



Data for 1900–1998 from reference (*12*); data for 2000–2009 from reference (*13*)

1990s: Adoption of the global malaria control strategy.

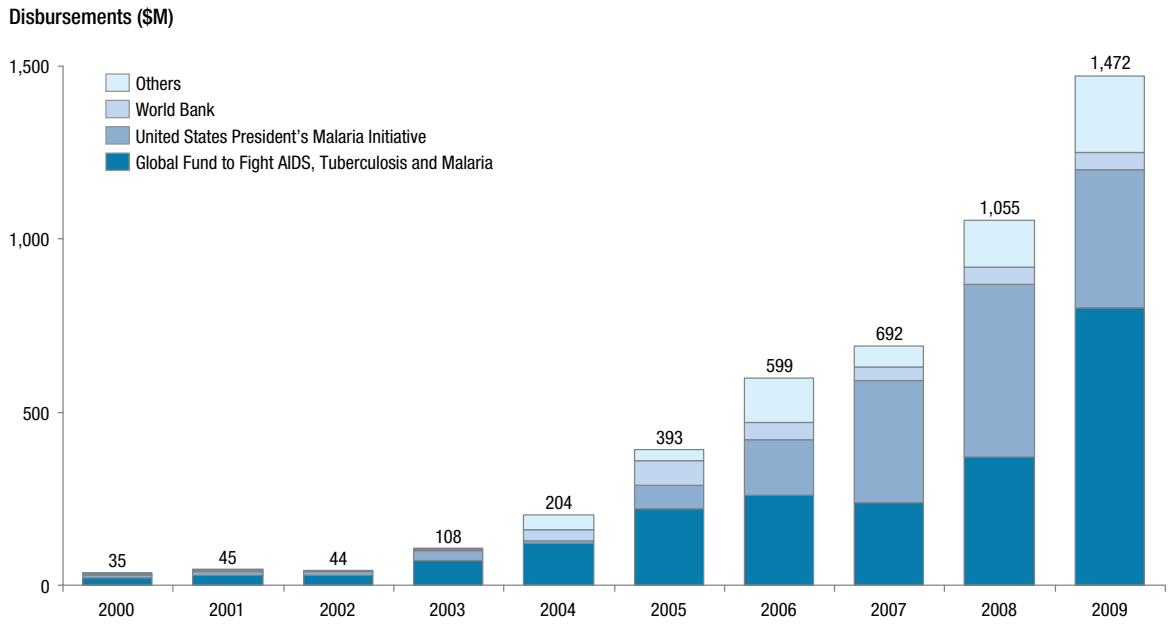
By the late 1980s, it had become clear that the malaria situation had deteriorated over the past few decades, with spread of parasite resistance to antimalarial drugs, increasing numbers of malaria cases in endemic areas (particularly in sub-Saharan Africa) and an increased frequency of epidemics. In reaction to the worsening situation, a revised global malaria control strategy was approved by the World Health Assembly (*14*), after a ministerial conference held in Amsterdam in 1992, which reaffirmed that vector control should be one of the four pillars of the strategy (*8*). During the same period, insecticide-treated bednets were developed and proved to be highly effective against malaria vectors, extending the arsenal of tools that could be used for vector control. The development of long-lasting insecticidal nets increased the duration of insecticide efficacy and did not require re-treatment of nets with insecticide, significantly increasing the scalability of this intervention.

2000s: Raising the profile of malaria and increasing funding.

During the next decade, several new resolutions were adopted to fight malaria, which raised the disease profile and put vector control at the heart of malaria control strategies (e.g. the Organization of African Unity Harare Declaration in 1997, the Abuja Declaration in 2000, the Roll Back Malaria Goals and the Millennium Development Goals). Vector control was implemented on a global scale, and major donors, such as the Global Fund, the World Bank and the President's Malaria Initiative, significantly increased funding for malaria control and especially for coverage with long-lasting insecticidal nets (LLINs) and IRS in endemic countries. Several other initiatives, such as the Roll Back Malaria Partnership and the United Nations Special Envoy's Office for malaria, and the African Leaders Malaria Alliance (ALMA) have also raised the political profile of reaching universal coverage with vector control for populations at risk.

Vector control remains the single largest spending category in malaria control for global donors (Figure A1.3). For example, about 39% of Global Fund expenditure in 2009 and 59% of that of the President's Malaria Initiative in 2010 were estimated to be dedicated to LLINs and IRS (*15*). Estimates of future funding requirements for malaria control suggest that vector control will require almost two thirds of spending through 2025 (*16*).

Figure A1.3: International donor disbursements to malaria endemic countries in 2000-2009



From the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), World Bank, United States President's Malaria Initiative (US-PMI), Organisation for Economic Co-operation and Development database for 2008 and Institute for Health Metrics and Evaluation database for 2000–2007 and 2009 (*15*)
PMI disbursements are for the first three quarters of 2009; those of the World Bank and other agencies are assumed to be equal to those disbursed in 2008.

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ANNEX 2 LONG-LASTING INSECTICIDAL NETS, INDOOR RESIDUAL SPRAYING AND OTHER VECTOR CONTROL INTERVENTIONS

Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are the mainstays of any malaria vector control strategy because of their effectiveness, relatively low cost and possibility for scaling up. LLINs and IRS have each brought about significant reductions in malaria incidence or child mortality in trials and pooled observational analyses.

- **LLINs.** A Cochrane review in 2009 (*1*) showed that insecticide-treated nets reduced the incidence of episodes of uncomplicated malaria in areas of stable malaria transmission by 50% in comparison with no nets, and reduced child mortality from all causes by 17%. A pooled analysis of observational data from 22 sub-Saharan countries in 2011 (*2*) showed that household ownership of at least one insecticide-treated net was associated with a relative reduction in child mortality of 23%, consistent with the earlier Cochrane review.
- **IRS.** Historical and programme documentation has clearly established the effectiveness of IRS. A Cochrane review in 2009 of one randomized controlled trial in the United Republic of Tanzania, showed that IRS reduced re-infection with malaria parasites by 54%. In regions of unstable malaria transmission, the reduction in malaria infections ranged from 30% to 90% (*3*).
- **'Community effect' of LLINs and IRS.** Studies have shown that high coverage rates with LLINs and IRS (e.g. > 80%) lead to a 'community effect', reducing vector survival and the contact between vectors and humans and therefore indirectly protecting people who are not necessarily using a treated net or sleeping in a sprayed house (*4*,*5*).

In most settings, LLINs and IRS are the most affordable interventions available, as they are based on simple techniques with standardized, scalable manufacture and distribution.

- **LLINs.** Although it is relatively inexpensive and easy to distribute LLINs, their lifespan is variable, with an average of less than 3 years, so that worn nets have to be replaced regularly. Net programmes generally achieve high initial coverage through mass distribution and then sustain the initial coverage, for instance by targeted distribution in antenatal clinics and routine child immunization programmes. Such maintenance strategies are essential for maintaining universal coverage, as sustained, intense advocacy campaigns are required to ensure that communities continue to use LLINs appropriately.
- **IRS.** IRS is also based on a standardized application procedure (use of mechanical spray pumps and insecticides) but requires trained staff to apply it. Teams spray all households in target areas once or twice a year, depending on the length of the transmission season and the insecticide used. Although IRS requires more logistic and technical capacity than net distribution, the working methods can easily be standardized and implemented across regions, even if an element of local adaptation is inevitably required. IRS programmes can therefore achieve significant economies of scale.

Other vector control interventions are appropriate under specific conditions.

Other interventions, such as environmental management and larviciding (*6*), can be useful under specific conditions, depending on the target vector and the local situation. Because of logistic and operational limitations, these methods cannot be implemented efficiently in all areas, but in specific settings they may be complementary to LLINs and IRS.

- **Environmental management** involves modifying or manipulating environmental factors to reduce vector breeding. It can result in permanent, sustainable change without the use of chemicals, but it can be used only in settings where the vector breeds in permanent breeding sites. It is also time- and skill-intensive and requires significant logistical support and active community participation.
- **Larval control** reduces vector population growth by point application of chemical (larviciding) or biological toxins, or by the introduction of larvivorous fish (biological control) at identified vector breeding sites. Although larviciding is useful in certain settings, it is feasible only in areas where most breeding sites are relatively fixed geographically, so that they are consistently identifiable and, as such, can be fully covered by the intervention. The requirement for consistently identifiable breeding sites means that specialized local entomological studies must be conducted to ensure success. The method has less of an impact on transmission than use of insecticides against adult mosquitoes, as it reduces the density (number) of mosquitoes but does not shorten their lifespan. Furthermore, it often entails high costs and intensive operational input, as most larvicides must be applied at 1–8-week intervals. The generalizability of the data on the effectiveness of larval source control is limited; however, studies suggest that larval control can be successful in appropriate settings: it reduced malaria transmission by 30% in targeted areas in Dar-es-Salaam, United Republic of Tanzania (*7*), and had a significant complementary effect to LLINs in western Kenya (*8*).

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ANNEX 3 HISTORY OF INSECTICIDE RESISTANCE IN MALARIA VECTORS

Insecticide resistance has been one of the most important technical problems facing vector and pest control programmes in agriculture and public health during the past six decades.

Early evidence of insecticide resistance.

The first cases of resistance to dichlorodiphenyltrichloroethane (DDT) in malaria vectors were identified in 1951 in Greece, in the Islamic Republic of Iran, and in Turkey. Resistance to dieldrin was observed in 1956. Resistance to these insecticides subsequently emerged in many other areas, in Asia, the Americas and Africa. By 1960, 43 mosquito species were resistant to one or more insecticides, and the number had increased to 56 by 1970, and to 99 by 1980 (*1*).

Global Malaria Eradication Programme.

Resistance was both a stimulus for speeding up and a major obstacle to the global malaria eradication programme of the 1950s and 1960s (*2*). In view of the resistance developing in Anopheline vector species, the head of WHO's Malaria Section in 1954, E.J. Pampana, urged countries to work towards eradication faster and more efficiently so that the campaign could be completed before resistance affected vector control (*3*). Continuing evolution of insecticide resistance, particularly to dieldrin, however, soon became an obstacle to the eradication programme. Unfortunately, the intensity of the drive towards eradication appeared to accelerate insecticide resistance. For example, widespread resistance to dieldrin rendered this insecticide essentially useless for malaria control in Africa.

The 1970s to 1990s.

Throughout the 1970s, resistance continued to be a problem, and vector control operations were affected, particularly in India and Latin America, by extensive use of agricultural pesticides. Resistance also became a problem in a few areas of Africa where indoor residual spraying was conducted intensively. With the introduction of pyrethroids in the 1970s, resistance became more stable during the 1980s and 1990s, with few new reports of resistance outside of several known hot spots. It should be noted, however, that there was limited monitoring of resistance during this period.

After 2000.

The threat of resistance to malaria vector control initiatives re-emerged with the resurgence of malaria in South Africa from 1996 to 2000 (see details on p34), which was attributed largely to resistance to pyrethroids. In the past few years, particularly since 2009, more intensive monitoring has revealed widespread resistance to pyrethroids and DDT and, to a lesser extent organophosphates and carbamates.

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ANNEX 4 CHALLENGES IN MEASURING THE IMPACT OF INSECTICIDE RESISTANCE ON THE EFFECTIVENESS OF VECTOR CONTROL

Why randomized controlled trial methods cannot be used.

When we ask "what is the impact of resistance on vector control?", what exactly does this question mean?

We expect vector control to cause a reduction in the intensity of malaria transmission, not a complete and immediate interruption. However, malaria transmission is also affected by many other factors – confounding factors – such as the local environment, the weather and the health system. Normally, in order to measure the effect of a new form of vector control in isolation from these confounding factors, we would use standard "randomized control trial" (RCT) methods. Well-studied RCT methods have been developed for a variety of situations and purposes, but in the case of vector control, the basic idea is that a set of communities is randomly divided into two groups, one that will receive the new form of vector control, and a comparison group that will receive the old form of vector control or nothing.

Adding resistance into the question adds a further level of difficulty. The question now becomes "does vector control produce a smaller reduction in malaria if the vector mosquitoes are resistant than it would have done if they were susceptible?". The key difficulty is that it is impossible to address this question using RCT methods, simply because resistance is not the kind of factor that can be allocated randomly to some communities and not to others. This is important, because many health scientists regard evidence from randomized-controlled studies as the only reliable basis for decision-making in public health.

Alternative methods and their limitations.

The nearest alternative is to study observed variations in resistance, and investigate whether the observed effectiveness of vector control is associated with these. For example, vector control can be introduced into an area where there is a high frequency of resistance in some village mosquito populations and a low frequency in others, with subsequent monitoring to see whether the observed effect of vector control tends to be lower on average in villages with high levels of resistance. This so-called "ecological" approach is useful, but it has some important limitations.

One limitation is that the effect of confounding factors can never be excluded with confidence with such a design. For example, there may be more resistance in some villages than others because of variations in the quality of vector control operations, or in mosquito behaviour. These are both factors that could produce stronger selection for resistance in some villages than others, and they are also expected to have direct effects on the effectiveness of vector control.

Another limitation is that in most cases, the spread of resistance happens over a large scale, not village by village but district by district or province by province. In Benin, for example, there are no more fully susceptible areas that could be used as control sites.

The importance of good quality surveillance data.

As resistance genes spread from province to province and country to country, it is of course meaningful and very useful to observe whether and how much this spread is accompanied by an increase in routine reports of malaria incidence as recorded in local health facilities. However, in poor and remote areas, routine epidemiological data of this kind may not be sufficiently reliable for this purpose: in particular it may be based on clinical diagnosis without parasitological confirmation. In these circumstances, experience suggests that major resurgences of malaria, reflecting complete control failure, may indeed be detected by routine case reporting systems, but a less dramatic increase in the number of cases might not be noticed immediately. This is of real concern, as good data are essential for detecting increases in the number of malaria cases and providing an opportunity to prevent full control failure by taking responsive action. Improvements in malaria diagnostic testing and routine surveillance, which are underway

in many countries, will improve understanding of the impact of insecticide resistance.

Alternative ways to measure operational impact.

Given the many obstacles to measuring the epidemiological impact of resistance, the alternative has been to measure proxy entomological outcomes, such as the relative mortality and feeding success of resistant and susceptible vectors in experimental huts. Although such results can be remarkably clear, and definitively linked to resistance, experimental hut methods have their own limitations. For example, they are small-scale studies with entomological outcomes; additional assumptions are needed to link them with outcomes of public health importance.

In one type of experimental hut trial, the efficacy of the same insecticide is compared in resistant and susceptible areas (*2, 3*). In another, the effectiveness of different insecticides is compared in a mosquito population that is resistant to one of the insecticides (*4*). In a third approach, the study focuses on a resistance gene that can be detected by DNA methods even in dead insects, and is performed in an area where the local mosquito population includes both resistant and susceptible insects; this allows a direct measure of the relative survival and feeding success of resistant and susceptible insects in the presence of different forms of vector control (*5*).

An extension of this would be to investigate associations between resistance genes or resistance phenotype (survival in a bioassay) and either indicators of transmission (parasite infection in a mosquito) or components of vectorial capacity (especially longevity). For example, in an area under malaria vector control with a mixture of resistant and susceptible vectors in the same local species, samples could be taken to compare the sporozoite rate (= the proportion of female mosquitoes that are infective, i.e. with malarial parasites in the salivary glands ready for transmission to people) in resistant and susceptible insects. This comparison gives an indication of how much more intense transmission is expected to be when the vector population is fully resistant, compared to that when it was fully susceptible.

A WHO project supported by the Bill and Melinda Gates Foundation is conducting trials to measure the impact of resistance in four countries in Africa and in India, with a variety of methods.

Possible reasons for widespread insecticide resistance with no obvious impact on the effectiveness of vector control.

- **The effect of resistance may be visible only when combined with poor implementation, gaps in coverage and aging insecticide deposits.** IRS and LLINs are useful in vector control not only because they have a powerful immediate impact on transmission, but also because they are often found to be still effective even when they are not implemented perfectly, when coverage is incomplete or when the spray deposits/nets are old in relation to their expected lifespan. In other words, they are robust and long-lived and tolerant of imperfect conditions, and for programmatic purposes this is as important as their immediate impact on transmission. This points to the hypothesis that resistance may erode the robustness of an intervention, so that its impact on vector control may be seen most clearly when implementation is poor, when there are gaps in coverage, or when the intervention gets older. In other words, in the presence of resistance, previously robust interventions may require perfect implementation and complete coverage in order to be effective, and the duration of effective control may be reduced.
- **A higher threshold of resistance is required.** One hypothesis is that a higher threshold of resistance may be required before the number of malaria cases increases, and that threshold has not yet been reached in many places. Therefore, only reduced effectiveness is seen initially, whereas control failure may occur only after the strength and frequency of resistance have increased.
- **IRS may have a greater potential for failure.** The physical barrier of insecticide-treated nets provides a degree of protection, even if the insecticide is no longer effective, whereas IRS does not have this physical protection effect.
- **Vectors are still killed because of multiple exposures to an insecticide in the field.** Vectors may still be killed by an insecticide if they come into contact with it on many occasions within a short time (*6*). While a single standard dose of insecticide might not have the desired effect, multiple exposures in the field (for example landing on a sprayed surface three to four times) can lead to a higher accumulated dose of the insecticide, which may be sufficient to kill the vector. Similarly, vectors that are resistant may have a lower excito-repellent response when exposed to pyrethroids. Therefore, they may remain exposed to the insecticide for longer and receive a larger dose, and thus be killed anyway (*3*).
- **Older vectors are more susceptible.** Metabolic resistance is in some cases expressed more strongly in young mosquitoes, but, when they are older, susceptibility returns. Therefore, insecticides still kill older mosquitoes (7). Since it is these old mosquitoes that transmit malaria, the resistance may not cause an increase in transmission.
- **Resistant vectors are less capable of transmitting malaria.** It has been suggested that the ability of resistant vectors to transmit malaria might be reduced as, even if they are not killed by an insecticide within 24 hours, the insecticide might still inhibit their ability to live for the 12 days necessary to develop the malaria parasite. Alternatively, a vector's resistance to an insecticide might be offset by a lower level of infection, which is not as great a threat to the human population.

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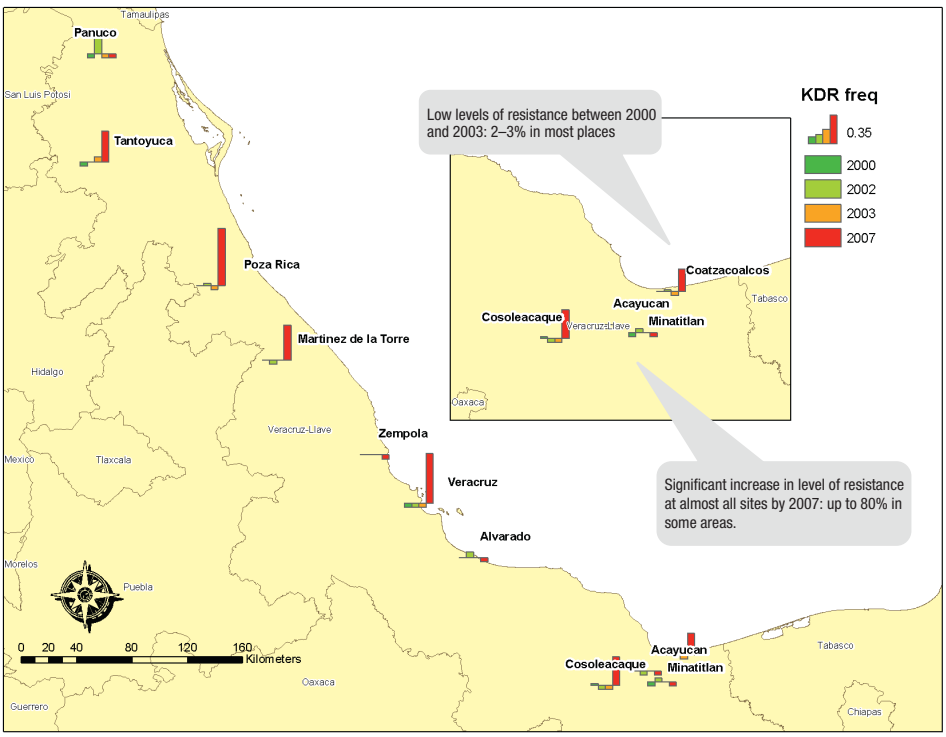
ANNEX 5 EXAMPLE OF 'TIPPING-POINT' IN RESISTANT *AEDES* MOSQUITOES

The evolution of *kdr* resistance to pyrethroids in *Aedes* mosquitoes in Mexico demonstrates the 'tipping-point' concept. Between 2000 and 2003, the frequency of resistance was very low (≤ 10%) at most sentinel sites. At some time between 2003 and 2007, however, because of continuous selection pressure from the same insecticide, the tipping-point was reached, and resistance increased significantly in six sites, reaching frequencies of ≤ 80% by 2007 (Figure A5.1).

Figure A5.1: Frequency of kdr resistance to pyrethroids in Aedes mosquitoes in Veracruz, Mexico, 2000-2007



From J Hemingway and Liverpool School of Tropical Medicine
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ANNEX 6 SELECTION PRESSURE: ROLE OF PUBLIC HEALTH, AGRICULTURE AND OTHER FACTORS

Role of public health.

There is increasing awareness of the role of public health insecticides in causing selection pressure. Smaller quantities of insecticides are used for public health than for agriculture. However, for public health purposes insecticides are used in highly targeted strategies and persist for longer, therefore allowing significant build-up of selection pressure over many generations of vectors. The massive scaling-up of use of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) for malaria control, especially in the past 5 years, has resulted in increased selection in malaria-endemic countries.

Role in emergence of resistance. In some areas, resistance has emerged where there was no agricultural use of insecticides but where vector control interventions were introduced recently. In one area of Sudan, a high frequency of resistance was seen by 2011 after distribution of long-lasting insecticidal nets (LLINs) to children and pregnant women began in 2004.

Role in increasing the level of resistance. In other places, the scaling-up of interventions appears to be linked to an increased frequency of resistance genes, even if they were not the initial cause. In western Kenya, a marked increase in the frequency of the *kdr* allele occurred between 1996 and 2009 in the Asembo and Seme areas, suggesting that *An. gambiae* had undergone strong selection pressure from LLINs. Nevertheless, while LLINs may have resulted in a significant increase in resistance genes, *kdr* resistance had already been identified in 1996, albeit at a very low level, perhaps from previous DDT selection (*1*). Similarly, in Benin and Niger, the increased use of LLINs appeared to increase *kdr* frequency but did not cause its initial emergence (*2*). In Niger, resistance had increased significantly in *An. gambiae* by 2007 after distribution of LLINs began in 2005 *(3)*. Similar examples have been seen with IRS. In Burundi, the proportion of *An. gambiae* with the *kdr* gene was 1% before an IRS programme began in 2002 and had increased to 86% by 2007 (*4*). This emphasizes the importance of early and effective IRM as countries continue to increase coverage with vector control by scaling up use of IRS and LLINs. In doing so, they are likely to increase selection pressure for resistance.

Role of agriculture.

Crops that require heavy insecticide use and therefore result in selection pressure. The exposure of malaria vector mosquitoes to agricultural insecticides is particularly associated with cotton crops, rice crops, and market gardening.

Some reports have shown a clear link between resistance and agriculture pressure, with seasonal fluctuations of resistance in major agriculture regions reflecting the timing of insecticide application to the main crops in the region and the highest frequencies of resistance in areas of intense agricultural pressure. In Burkina Faso, the *kdr* mutation is present at many cotton-growing sites, and the highest frequencies of resistance occur in the 'cotton belt'. Similarly, a study of six towns in Côte d'Ivoire showed resistance to pyrethroids and dichlorodiphenyltrichloroethane (DDT) in the regions in which agriculture was particularly intense (*5*).

In some cases, however, agriculture has been blamed for the emergence of resistance, until further investigations have shown that resistance was more likely to be related to use of insecticides for malaria control. In Sri Lanka, insecticides on rice crops did not account for the resistance to carbamates and organophosphates, as the main vectors were not breeding in rice; it therefore became clear that selection pressure was due to malaria control efforts (*6*). In Sudan, stopping malathion use in IRS caused a reversion of resistance, even when there was no change in the insecticide used on cotton crops. The link between agricultural use of pesticides and resistance depends on both the type of crop and vector behaviour. A link can be assumed only if significant quantities of insecticide are used on a given crop and the same crop is a breeding ground for the vector at the times when the insecticide is applied.

Role of other factors.

Recent studies have indicated other factors that contribute to selection pressure, although their role is limited.

Hydrocarbon pollution. Of greatest concern is recent evidence that metabolic resistance can be selected by multiple pollutants in the environment. In Benin and Nigeria, pollution with hydrocarbons of groundwater used as breeding sites by malaria vectors has been associated with the emergence of oxidase-based metabolic resistance in *An. gambiae,* which makes them resistant to pyrethroids. Although there are few examples, this resistance is particularly intense and is extremely worrying, as there is little that can be done to stop its evolution.

Other factors. The other factors that are believed to contribute to a small degree to selection pressure are heavy domestic use of insecticides, especially aerosols and coils (for example in Benin, India, Sri Lanka and Latin America), poor-quality insecticides and larviciding, although its use in Africa is limited.

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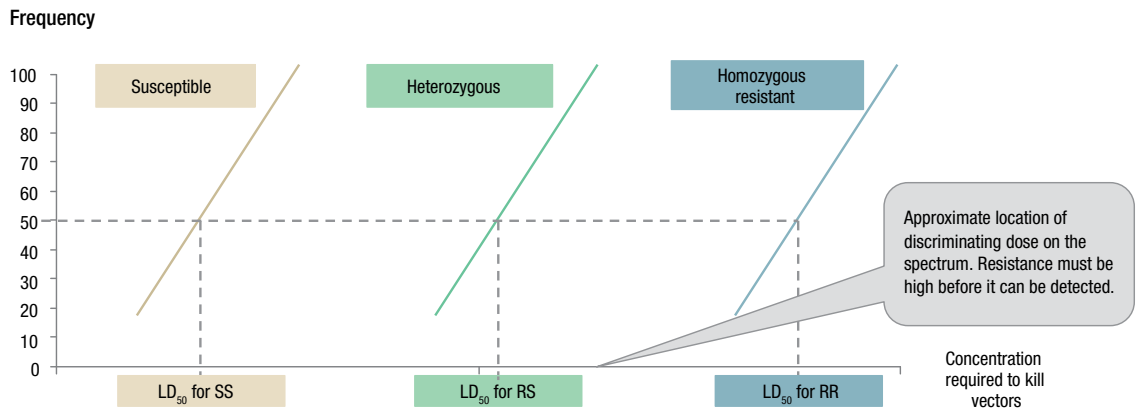
ANNEX 7 IMPLICATIONS OF DISCRIMINATING DOSES OF INSECTICIDE ON DETECTION OF RESISTANCE

The dosage of insecticide used in susceptibility testing plays a role in determining how long insecticide resistance can remain hidden before a detectable percentage of survivors is identified in the test. For a semi-dominant gene, the 'lethal dose 50' (LD_{50}, dose required to kill exactly 50% of exposed insects) is different for homozygous susceptible, heterozygous or homozygous resistant (Figure A7.1).

Figure A7.1: Diagram illustrating the LD_{50} of semi-dominant homozygous susceptible, heterozygous or homozygous resistant for a semi-dominant gene (illustrative data only)



From the WHO Global Malaria Programme

Depending on where the discriminating dose is on this spectrum, the estimate of susceptibility will be different, even with the same gene frequency. If the dose is too high, heterozygous mosquitoes will remain undetected, and resistance will not be detected until homozygous resistant mosquitoes are firmly established in the population, at which point it is extremely difficult to slow the spread of resistance as IRM options will be very limited.

ANNEX 8 MAIN HYPOTHESES USED TO MODEL THE IMPACT OF INSECTICIDE RESISTANCE ON MALARIA BURDEN

Several experts were consulted in designing modelling for the GPIRM. These included teams from the MRC Centre for Outbreak Analysis and Modelling, Imperial College London, and Tulane University School of Public and Tropical Medicine.

Inputs.

The model is based on data on current populations at risk in each country, malaria incidence rates (*1*), coverage rates with indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs), the protective efficacy[1] of IRS and LLINs, and estimates of insecticide use for IRS and LLINs (pyrethroids and non-pyrethroids).

In the case of full protective efficacy, malaria-related mortality of children under 5 years of age is assumed to be reduced by 55% when LLINs or IRS are used (*2*), whereas malaria transmission incidence is assumed to be reduced by 50% with LLINs (*3*) and by 55% with IRS (as found in a randomized controlled trial in the United Republic of Tanzania) (*4*). There is limited evidence for the protective efficacy of IRS and LLINs in adults, and it is assumed to be half that in children.[2]

In the case of failure of pyrethroids, the protective efficacy of an LLIN is assumed to be 25% (close to that of an untreated net [*5*]) and that of pyrethroid-based IRS to be 10%. Sensitivity analyses show an efficacy of 15–35% for LLINs and 0–20% for pyrethroid-based IRS. For the estimates of child mortality, antimalarial treatment is assumed to be constant at current levels. These assumptions are summarized in Table A8.1.

1 'Protective efficacy on cases': reduction in malaria incidence with a given control tool; 'protective efficacy on mortality': reduction in mortality from malarial episodes with a given control tool

2 Based on the assumption that adults are not directly protected by nets and IRS to the same extent as children because they spend less time under an LLIN or in a sprayed house.

Table A8.1: Assumptions about protective efficacy of vector control tools

Scenario	Protective efficacy of vector control on malaria cases (children / adults) (%)			Protective efficacy of vector control on deaths from malaria in children under 5 years of age (%)		
	LLINs	IRS with PYR	IRS with non-PYR	LLINs	IRS with PYR	IRS with non-PYR
Current vector control	50 / 25	55 / 27.5	55 / 27.5	55	55	55
Failure of PYR: worst case	15 / 7.5	0 / 0	55 / 27.5	15	0	55
Failure of PYR: middle case	25 / 12.5	10 / 5	55 / 27.5	25	10	55
Failure of PYR: best case	35 / 17.5	20 / 10	55 / 27.5	35	20	55

LLINs, long-lasting insecticidal nets; IRS, indoor residual spraying; PYR, pyrethroids
Data on current situation from references (*2*) and (*3*)

Outputs and method.

Firstly, the data are used to calculate the impact of vector control interventions on the burden of malaria, assuming full protective efficacy of vector control ('averted deaths and cases'). The numbers of deaths and cases averted are estimated on the basis of today's rate of coverage with LLINs and IRS and also for the scenario of a rapid scale-up to universal coverage (assuming constant population size).

Second, the data are used to calculate the deaths and cases not averted if pyrethroids 'fail', in the event of a significant decrease in the protective efficacy of LLINs and pyrethroid-based IRS.

Results for malaria deaths: With universal coverage, failure of pyrethroids could lead to approximately 259 000 additional child deaths each year in WHO African Region (see Figure 14, page 39).

With current levels of LLIN and IRS coverage, about 217 000 deaths of children under 5 would be averted each year in the WHO African Region. The model suggests that if pyrethroids were to fail, about 56% of the benefits on child mortality resulting from vector control would be lost, resulting in about 120 000 deaths of children under 5 that are not averted.

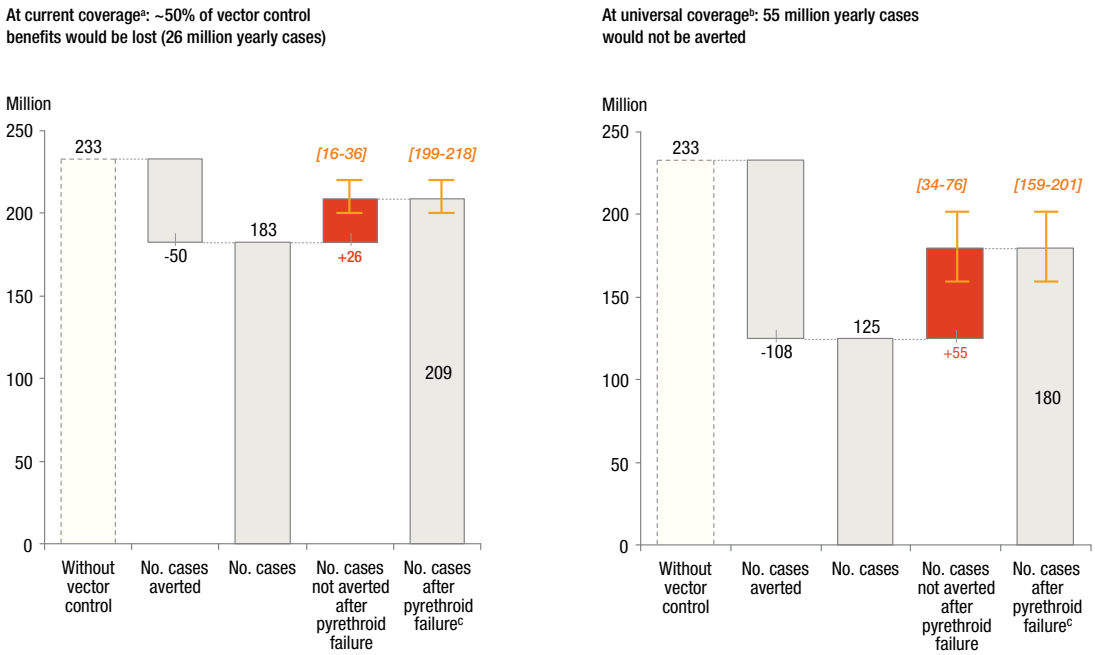
With universal coverage with LLINs and IRS. If universal coverage is reached in the WHO African Region, about 417 000 malaria-related child deaths would be averted by vector control each year. If pyrethroids were to fail, the model results suggest that about 259 000 deaths would no longer be averted each year.

Results for malaria cases: With universal coverage, failure of pyrethroids could lead to approximately 55 million additional cases each year in the WHO African Region (Figure A8.2).

With current levels of LLIN and IRS coverage. The model results suggest that vector control averts 50 million cases in the WHO African Region each year. In pyrethroids were to fail, about 50% of the current impact of vector control would disappear, and 26 million cases would not be averted each year.

With universal LLIN and IRS coverage. If universal coverage is achieved, vector control would avert about 108 million cases each year in the African Region, according to the model. If pyrethroids were to fail, the impact of vector control would be halved, leading to an additional 55 million malaria cases in the region each year.

Figure A8.2: Estimated impact of insecticide resistance on number of malaria cases



a At current levels of vector control, diagnosis and treatment
b At universal coverage of vector control tools, malaria diagnosis and treatment
c Assumption: If pyrethroids fail, and no other malaria control measures are introduced in the areas where pyrethroids are used.

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ANNEX 9 USE OF INSECTICIDE RESISTANCE MANAGEMENT STRATEGIES (ROTATIONS, COMBINATIONS, MOSAICS AND MIXTURES)

Rotations.

How do rotations work?

Rotations are particularly effective if the resistance gene has an associated fitness cost: in other words, if resistant insects are at a selective disadvantage, compared to the susceptible 'wild type' insects, in the absence of the insecticide (*1*). This is also sometimes referred to as "back-selection" (see section 1.2.4).

For example, let us consider a rotation system where the insecticides A, B and C are used in succession, and assume that the target insect population includes, at low frequency, a small number of genes (R^A, R^B and R^C), conferring specific resistance only to A, only to B, or only to C, but there are no genes conferring cross-resistance to more than one insecticide. In this situation, we would normally expect the frequency of R^A genes for resistance to go up during the period when insecticide A is being used. During the periods when B and C are being used, the frequency of R^A could remain constant (if there is no fitness cost at all), but in most cases it is likely to decline, at a rate depending on the magnitude of the fitness cost, until the time comes to use insecticide A again. The same process goes on with R^B and R^C: they increase during periods when the corresponding insecticide is in use, and may decline in the intervals between these periods. Rotations therefore help to preserve susceptibility.

Rotations have been successful in many applications in agriculture and are considered to be effective in slowing the evolution of resistance (*2*).

What should be considered when implementing rotations?

As in all resistance management strategies, the current status of resistance must be known when implementing rotations. Significant resistance to any mode of action of the insecticide used in the rotation can jeopardize the efficacy of the programme. Further, any mechanisms that confer cross-resistance between insecticides must be understood in order to choose the appropriate insecticides for rotation.

The pragmatic approach is to rotate insecticides annually. Changing insecticides more than once a year (which could be the case in areas where two spray rounds are conducted each year) is not recommended, mainly because of procurement and other logistical challenges. Changing less frequently than once a year is also not recommended, as using an insecticide for longer makes it more likely that resistance will evolve to a frequency that is too high for rotations then to be effective in reducing it.

Detailed planning is required before implementation. Rotations require more logistical planning than indoor residual spraying (IRS) with a single compound. The insecticides used may have different toxicity for humans, IRS teams must be appropriately trained and equipped, and adequate supplies of all the chemicals in the rotation must be available and approved by regulatory authorities.

The costs of an IRS programme using a rotation are likely to increase, mainly because the available alternatives to pyrethroids and dichlorodiphenyltrichloroethane (DDT) —the carbamates and organophosphates—are currently more expensive (*3*). Given the differences in the cost of insecticides, costs should be calculated on the basis of an average year in the rotation cycle (*1*), as some insecticides have shorter residual efficacy, thus requiring more than one round of spraying in each year. This will enable better programme planning and balancing of expenses between years.

Another consideration is local capacity to monitor and enforce the rotations strategy. Countries should build the necessary human capacity for entomology and management to ensure that the rotations strategy is fully understood and followed. The quality of spraying operations and insecticides must be carefully monitored and safety standards maintained.

Combinations.

How do combinations work?

Combinations expose the vector population to two insecticides, such that a mosquito that survives contact with the LLIN is exposed to IRS, or vice versa. Exposure to both insecticides is not guaranteed but experience to date indicates that this is likely (*4*). The effectiveness of combinations in IRM does not depend on the ability to reduce the level of resistance, but on the ability to kill the vector despite the existence of resistance, through the use of another insecticide or intervention, which compensates for resistance. The combination should not contain insecticides with same mode of action,(e.g. pyrethroids for both IRS and LLINs), as this would increase selection pressure rather than reducing it.

What should be considered when using combinations of interventions?

As combinations require doubling of interventions, they cost significantly more than rotations and mosaics. This might nevertheless be warranted in some circumstances, for example where malaria transmission is very high or where targeted IRS can help overcome identified resistance to pyrethroids in areas with high LLIN coverage (see Part 3 for the criteria for use of combinations).

It should be noted that combination strategies are not designed to make up for poor implementation of either intervention. Both LLINs and IRS should be implemented well and fully.

Mosaics.

How do mosaics work?

Mosaics involve spraying insecticide A in one area (sector 1), and insecticide B in an adjacent area (sector 2); A and B should be from different insecticide classes, preferably with different modes of action. The effect is to reduce the proportion of the vector population exposed to either insecticide. Over the course of generations, mosquitoes susceptible to insecticide B will migrate from sector 1 to sector 2 where B is being sprayed, and this dilution effect will slow the rate of selection of B. Similarly, mosquitoes susceptible to insecticide A will migrate from sector 2 into sector 1 where A is being sprayed and slow the rate of selection of insecticide A. The aim of this strategy is to preserve susceptibility by spatial restriction of insecticides. Some immigrating mosquitoes resistant to B will be killed by A, and vice versa, and this also will help to preserve susceptibility.

This strategy has been successful in agriculture, and there is some empirical evidence for success in public health.[1] The scale at which a mosaic needs to be applied has not been established. In South Africa for example, different insecticides have been used in different types of houses within the same community and this is considered by some to be a mosaic-like strategy. Further operational research is required to establish the applicability and effectiveness of mosaics and combination strategies for malaria control.

What should be considered when implementing mosaics?

A number of considerations must be taken into account when using mosaics. As for rotations, the current status of resistance must be understood. Another aspect is the logistical challenge of implementing mosaics. The spraying authority must ensure that proper areas are sprayed with the right insecticide at the right time and keep track of which house was sprayed with what insecticide. Spray teams must also be trained to handle multiple products appropriately, and appropriate amounts of insecticide must be purchased in advance.

Mixtures.

How do mixtures work?

If two insecticides A and B, with independent resistance mechanisms, are applied together in a mixture, and if resistance to A and resistance to B are both rare, then we expect doubly resistant insects to be vanishingly rare, and almost all insects resistant to A will be killed by B, and vice versa. This system of "redundant killing" means that resistance to the two insecticides will evolve much more slowly than if either had been used on its own. (*1*). This principle is similar to that of artemisinin-based combination therapy in malaria treatment. Unlike rotations, the effectiveness of mixtures is not related to the degree of resistance fitness cost. Rather the mixture aims to overpower resistance instead of preserving susceptibility. Further, theoretical models suggest that mixtures might delay resistance longer than rotations or broad mosaics (*1*).

What should be considered when using mixtures, when they become available?

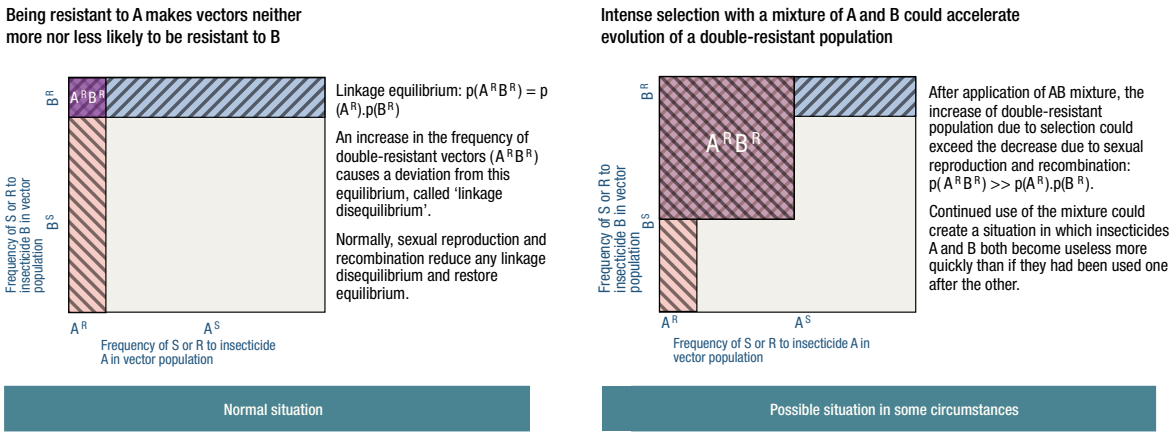
With the currently limited range of insecticides recommended for IRS and LLINs, potential mixtures of active ingredients are limited. Other products, such as insect growth regulators, might be included in mixture formulations. The active ingredients should ideally decay at the same rate to preserve the IRM attributes of the mixture; the toxicology analysis must account for any additive effect of combining the pesticides; and WHO and countries will need to prepare new safety and efficacy standards when mixtures become available in the future. All mixtures will need to be approved by WHOPES. The current view is that neither operators nor programmes should create ad hoc mixtures simply by mixing insecticides.

1 Trial on *Anopheles albimanus* in Mexico (*2*)

With the currently limited range of insecticides recommended for IRS and LLINs, potential mixtures are also very limited. To be fully effective for resistance management, resistance to both components of the mixture must be rare. However, there is general agreement that LLIN mixture products, when developed, could still contain pyrethroids, since the pyrethroid may still contribute to the effectiveness of the net despite resistance (this needs to be confirmed). Some agree that the rationale applies to IRS, and that pyrethroid mixtures could be considered in areas of pyrethroid resistance; others believe that this is inadvisable and likely to lead to rapid evolution of double resistance. It is not yet clear how much the addition of a second active ingredient will add to the total cost of manufacturing: since the cost of insecticide currently represents a substantial proportion of the total cost of IRS, but a very small proportion of the total cost of LLINs, the additional cost of switching to mixture products would likely be greater for IRS than for LLINs.

Before a mixture would be able to be used, the status of resistance would have to be known. Pre-existing resistance to one insecticide in the mixture could accelerate the development of double-resistant vector populations because of linkage disequilibrium (Figure A9.1). Although the risk of accelerating resistance through linkage disequilibrium has been modelled theoretically, further field investigation will be required during the development phase of such products. The current theory is based on models suggesting the existence of the phenomenon, postulating that the risk of disequilibrium is greatest if genes are tightly linked and dominant and the whole population is exposed (*5*). There is, however, no empirical evidence of linkage disequilibrium in mosquito populations. Some limited disequilibrium has been found in other organisms, but these results are not directly relevant for malaria control (*6*).

Figure A9.1: Mixtures and the concept of linkage disequilibrium



From references (*5*, *7*, *8*)
S, susceptible; R, resistant

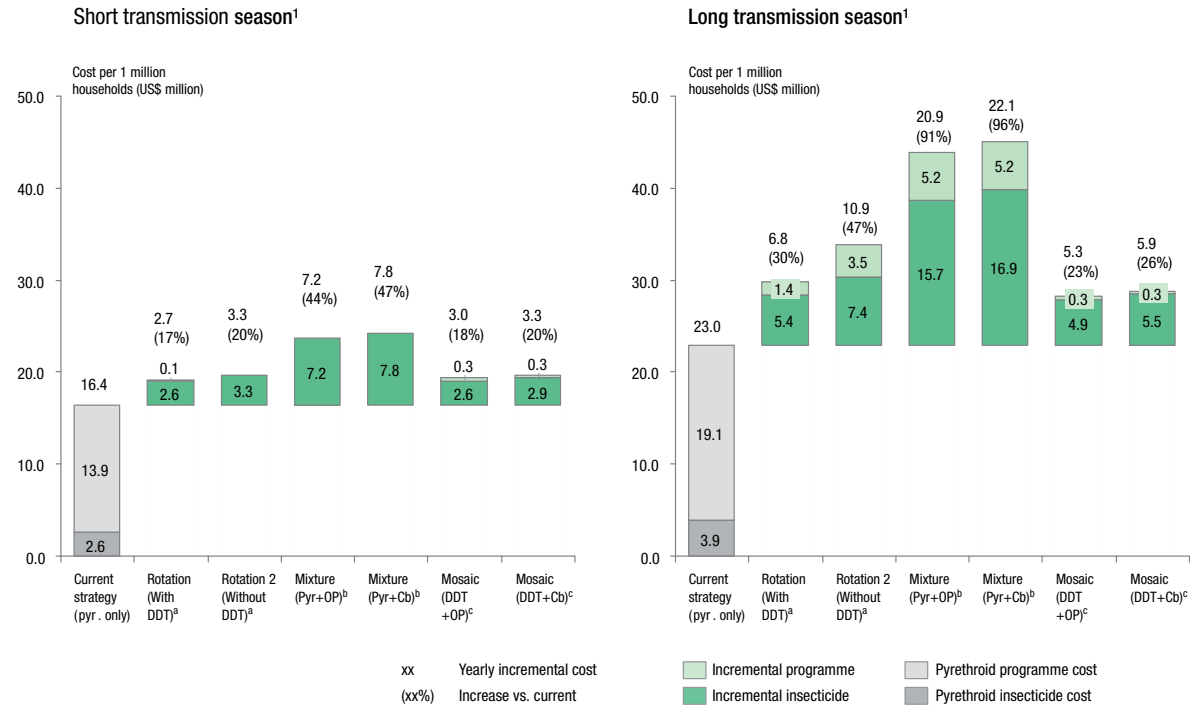
Even though the risk for linkage disequilibrium exists, mixtures may still be the most attractive IRM tool, particularly for LLINs. As long as appropriate monitoring is conducted to identify any linkage disequilibrium in the mosquito population, mixtures could be very successful in staving off resistance to pyrethroids and preserving the efficacy of vector control in resistant populations.

Cost increases associated with insecticide resistance management.

All IRM strategies are likely to be associated with a near-term cost increase. The size of the increase depends on the strategy but mainly on the duration of the transmission season. Hence, with current vector control tools, IRS-based strategies will be significantly more expensive in areas with long transmission seasons (Figure A9.2).

At current prices, rotations and mosaics are estimated to have the lowest cost effect among the IRS-based IRM interventions. They would increase the annual cost by 20–50%, whereas use of mixtures for IRS once developed, are projected to increase the cost by 30–100%, depending on the duration of the transmission season. Because mixtures have not yet been developed or marketed, the final cost could be higher or lower than current projections.

Figure A9.2: Incremental annual costs of different types of indoor residual spraying for insecticide resistance management



From references (*3, 9, 10)*

Pyr, pyrethroids; OP, organophosphates; Cb, carbamates

Assumption: all insecticides sprayed only once in short transmission seasons; while in long season DDT sprayed once, pyrethroid 1.5 times, organophosphate twice and carbamates twice. Programme costs do not include cost of training and equipping new spray teams, or other unique transition costs. Incremental programme and insecticide costs indicate net increases over cost of current strategy.

a Cost differences calculated both for short (i.e. about 3 months) and for long (about 6 months) transmission seasons, per 1 million houses covered.

b Cost differences calculated over four transmission seasons and averaged.

c Assuming 100/100 mixture for insecticide cost; shorter of two durations used to estimate spraying season; programme costs do not include those for mixture development or spraying.

For most IRM strategies based on LLINs, the cost effects of the use of insecticides other than pyrethroids are difficult to estimate, as the alternative insecticides are not yet available on the market. In settings in which LLINs are used, combination strategies to delay the spread of resistance should be highly targeted in order to contain the additional costs (see section 1.4). Furthermore, although IRS mixtures, once developed, could entail significant cost increases, applying mixtures to LLINs would likely not have the same effect, as insecticides represent a smaller proportion of the total cost of the intervention.

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ANNEX 10 GENETIC RESEARCH AGENDA

Background: With limited genetic information on resistance genes, it is difficult to track and anticipate the course of resistance, and understand which IRM strategies would be most effective. The evolution of resistance and the possibility of reducing and even reversing resistance cannot be predicted because of limited information on factors such as baseline frequency (mutation rates), fitness cost, genetic mode of inheritance and the selection pressure due to different uses of insecticides in agriculture and public health. Inability to track resistance genetically makes the consequences of insecticide resistance more difficult to anticipate; it is also difficult to measure the efficacy of IRM strategies.

Research agenda: The genes that confer metabolic resistance must be identified in order to answer several important research questions. Outputs from this research agenda would have immediate practical implications for decisions on resistance management taken in national malaria control programmes. The topics for research should include genetic dominance, fitness cost, cross-resistance, linkage disequilibrium, drivers of selection pressure and behavioural resistance.

The elements for research should include:

- *Insecticide resistance management strategies:* Study the potential to prevent the selection of resistance (manage resistance) by testing high and low dosages of currently available insecticides, small scale mosaics, combinations of indoor residual spraying and long-lasting insecticidal nets, and mixtures (when they become available). This can be done in experimental huts by monitoring the differential survival of resistant and susceptible genotypes.
- *Genetic dominance*: Investigate effective genetic dominance for target sites and metabolic mechanisms in the field (experimental huts).
- *Fitness cost*: Investigate the degree of fitness cost in resistance genes. This requires careful study because a reduction in resistance gene frequency might be due either to fitness cost and back-selection or to dilution from immigration of susceptible insects from outside the resistance area; the former is more promising for intervention than the latter. The possibility that fitness disadvantage may be lost through evolution of a fitness modifier must also be considered.
- *Cross-resistance*: Investigate the cross-resistance patterns of specific metabolic enzymes, including (a) cross-resistance extending from oxidase- and esterase-based pyrethroid resistance to other insecticide classes (e.g. carbamates) and (b) whether cross-resistance between different pyrethroids is invariably 100% complete. Different cases of oxidase-based pyrethroid-resistance may have different characteristics in this respect.
- *Spread of unique mutations*: Determine whether cases of resistance are due to unique mutations that then spread, or to de novo mutations occurring in diverse locations, or to some combination of the two.
- *Linkage disequilibrium*: Assess potential linkage disequilibrium between resistance genes arising as a result of selection by mixtures. Such research could initially be conducted using ad hoc mixtures in advance of co-formulated mixtures being developed by industry.
- *Determinants of selection pressure*: Develop methods to assess the selection pressure for resistance from different sources, including use of insecticides for public health, use of insecticides for major crops (including tobacco), domestic use of insecticides, and hydrocarbon pollution. In addition, distinguish between (a) selection that creates genetic variation at resistance loci and allows resistance genes to be maintained at low frequency and (b) selection that drives resistance genes to high frequency.
- *Behavioural resistance*: Improve understanding of behavioural avoidance traits. These traits could alter the effectiveness of vector control; outdoor resting and biting may increase the importance of outdoor malaria transmission and necessitate new tools. Such research may also help to distinguish between true behavioural resistance and species substitution as a result of vector control interventions.

ANNEX 11 FINANCIAL MODELLING

Several experts were consulted in the development of the financial model for the Global Plan for Insecticide Resistance Management in malaria vectors. These included teams from the United States President's Malaria Initiative (PMI), the United States Agency for International Development (USAID) and several WHO offices.

Hypotheses used to model the cost of insecticide resistance management in geographical areas in which indoor residual spraying is the main form of vector control.

Inputs. The costs of insecticide are based on average sachet costs reported by the PMI in 2010 (*1*).[1] The costs for indoor residual spraying (IRS) programmes are based on the average amortized costs of large-scale IRS programmes in Benin, Ghana, Madagascar, Rwanda and Senegal, supported by PMI in 2008–2010 (based on a draft version of a cost study by USAID and RTI International [*2*]). To account for the fact that PMI-supported programmes may cost more than those conducted only by national malaria control programmes, the costs of international and other external labour as well as international technical assistance were excluded from this analysis.

Outputs.

- *Cost per million households and per person covered.* Costs are expressed per million households (one household being defined as five people/150 m^2) and per person covered to facilitate comparisons and planning.
- *Short and long transmission seasons.* The number of spray rounds required in an IRS programme depends on the residual efficacy of the insecticide used and the length of the malaria transmission season. The model outlines the costs of a short transmission season (≤ 3 months) and of a long transmission season (> 3 months).
- *Cost breakdown.* The costs are given for insecticides, operations[2] and administration.[3]

Table A11.1 gives the results of similar studies. The estimates in the GPIRM for pyrethroid-based IRS are the range of average costs in these studies, generally US$ 2–5 per person protected.

1 Insecticide costs were based on the cost of an average sachet (to cover about 250 m^2) of US$ 4.30 for pyrethroids, US$ 5.35 for organochlorines, US$ 12.00 for organophosphates and US$ 13.00 for carbamates (*1*).

2 Planning and logistics; environmental compliance, including construction of a soak pit and evaporation tank; training; information, education and communications; warehousing; short-term labour; transport; medical costs; 'mop-up' operations; post-spray meetings; monitoring and evaluation; shipping; spray equipment; and personal protective equipment.

3 National labour; local office leases, utilities and maintenance; office equipment and supplies; office services and management transport. Considered to be a yearly fixed cost (occurring once, regardless of the number of sprays).

Table A11.1: Cost of indoor residual spraying in other studies

Location	Cost per person (US$)
United Republic of Tanzania	2.45 (*3*)
Kenya highlands	0.88 (*4*)[a]
KwaZulu Natal, South Africa	4.93 (*3*)
	4.15 (*5*)
Rural Lubombo Spatial Development Initiative, Mozambique	4.94 (*3*)
	4.78 (*5*)
	4.96 (*6*)
Peri-urban Lubombo Spatial Development Initiative, Mozambique	3.48 (*3*)
	2.85 (*6*)
Not specified	5.76 (*7*)[b]

From reference (*8*)
a Only cost of insecticide
b Cost per child under 5 years of age

Hypotheses used to model the cost of IRM in geographical areas in which long-lasting insecticidal nets are the main vector control tool.

Inputs. The costs of IRS are based on the same source as above; the costs of insecticide-treated nets are based on a review of 14 programmes for the distribution of long-lasting insecticidal nets (LLINs) in five countries cited in the *Roll Back Malaria Progress and Impact Series* (*9*), in which the cost of LLINs per treated-net year of protection was estimated to be US$ 2.70.

Results of similar studies. Yukich et al. (*5*) estimated the costs of two IRS and five insecticide-treated net programmes including mass, targeted public and private distribution strategies. The cost per person-year of protection in IRS programmes was US$ 3.27 in KwaZulu Natal (one annual spray of DDT and pyrethroids) and US$ 3.90 in Mozambique (one annual spray of DDT and two sprays of carbamates), whereas the cost of LLINs per treated-net year of protection ranged from US$ 2.04 in Malawi to US$ 4.14 in Senegal. If the interventions studied were to be implemented in combination, the costs would be similar to those of pyrethroid-based IRS and LLIN combinations as outlined in section 2.5 of the GPIRM.

Detailed costs of resistance monitoring.

Cost of designing a monitoring plan. For national malaria control programmes with the required entomological capacity, preparation of a monitoring plan will be a routine task and will not entail significant additional costs. For countries that lack capacity, external support may be required, which would imply additional costs ranging from US$ 5000 (for a local workshop) to US$ 25 000 (for a workshop with two or three international experts).

Cost of building national capacity for routine monitoring of insecticide resistance. Routine monitoring requires the collection of mosquitoes and routine susceptibility testing. Information on monitoring of insecticide resistance in Senegal, the United Republic of Tanzania and Zambia indicates that training in basic field entomology and insecticide resistance testing could cost US$ 30 000–36 000. Training is generally required annually, but the scope could decrease after the first year, depending on the level of staff turnover and modifications in operational procedures.

Cost of routine susceptibility testing to identify resistance. Such testing generally includes basic general entomological surveillance, such as species identification. The cost of collecting and testing mosquitoes usually includes staff wages and per diem (for supervisors, field technicians and assistants), field equipment (susceptibility test kits, cooler boxes, torches and other consumables), transport costs, and computer and information technology costs. The cost depends largely on the number of sentinel sites. In Senegal and the United Republic of Tanzania, where project leaders are employed to oversee monitoring, the annual cost per sentinel site of routine monitoring with susceptibility tests is about US$ 5500 and US$ 8000, respectively. In Zambia, where the chief country entomologist is the project leader, the annual cost is approximately US$ 2500.

Cost of testing to identify resistance mechanisms. According to the WHO *Test procedures for insecticide resistance monitoring in malaria vector mosquitoes (10)*, if the mortality rate of the sampled mosquitoes in susceptibility tests is lower than 98%, molecular, biochemical or synergy testing should be performed to assess the resistance mechanism.

- ***Molecular testing.*** Molecular testing can be conducted either by outsourcing it to regional laboratories or building national laboratory and testing capabilities. If testing is outsourced, the approximate cost per mosquito tested is US$ 10, which includes DNA extraction, species identification, genotypes of *kdr* and ace-1 and testing for sporozoites.[1] This cost is based on the assumption that laboratory capacity is available in research institutes, which should be funded and equipped appropriately. If 150 mosquitoes are tested with the four insecticide classes, the testing cost would be US$ 1500 per sentinel site, with an additional cost for freight or courier of US$ 20–70, depending on the location of the laboratory.
- ***Cost of building and maintaining national laboratory and testing capabilities.*** If countries decide to invest in facilities for molecular testing, they must foresee initial set-up costs (principally the cost of building the laboratory and a full set of equipment and training) and then annual running costs (principally reagents, other materials and personnel). Information from Sudan suggests that, for a large country with 15 sentinel sites, the initial set-up cost is about US$ 300 000, and the annual cost is about US$ 30 000.
- ***Biochemical testing.*** As discussed in section 1.2, biochemical testing is less technically demanding than molecular testing but still requires laboratory equipment. This type of testing is generally done in countries, as it requires fresh mosquitoes, which are difficult to transport. The cost of biochemical assays includes running costs of about US$ 1–2 per mosquito[2] and an investment in equipment of about US$ 5000 (for purchasing a refrigerator and spectrophotometer).[1] For countries with limited entomological capacity, additional costs should be foreseen for training in biochemical testing (not presented here).

Hypotheses used for estimating overall costs of implementing the GPIRM (see Table 3, page 76).

- **Pillar 1.** The costs shown in Table 3 are based on the assumption that a comprehensive situation analysis was conducted in all malaria-endemic countries and that IRM strategies are implemented. The cost of IRS rotations has been estimated for all countries in sub-Saharan Africa currently using IRS. In addition, the costs of combinations of interventions have been estimated for 5% of sites currently using LLINs. To account for other regions of the world that are implementing IRM strategies, a 20% increment was used.
- **Pillar 2.** The estimated cost of monitoring presented in Table 3 is based on the assumption of routine susceptibility testing in all malaria-endemic countries at 10 sentinel sites each, general entomological surveillance in 50 countries that do not currently have it, external molecular testing in 80 countries, the setting up of laboratories in 20 countries and the establishment of a national database in all countries.
- **Pillars 3, 4 and 5.** The estimated cost of development of new vector control tools includes a 10% annual increase over the estimate of the RBM Global Malaria Action Plan for research and development in vector control. The estimated cost of filling gaps in knowledge on insecticide resistance takes into account measuring operational impact in 50 countries, genetic and metabolic research, and research into management strategies. The estimate for enabling mechanisms take into account a quarterly data review in order to coordinate functional national technical advice in all countries, two annual meetings between national advisory committees and experts, travel of technical experts to countries to provide ad hoc support, and one annual meeting to coordinate all measures.

1 Estimate by researchers at the Liverpool School of Tropical Medicine

2 As most of this cost is for labour, it can vary greatly depending on location.

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ANNEX 12 DEFINITIONS

Combination	Use of two or more tools for vector control; often refers to the combined use of insecticide-treated nets and indoor residual spraying.
Concurrent resistance mechanisms	Both target-site and metabolic resistance mechanisms are present in the same vector.
Control failure	An intervention has virtually no effect on transmission or fails to prevent an uncontrolled resurgence in malaria cases.
Cross-resistance	Resistance to one insecticide confers resistance to another, even if the insect has not been exposed to the second insecticide.
Fitness cost	Populations of insects that have never been exposed to insecticides are usually fully susceptible, and resistance genes are rare in those populations. This is assumed to be due to a 'fitness cost', in that insects that have the resistance gene are somehow weaker and there is therefore selection against the resistance genes in the absence of the insecticide.
Frequency of resistance	Degree to which resistance is present in a vector population , depending on two factors: the gene frequency of the resistance in the local vector population, and the strength of the resistance conferred by the gene (that is, the degree to which higher doses of insecticide are tolerated by individual insects carrying the gene).
LD50	Lethal dose 50%: the dose expected to kill exactly 50% of exposed insects.
Metabolic resistance	Changes in the amount or specificity of a metabolic enzyme so that it detoxifies an insecticide before it reaches the target site.
Mixture	Two or more compounds of different insecticide classes mixed in a single product or formulation so that the mosquito is guaranteed to come into contact with both classes at the same time; approach similar to drug combination therapies.
Mosaic	Application of two or more insecticides by subdividing a given geographic area, such that each subdivided sector is sprayed with a different class of insecticide.
Multiple resistance	Two or more different resistance mechanisms are present in one vector. The different resistance mechanisms may combine to result in resistance to multiple classes of products.
Phenotypic resistance	Development of an ability, in a strain of insects, to tolerate doses of toxicants, which would prove lethal to the majority of individuals in a normal population of the same species.
Polymerase chain reaction	Technique used in molecular biology to amplify a single or a few copies of a piece of DNA by several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.
Protective efficacy against malaria deaths	Reduction of malaria-associated mortality with a given vector control tool.
Protective efficacy against malaria incidence	Reduction in malaria incidence associated with a given vector control tool.
Reduced effectiveness	An intervention still results in a degree of transmission reduction but performs less well or with a shorter duration of effectiveness than in the absence of resistance.
Resistance ratio	A measure of the strength of resistance; ratio of how much more insecticide is required to kill resistant vectors than susceptible ones.
Rotations	Rotating a set number of insecticide classes such that vectors are exposed to a different class in each transmission season.
Susceptibility tests	Vectors are given a controlled dose of insecticide and observed to see whether they die or survive; a measure of phenotypic resistance.
Synergist	A synergist is a chemical that enhances the effect of the primary insecticide used; it increases the exposure of an insect to the insecticide as though the dose had been increased.
Target-site resistance	Changes in the target site that reduce the binding of insecticides, e.g. on the surface of nerves.

For more information, please contact:

Vector Control Unit
Global Malaria Programme
World Health Organization
20 avenue Appia
1211 Geneva 27
Switzerland
gmpvectorcontrol@who.int
http://www.who.int/malaria.

ISBN 978 92 4 156447 2

Control of residual malaria parasite transmission

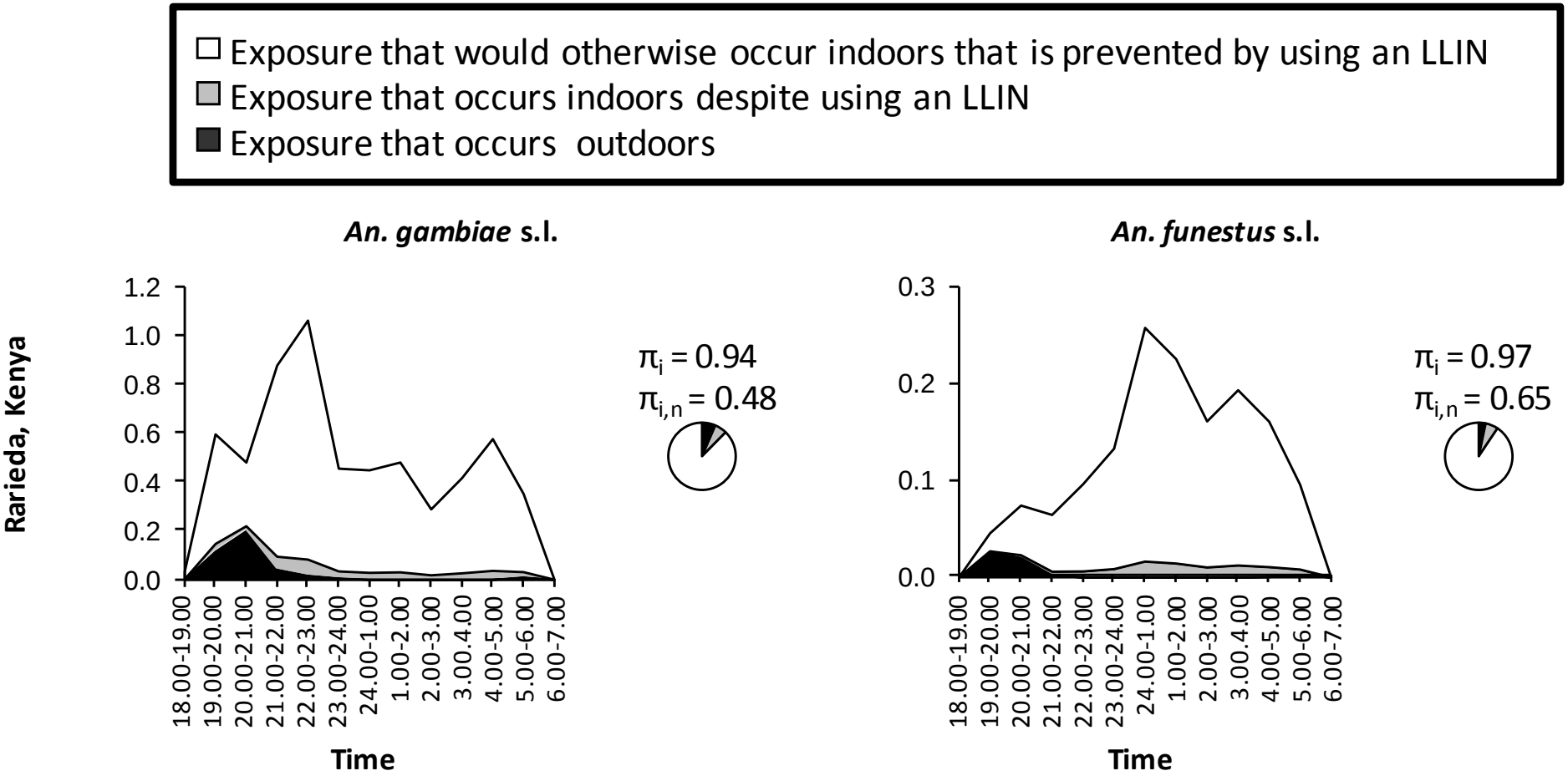
Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 10 September 2014

Gerry Killeen
on behalf of Malaria Vector Control Technical Expert Group

World Health Organization

GLOBAL MALARIA PROGRAMME

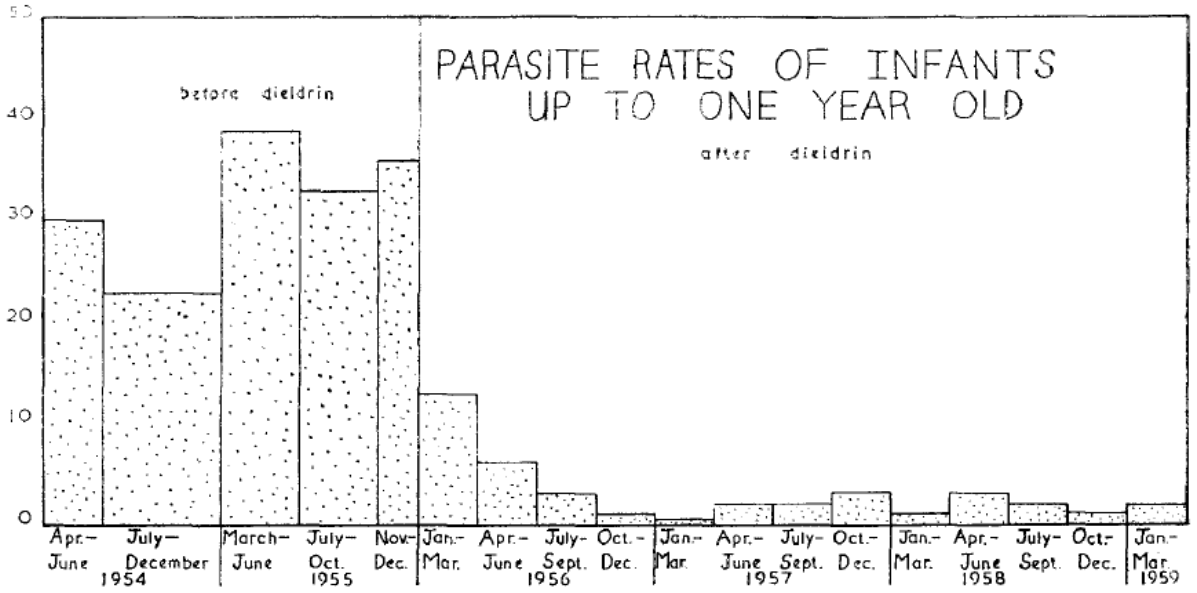
Stereotypical African malaria vectors



Int J Epidemiol (2013) 42: 235
Malaria Journal (2014) 13: 330

Persisting residual transmission

- Indeed, evidence from a variety of settings over the last half century indicates that residual malaria parasite transmission occurs even in the presence of well-implemented LLINs or IRS, or in other situations where LLIN use or IRS are not practical.

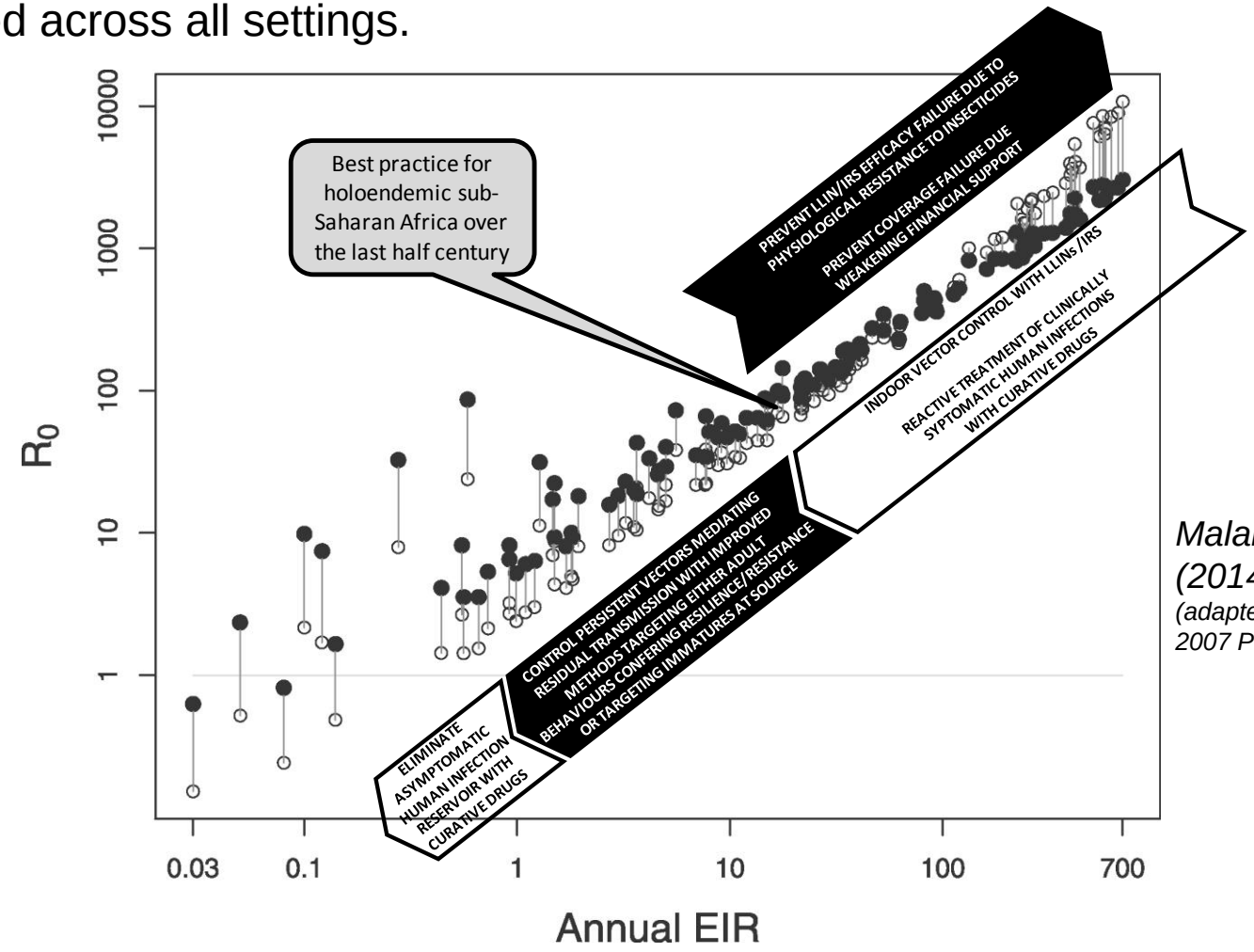


TRSTMH (1960) 54: 342

- Such transmission is maintained due to a combination of human and vector behaviours, for example when human populations are away from houses, or when local mosquito vector species exhibit one or more behaviours that allow them to avoid the core interventions.

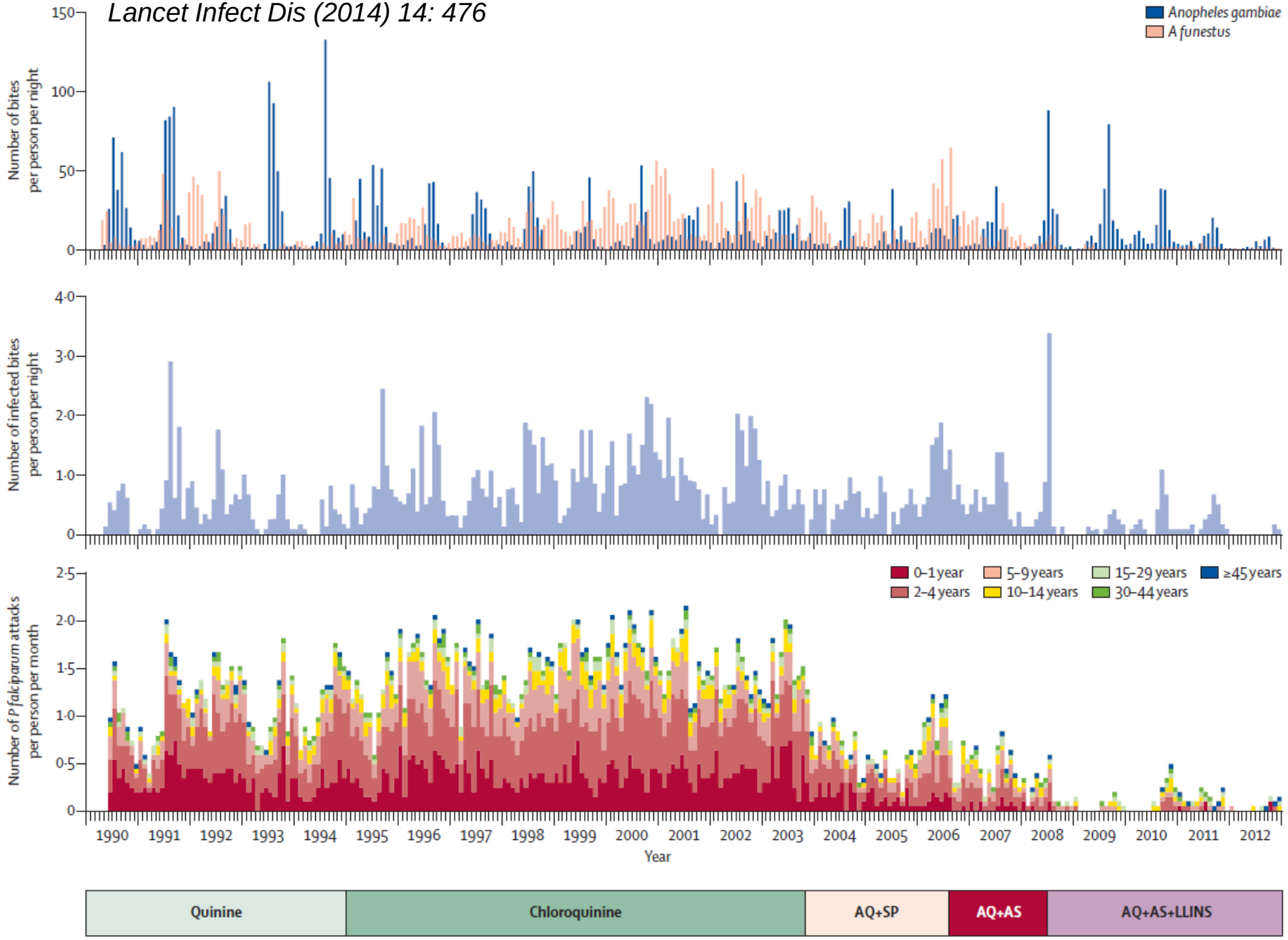
Closing the vector control gap

- While the factors that can limit the effectiveness of existing interventions are indeed of vital importance and require due attention, it is unlikely that, even in the event of full and correct deployment, malaria parasite transmission would be halted across all settings.



Malaria Journal (2014) 13: 330
(adapted from Smith et al. 2007 PLoS Biol 5:e42)

Lancet Infect Dis (2014) 14: 476



A sticky situation

Residual Transmission of Malaria: An Old Issue for New Approaches

Lies Durnez and Marc Coosemans

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55925

From Wikipedia, the free encyclopedia:

- **Residual:** A remainder left over at the end of some process.
- **Residue:** Whatever remains after something else has been removed.

1. Natural or insecticide-induced behavioural avoidance of treated surfaces indoors

PLoS One (2012) 7: e31481

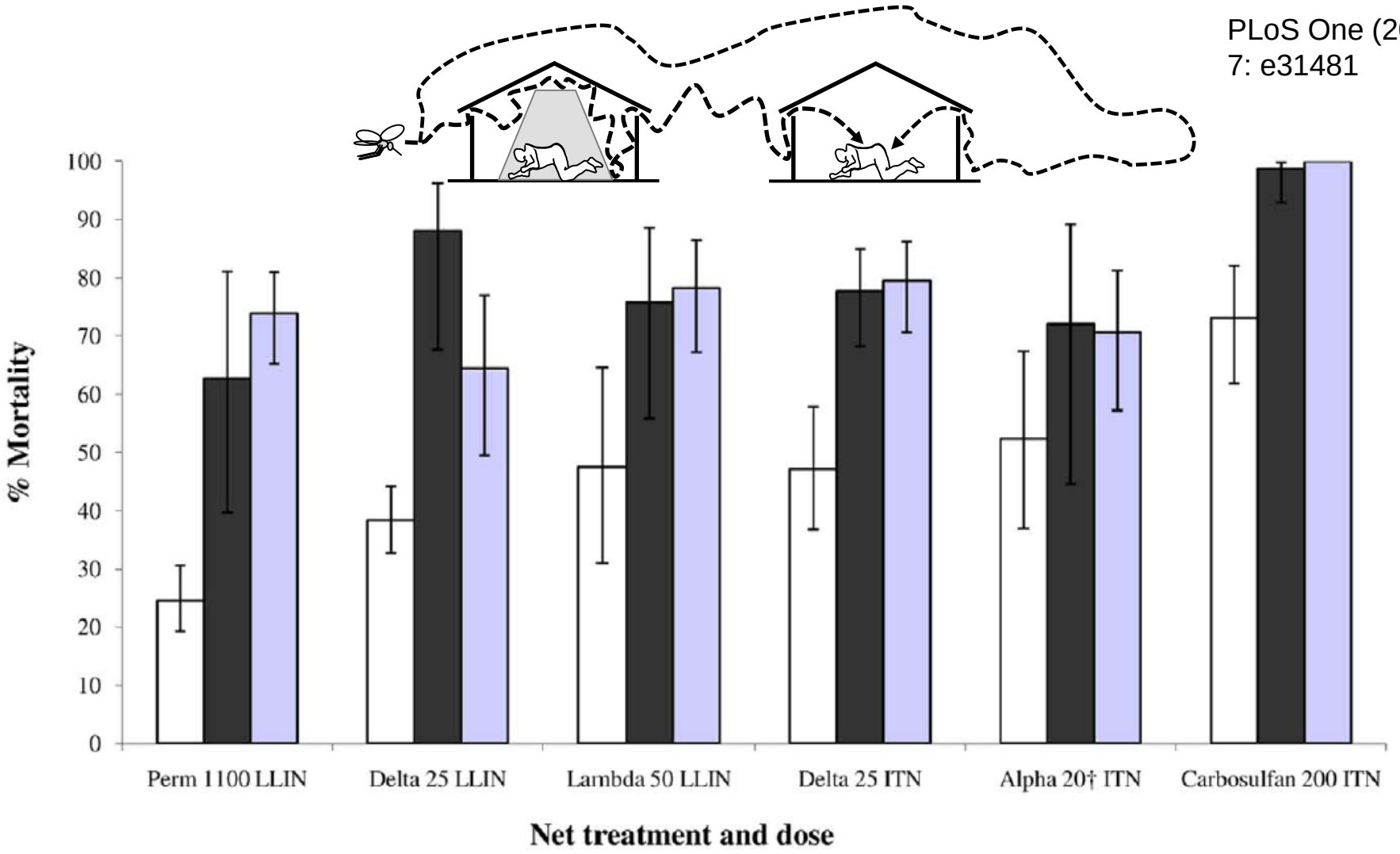


Figure 2. Overall mortality of free flying mosquitoes ±95% confidence interval. *Anopheles arabiensis* (white), *An. gambiae* (black) and *An. funestus* (grey) species.
doi:10.1371/journal.pone.0031481.g002

2. Exposure outside of houses or sleeping spaces

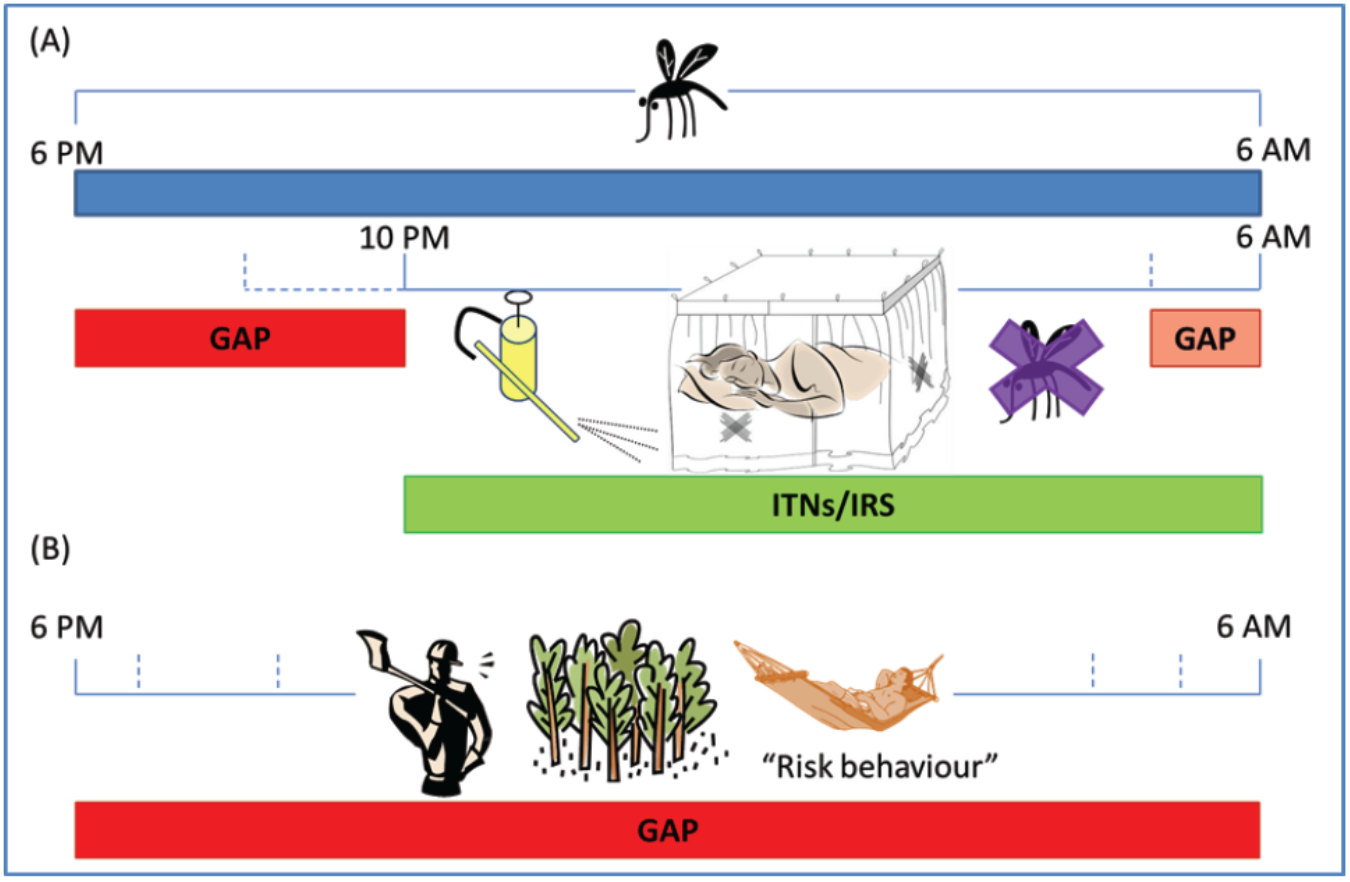
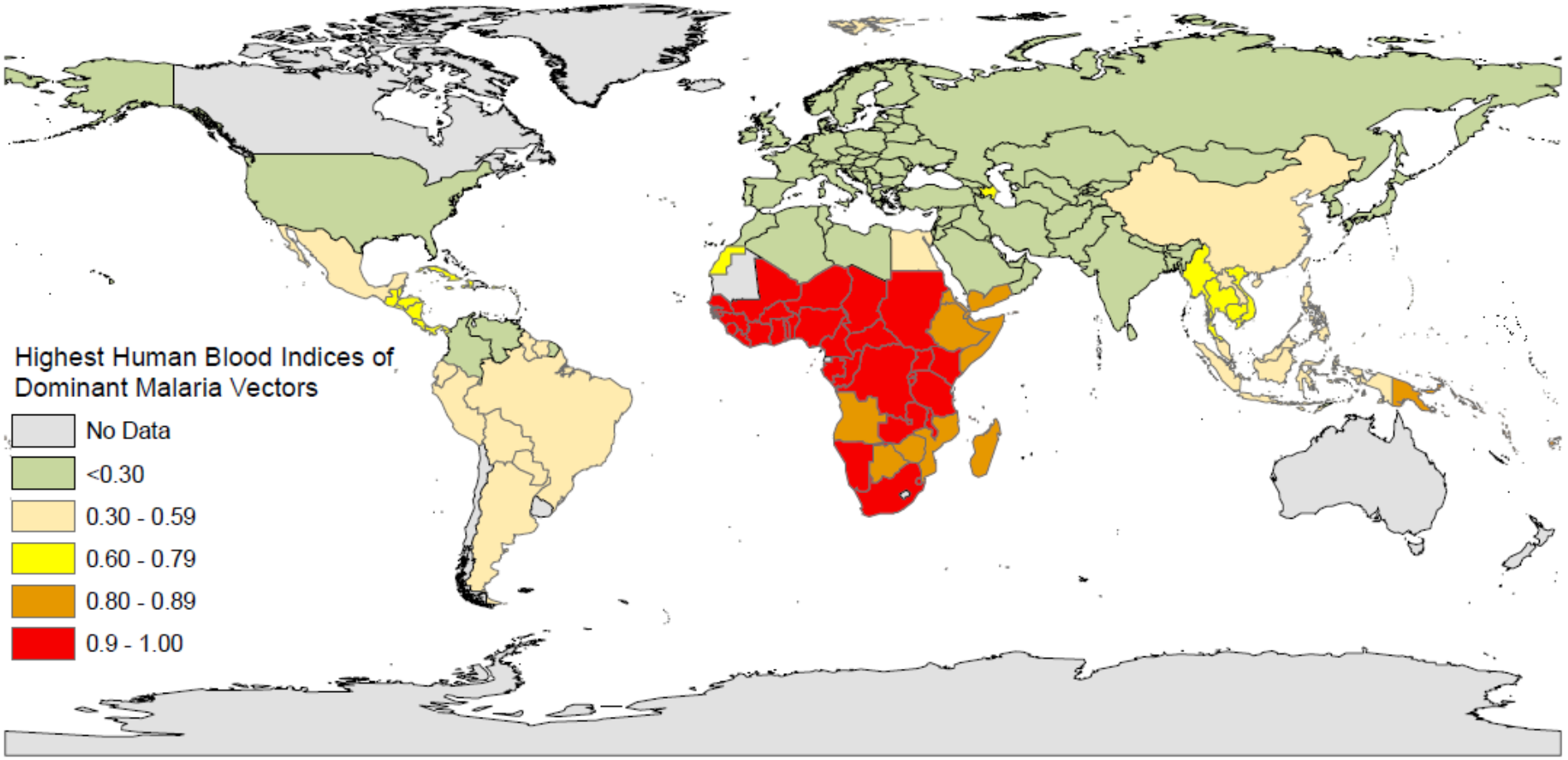


Figure 2. Protection 'gap' when only indoor insecticide-based vector control measures are applied. Anophelines generally bite between 6pm and 6am. ITNs will only protect from infective bites that are acquired indoors, and during sleeping time. IRS only target mosquitoes that rest indoors. Therefore, there is a gap in protection both indoors and outdoors before and after people go to bed (A), but also for people conducting outdoor activities during the night (i.e. 'risk behaviour') (B).

3. Feeding upon animals



Malaria Journal (2014) 13: 330

4. Resting away from indoor-treated surfaces

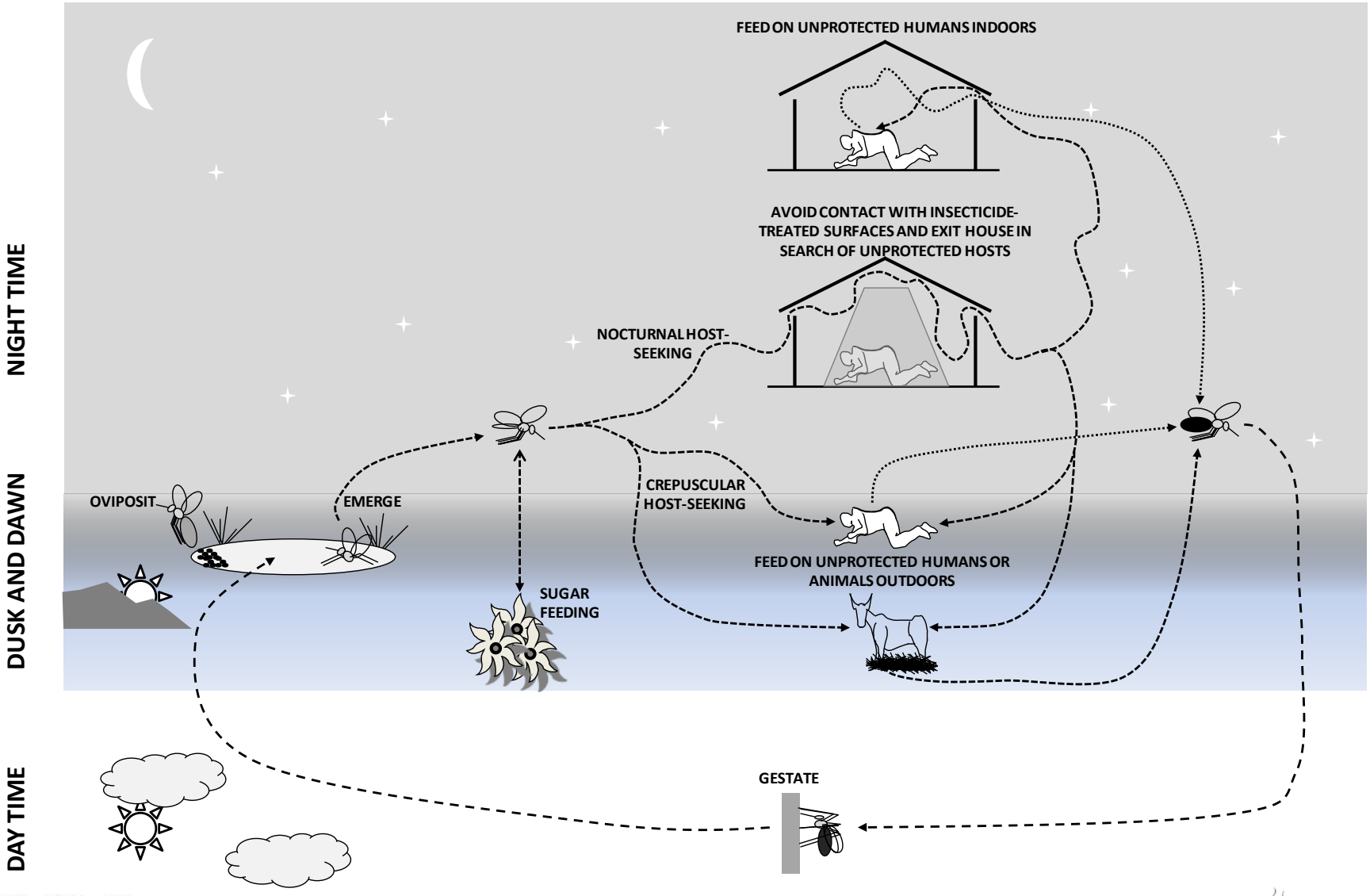
Figure 2 Barrier screens were constructed between village houses and potential resting and/or oviposition sites, as shown in Haleta village, Solomon Islands (A) and Mirap village, Papua New Guinea (B). Potential resting sites among the vegetation and the primary oviposition site (a brackish water swamp) can be seen to the right of the barrier screen while village houses and animal pens (seen to the left of the barrier screen) provide potential blood meals.

Malaria Journal (2013) 12: 49

Main vector behaviours maintaining residual transmission

1. Reduced house entry, diversion from contact with indoor treated surfaces or nets, or early exit from houses (such behavioural avoidance often occurs naturally but may be due to insecticide-induced irritancy, repellency and/or toxicity).
2. Feeding upon humans when and where they are not protected, including indoors at times when humans are not under nets, outdoors, or when away from sprayed houses due to occupational, domestic or recreational activities.
3. Feeding upon animals in preference to humans and thereby reduced contact with indoor treated surfaces or nets.
4. Resting outdoors away from indoor treated surfaces.

Causes of persisting residual transmission



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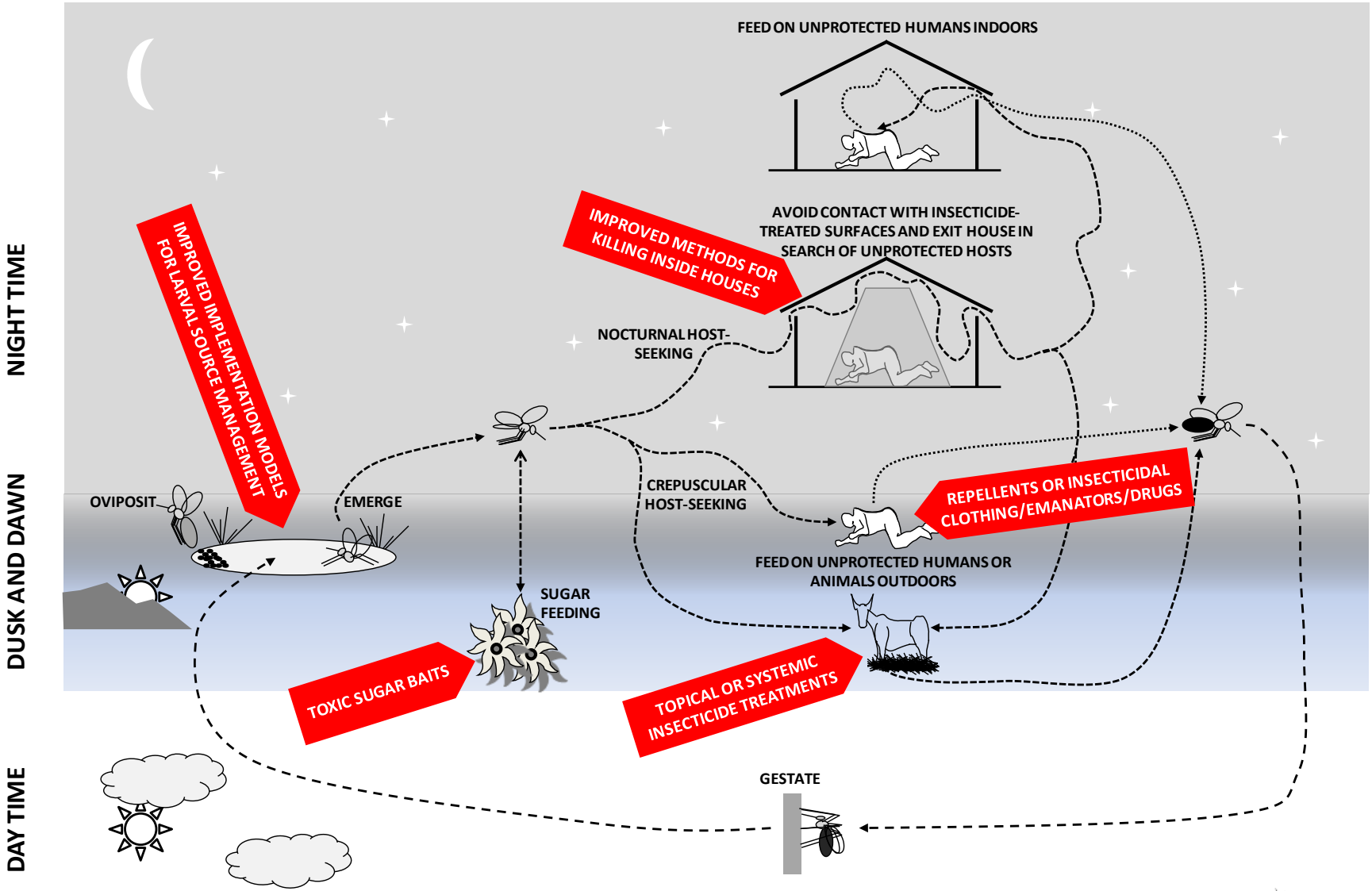
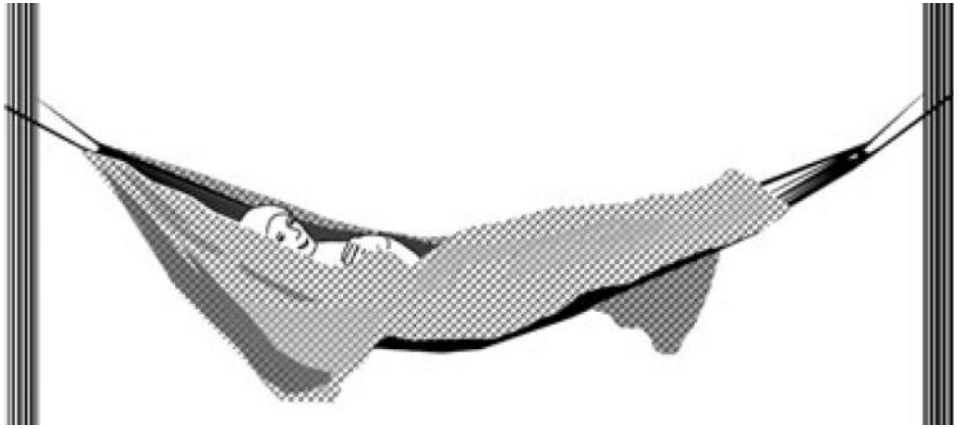
Solutions to persisting residual transmission



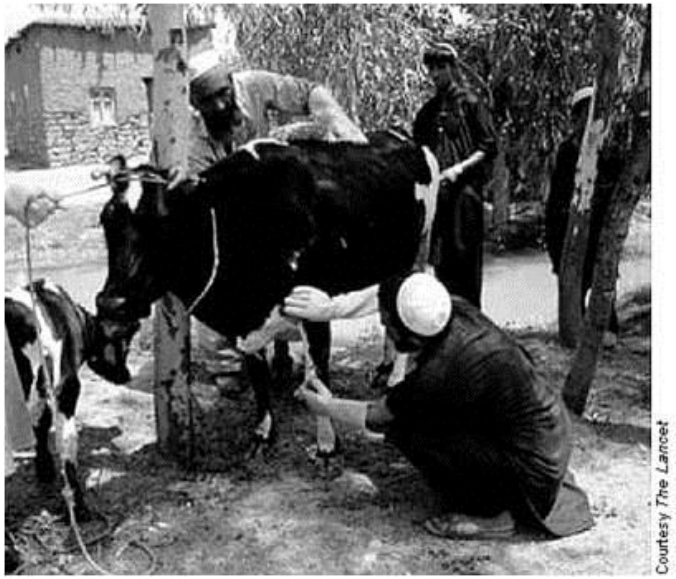
Protecting humans outdoors

WHILE ASLEEP



WHILE ACTIVE

Insecticide-treated livestock, attractive odor lures and sugar sources



Lancet (2001) 357: 1837

Parasites & Vectors (2010) 3: 12

PLoS One (2014) 8: e81468

Malaria Journal (2012) 9: 262

Need for new tools and strategies to address residual transmission

- National malaria control programmes must prioritise the implementation of current tools whilst improved or novel vector control interventions are under development and validation.
- Meanwhile, the focus should be to assess the following strategies for effectiveness, practicability and affordability:

1. Exclude or deter indoor entry, feeding and resting using physical screening barriers, repellents, or insecticides with no deterrent properties;
2. Prevent successful outdoor feeding by using insecticide-treated clothing or repellents to directly protect people;
3. Reduce adult vector densities or transmission potential otherwise by:
   a) Outdoor attractants to lure and trap/kill mosquitoes
   b) Topical or systemic insecticides for livestock that kill mosquitoes during or after feeding, or
   c) Applying insecticides to natural sugar sources or by introducing insecticidal sugar baits.

Learning by doing

- Following the establishment of a sufficient entomological surveillance and monitoring system, national malaria control programmes may consider selectively piloting at sub-national scales promising new vector control tools in order to generate local evidence on impact and acceptability.
- The deployment of new tools may be progressively adapted and expanded based on robust entomological and epidemiological surveillance and monitoring data.

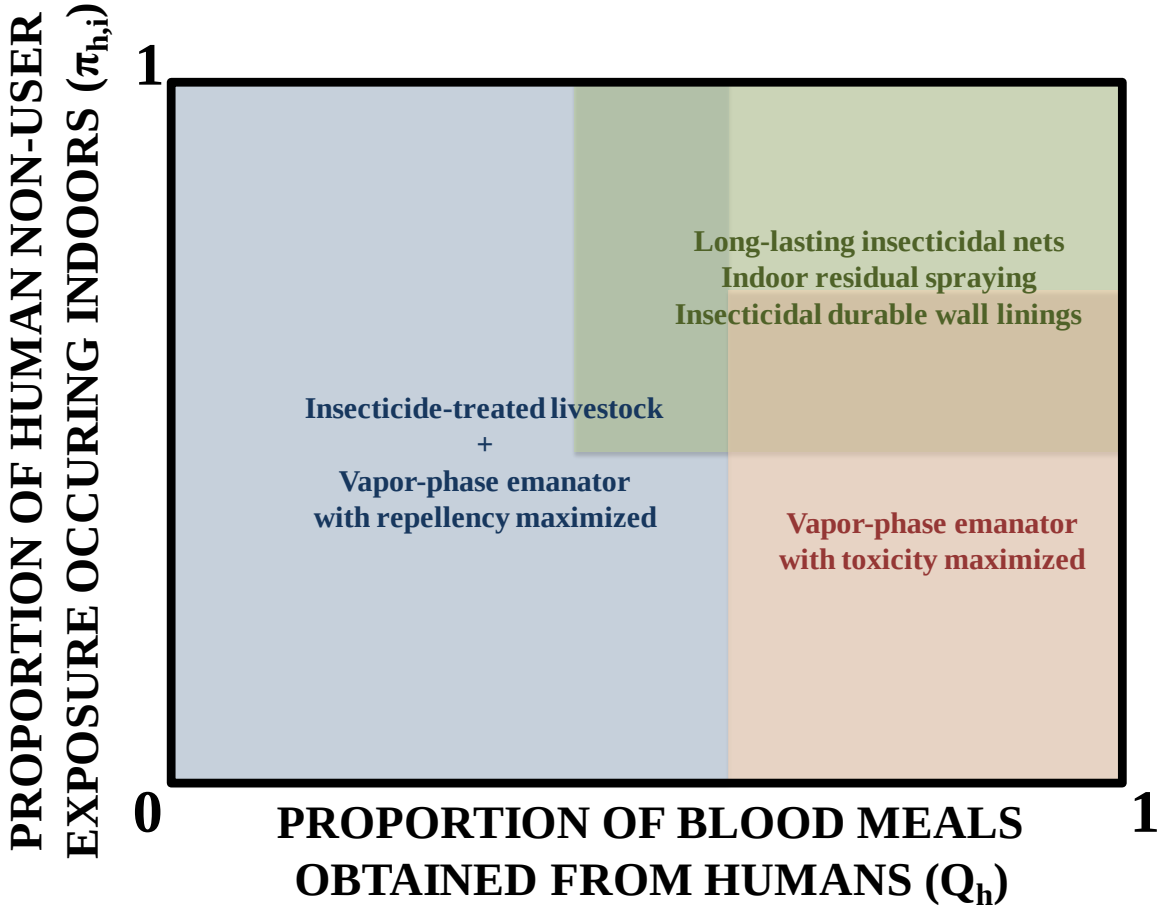
FIG. 52.—Antilarval inspector equipped for action.

FIGS. 50 and 51.—Mixing and broadcasting Paris green and dust.

- Such pilot implementation will not only allow optimization of the effectiveness of such tools at national level, but will also contribute to the global evidence base required to inform the development or improvement of tools and define the conditions for their deployment.

Stratification based on behaviour-matched interventions

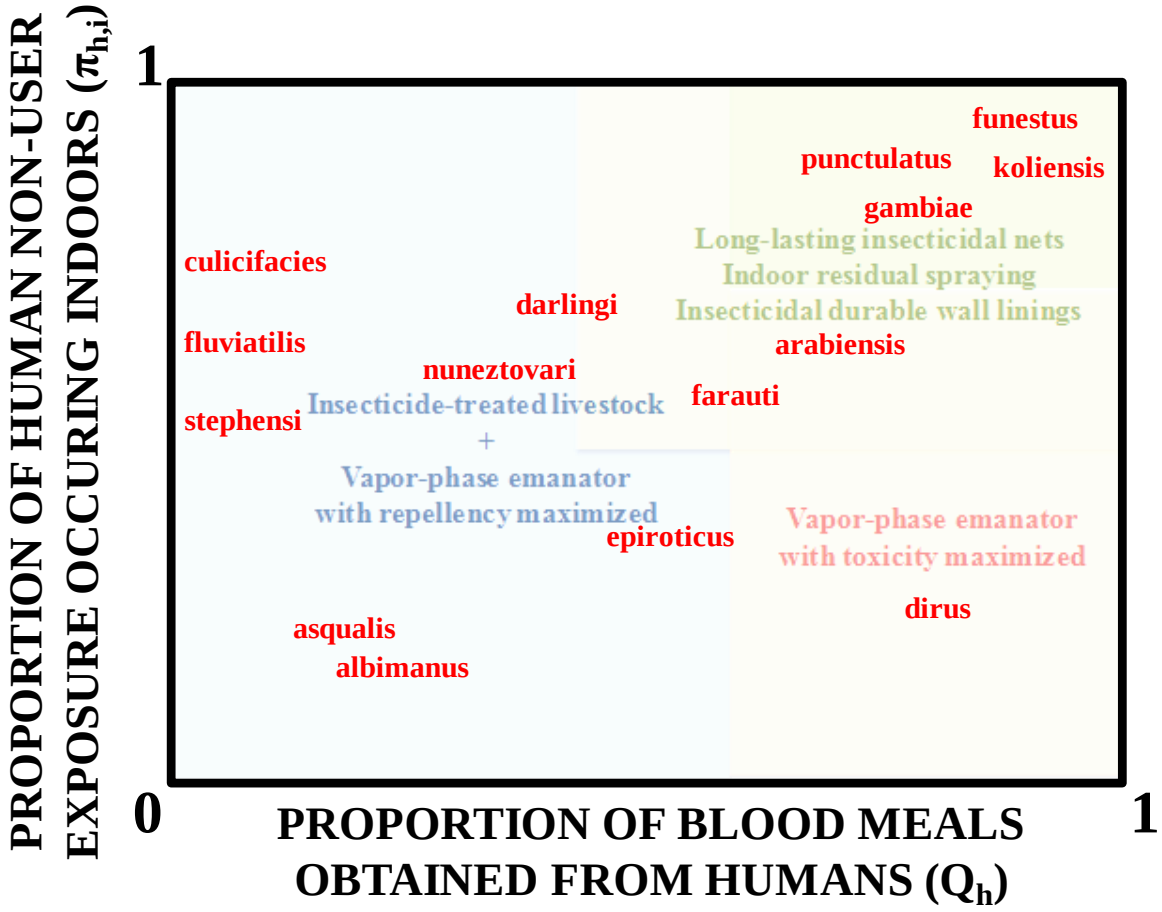
- Epidemiological stratification, sociological and demographic information, and entomological surveillance and monitoring data must be used to inform the implementation of existing and new vector control interventions across all settings.



Malaria Journal (2014) 13: 146

Stratification based on behaviour-matched interventions

- Epidemiological stratification, sociological and demographic information, and entomological surveillance and monitoring data must be used to inform the implementation of existing and new vector control interventions across all settings.



Malaria Journal (2014) 13: 146

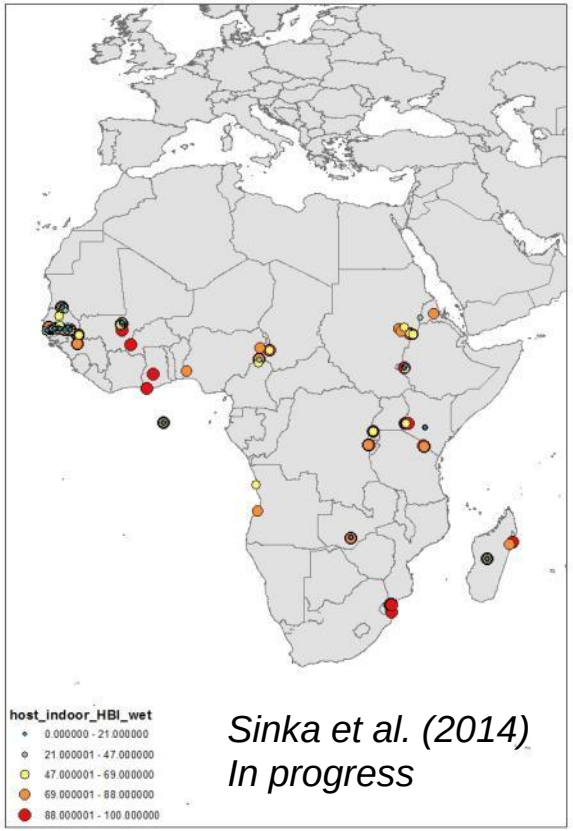
Limitations of existing data from research platforms

- Much of our knowledge on malaria vector biology and behaviour has been derived from small-scale research projects rather than longitudinal routine surveillance. This information is therefore of limited geographical scope and is often outdated.

WHERE AND WHEN HUMANS ARE EXPOSED TO MOSQUITO BITES

Int J Epidemiol (2013) 42: 235

PROPORTION OF MOSQUITO BLOOD MEALS OBTAINED FROM HUMANS



Sinka et al. (2014) In progress

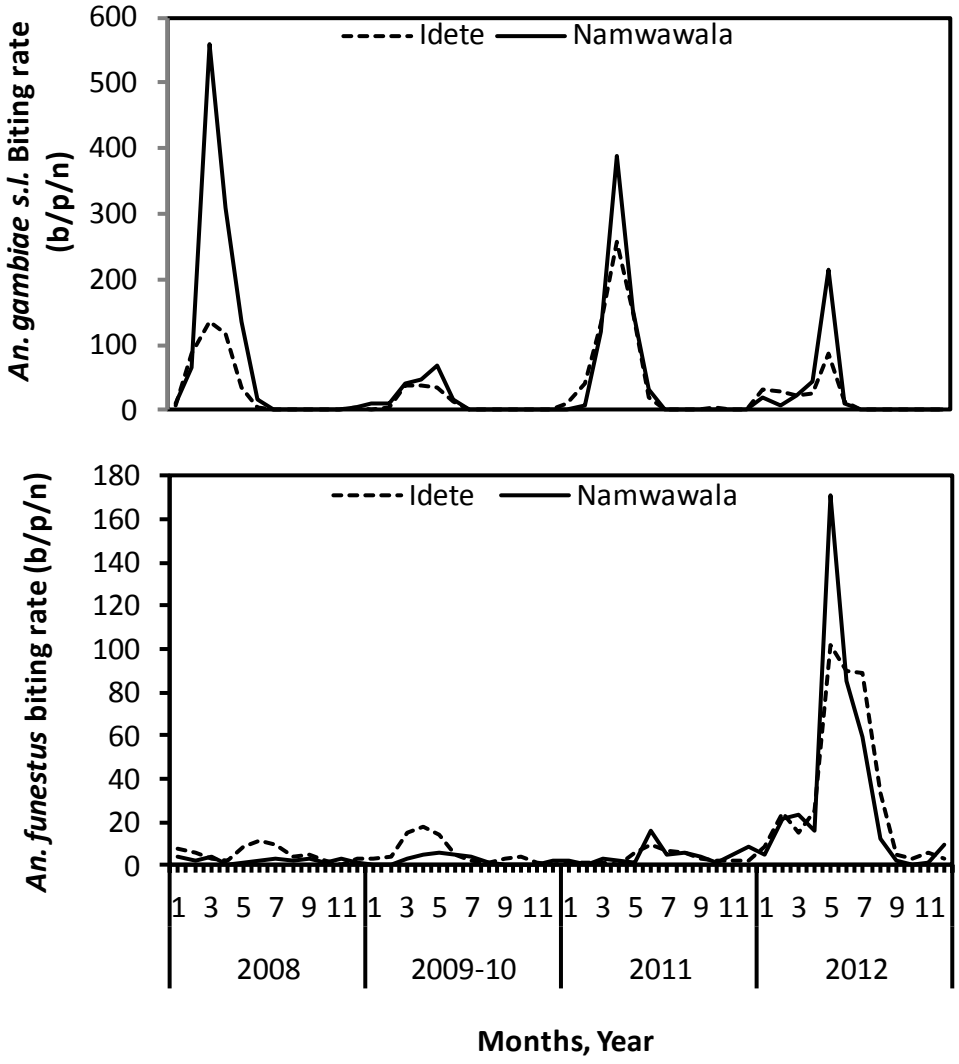
map malaria atlas project
seeg spatial ecology and epidemiology group
VecNet

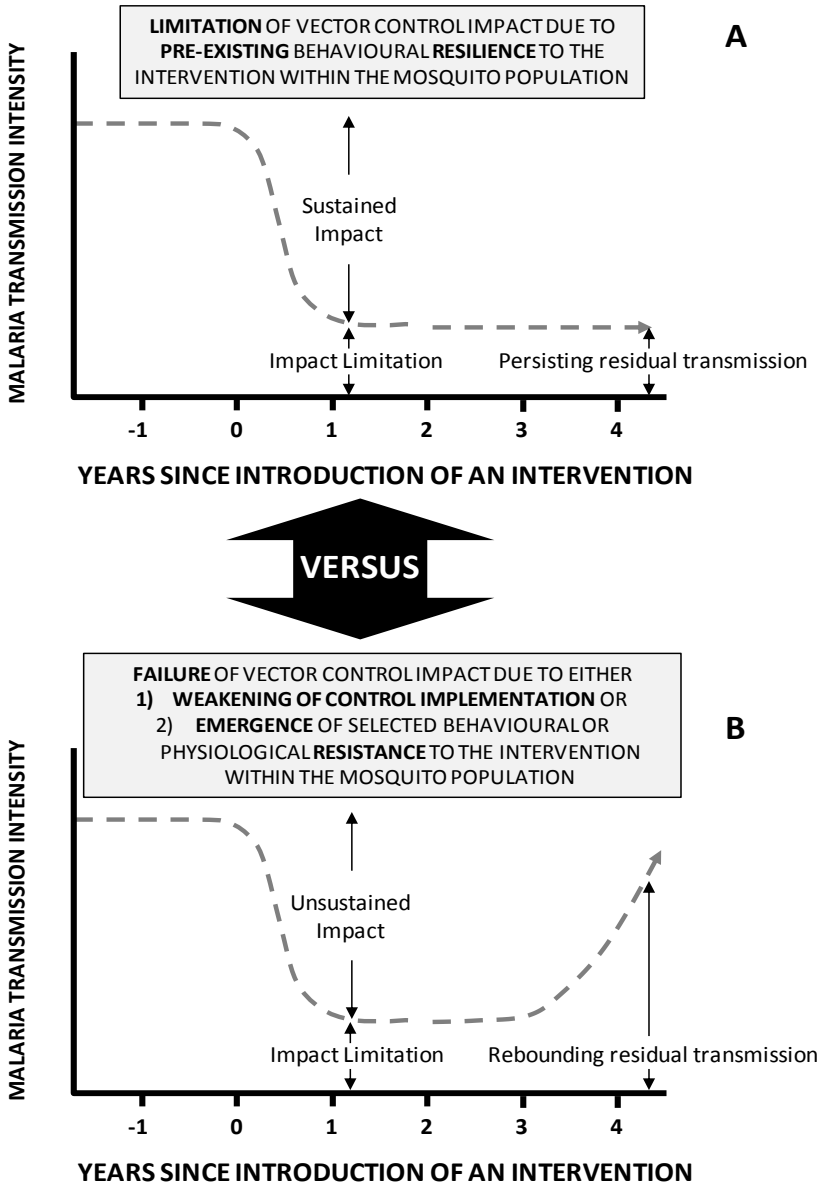
WHO Manual on Entomological Monitoring in Malaria Control and Elimination Programmes

- What are the major mosquito vectors present in the country and what is the specific contribution made to malaria transmission by each of the known or suspected vector species in each ecological zone?
- What are the long-term trends in vector species composition?
- What is the insecticide susceptibility status of the known or suspected vectors?
- Are the vector control interventions being implemented in the country effective against the vectors responsible for transmitting the malaria parasites in the different epidemiological situations encountered?
- Are those interventions still effective in the face of insecticide resistance and / or changes in mosquito behaviour?
- What are the specific behaviours of the mosquito vectors that may impact on the effectiveness of insecticide-based control interventions? (e.g. do they bite indoors or outdoors? Do they feed preferentially on humans or on domestic animals, or both? Do they rest inside houses or other structures, or do they rest outdoors? At what time of night do the different vector species bite?
- How does human behaviour and changes in human behaviour affect effectiveness of interventions?
- What are the characteristics of the preferred larval habitats of each of the known or suspected vectors and what is the geographic distribution of those sites?

Remaining challenges of assessing vector behaviour

The need to assess vector response to interventions





Malaria Journal (2014) 13: 331; 225 & 330

Recommendations

- National malaria control programmes in collaboration with academic or research institutions should generate local evidence on the magnitude of the problem of residual transmission, including information on human and vector behaviour, and intervention effectiveness.
- Industry and their partners are encouraged to develop new tools to address residual transmission. Financial, human and infrastructural resources are urgently needed to support development, evaluation and implementation of such tools.
- National regulatory authorities should ensure that registration processes support the rapid availability to the local market of validated new vector control products.

Thank you

World Health Organization

GLOBAL MALARIA PROGRAMME

Control of residual malaria parasite transmission

Guidance note – September 2014

Background

The current core malaria vector control interventions are long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), with larval source management (LSM) applicable in certain settings where mosquito breeding sites are few, fixed and findable.[1,2,3] Long-lasting insecticidal nets reduce malaria parasite transmission mainly by killing or blocking mosquitoes that attempt to feed upon humans under nets. Indoor residual spraying kills mosquitoes and reduces longevity when they rest on insecticide-sprayed surfaces inside houses or other structures, usually after they have fed on occupants.

The effectiveness of these interventions relies on a number of factors including susceptibility of mosquitoes to the insecticides used, adequate coverage rates, quality and timely implementation, and user acceptance or compliance. While factors that can limit the effectiveness of existing interventions are extremely important and must be addressed, even full implementation of core interventions would not halt malaria parasite transmission across all settings.

Indeed, evidence from a variety of settings over the last half century indicates that *residual malaria parasite transmission* occurs even with good access to and usage of LLINs or well-implemented IRS,[4,5,6,7] as well as in situations where LLIN use or IRS are not practical. A combination of human and vector behaviours are responsible for this transmission, for example when people reside in or visit forest areas or do not sleep in protected houses[8,9] or when local mosquito vector species exhibit one or more behaviours that allow them to avoid the core interventions.

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1 World Health Organization (2012). *Larval source management – a supplementary measure for malaria vector control. An operational manual*. Geneva, Switzerland.

2 World Health Organization (2013). *WHO recommendations for achieving universal coverage with long-lasting insecticidal nets in malaria control*. Geneva, Switzerland.

3 World Health Organization (2014). *WHO guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets*. Geneva, Switzerland.

4 World Health Organization (1980). *The Garki Project: research on the epidemiology and control of malaria in Sudan Savanna of West Africa by L. Molineaux and G. Gramiccia*. Geneva, Switzerland.

5 Govella et al. (2013) Entomological surveillance of behavioural resilience and resistance in residual malaria vector populations. *Mal J*, 12: 124

6 Durnez and Coosemans (2014) Residual transmission of malaria: an old issue for new approaches. *In* Manguin, S. (Ed.). *Anopheles Mosquitoes – New Insights into Malaria Vectors*. ISBN: 978-953-51-1188-7, InTech.

7 Killeen (2014) Characterizing, controlling and eliminating residual malaria transmission. *Mal J*, In Press.

8 Monroe et al. (2014) "People will say that I am proud": a qualitative study of barriers to bed net use away from home in four Ugandan districts. *Mal J*, 13: 82.

9 Bhumiratana et al. (2013) Malaria-associated rubber plantations in Thailand. *Travel Med Infect Dis*, 11(1): 37-50.

The main vector behaviours that maintain residual transmission are:

1. Behavioural avoidance such as reduced house entry, diversion from contact with indoor treated surfaces or nets, and early exit from houses. Such avoidance often occurs naturally but may also be due to insecticide-induced irritancy, repellency and/or toxicity[4,5,10,11];
2. Feeding upon humans when and where they are not protected. This includes indoors if not under nets, outdoors, and away from protected houses due to occupational, domestic or recreational activities;
3. Feeding upon animals in preference to humans, thereby having reduced contact with indoor treated surfaces or nets; and
4. Resting outdoors away from indoor treated surfaces.

While much of our knowledge on malaria vector biology and behaviour has been derived from small-scale research projects rather than longitudinal routine surveillance, vector species behaviour is known to vary considerably both within and between locations as well as between seasons and years. There is also evidence that changes in behaviour have apparently been selected as a consequence of vector control and environmental change. Numerous vector species have therefore been implicated in residual transmission and important examples include *An*. *arabiensis* in many parts of Africa,[4,7-9] *An*. *dirus* in South-East Asia,[12] and *An. albimanus and An*. *darlingi* in the Americas.[13,14] In many malaria-endemic areas this residual transmission, maintained through a combination of human and vector behaviours, will render malaria elimination extremely difficult in the absence of new vector control interventions.

Need for new tools and strategies to address residual transmission

National malaria control programmes (NMCPs) must prioritize the implementation of current tools whilst improved or novel vector control interventions are under development and going through the validation process. Meanwhile, the focus should be on assessing the following strategies for effectiveness, practicality and affordability:

1. Exclude or deter indoor entry using physical screening barriers or repellents;
2. Following entry, prevent successful indoor feeding and/or resting using exit or other barriers, repellents, or insecticides with no deterrent properties;
3. Prevent successful outdoor feeding by using insecticide-treated clothing or repellents to directly protect people;
4. Reduce adult vector densities or transmission potential by:
    a. outdoor attractants to lure and trap/kill mosquitoes;
    b. topical or systemic insecticides for livestock that kill mosquitoes during or after feeding; or
    c. applying insecticides to natural sugar sources or by introducing insecticidal sugar baits.

[10] Chareonviriyaphap et al. (2013). Review of insecticide resistance and behavioural avoidance of vectors of human diseases in Thailand. *Parasites and Vectors*, 6: 280.

[11] Coetzee et al. (2013) Malaria in South Africa: 110 years of learning to control the disease. *Sth Africa Med Journal* 103: 10 (Suppl 2).

[12] Trung et al. (2005). Behavioural heterogeneity of *Anopheles* species in ecologically different localities in South East Asia: a challenge for vector control. *Trop Med Int Health*, 10: 251-262.

[13] Campos et al. (2012). Integrated vector management targeting *Anopheles darlingi* populations decrease malaria incidence in an unstable transmission area, in the rural Brazilian Amazon. Mal J, 23(11): 351.

[14] Chareonviriyapha et al. (1997). Pesticide avoidance in *Anopheles albimanus*, a malaria vector in the Americas. J Am Mosq Assoc, 13(2): 171-183.

Some of these strategies are relatively new and are still under development and some need to be adapted and evaluated in different malaria eco-epidemiological and socio-cultural contexts. The evidence base for informed deployment of improved or novel tools, new paradigms or combined usage with existing interventions, is currently limited. There is heavy reliance on small-scale studies or theoretical analyses with mathematical models, and empirical observations are required at large-scale to verify the added value of these interventions. Once the supporting evidence base is available, policy setting mechanisms within WHO will make appropriate recommendations for implementation by national programmes.

Proposed approaches to accelerate the availability and uptake of new tools

The development, optimization, validation and evidence-based deployment of vector control tools to address residual transmission will require the concerted effort of NMCPs and their partners, including industry, research and academia, and WHO. Whilst new tools are under development and in the process of validation, NMCPs should ensure that the core interventions are implemented optimally.

In collaboration with academic or research institutions, NMCPs should continue to generate local evidence on the magnitude of the problem of residual transmission, including information on human and vector behaviour, and intervention effectiveness. A clear understanding of human behaviour regarding the time and place of exposure to mosquito bites is important.[15]

Industry is further encouraged to develop new tools and technologies for targeting vector populations, which are specifically designed to interrupt residual transmission and thereby address the practical limitations of existing interventions. A costing comparison should be undertaken to ascertain the economic feasibility and scalability of candidate tools and approaches. This will allow prioritization of development initiatives and help to identify where further guidance is needed. Such guidance could include standardized protocols that support the appropriate design and implementation of field trials to determine the effectiveness of candidates across different settings. These trials may be coordinated via research consortia, which are more likely to be able to generate the necessary funding to support large-scale multi-country trials. The steps, procedures and evidence required to validate new forms of vector control tools/paradigms and to introduce them to market are outlined in the report of the first meeting of the WHO Vector Control Advisory Group.[16]

National malaria control programmes and partners may consider conducting well-designed pilot trials of promising new vector control tools in order to provide conclusive evidence on their local efficacy and acceptability. Where feasible, the establishment of experimental hut facilities and semi-field systems (cages or biospheres) at one or two representative sentinel sites will enable assessments of the anticipated field efficacy of new interventions alone or in combination. The deployment of new vector control tools may be progressively adapted and expanded based on robust entomological and epidemiological surveillance and monitoring data. For example, local academic and research institutions may provide additional capacity for advanced assessment of key parameters. Such pilot implementation will not only allow optimization of the effectiveness of tools at national level, but will also contribute to the global evidence base required to inform the development or improvement of tools and define the conditions for their implementation.

[15] Moiroux et al. (2014). Human exposure to early morning *Anopheles funestus* biting behaviour and personal protection provided by long-lasting insecticidal nets. *PLoS One*, 9(8): e104967.

[16] http://www.who.int/neglected_diseases/vector_ecology/VCAG_resources/en/

Epidemiological stratification, sociological and demographic information, and entomological surveillance and monitoring data[17] must be used to inform the implementation of existing and new vector control interventions across all settings. Entomological surveillance must include periodic assessment of vector species composition and abundance, time and place of biting and resting, blood meal sources, and insecticide susceptibility status in representative eco-epidemiological settings. Accurate measurement of key vector behaviours may require new or adapted surveillance tools and approaches.

Also essential is the monitoring of coverage, quality and impact of interventions, including durability of LLINs, insecticidal residual efficacy, and user acceptability and compliance. This will help to define the extent and sources of residual transmission, or other factors that compromise effective coverage, so that interventions can be selected and targeted accurately.[18]

National regulatory systems should facilitate rapid registration of new and validated tools to allow timely deployment.[19] This will require close coordination between national regulatory authorities, NMCPs and vector control product manufacturers.

Establishment and maintenance of entomological surveillance and vector control monitoring systems as well as testing of new tools will require enhanced and sustained human and infrastructural capacity as outlined in previous WHO guidance.[20] Technical training and commitment of resources to entomological surveillance at national, provincial and district levels should be a priority. This also provides an opportunity to strengthen and institutionalize national expertise for operational research within NMCPs.

It is essential that global partners, including malaria endemic countries, continue to invest in local malaria research and control initiatives that support the development and field validation of new forms of vector control tools and technologies for controlling residual transmission. The WHO Vector Control Advisory Group will continue to support the evaluation of such tools, technologies and paradigms in order to speed up their availability for deployment. The WHO Pesticide Evaluation Scheme (WHOPES) requires strengthening and support to expand capacity to accommodate these new developments in the area of efficacy and safety for product specifications.

Conclusions

Universal coverage with LLINs or IRS where appropriate, remains the highest priority for investments in malaria vector control. However, there are many settings in which complete interruption of malaria parasite transmission cannot be achieved by these interventions alone, even with high levels of coverage and best practice implementation. There is therefore an urgent need for new WHO-recommended tools, technologies and guidance to address residual transmission of malaria parasites. Robust entomological surveillance, monitoring and operational research are also required to assess the extent and relative contribution of residual transmission to malaria burden across different settings. This information will inform the implementation of novel or improved vector control tools beyond the existing core malaria vector control interventions.

[17] Note that a malaria entomological surveillance and monitoring manual is currently under development by WHO.

[18] Any shift from universal coverage with the core interventions must be undertaken with caution, be well informed by robust local epidemiological and entomological data, and should consider the inherent transmission potential in the particular setting.

[19] Vontas et al. (2014) Framework for rapid assessment and adoption of new vector control tools. *Trends Parasitol*, In Press.

[20] World Health Organization (2013). *WHO guidance note on capacity building in malaria entomology and vector control*. Geneva, Switzerland.

Main recommendations

1. National malaria control programmes in collaboration with academic or research institutions should generate local evidence on the magnitude of the problem of residual transmission of malaria, including information on human and vector behaviour, and intervention effectiveness.

2. Industry and their partners are encouraged to develop new vector control tools to address residual transmission. Financial, human and infrastructural resources are urgently needed to support development, evaluation and implementation of such tools.

3. National regulatory authorities should ensure that registration processes support the rapid availability to the local market of validated new vector control products.

Antimalarial Dosage Recommendation Working Group Meeting 23-24 June 2014

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 10 September 2014

Karen Barnes, Nicholas White, Fred Binka, Gbenga Mokuolu, Elizabeth Juma, Paul Garner, Dave Sinclair, Joel Tarning, Sunil Parikh, (Anja Terlouw), Peter Olumese

World Health Organization

GLOBAL MALARIA PROGRAMME

Consolidated key recommendations

The following set of core principles, held by the guideline panel, form the foundation for the recommendations.

A: Prompt diagnosis and effective treatment

- Universal access to parasitological diagnosis of malaria beyond the reach of quality controlled microscopy, is possible with deployment of quality assured rapid diagnostic tests (RDTs), appropriate for use in primary healthcare and community settings.
- Uncomplicated malaria can progress rapidly to severe forms of the disease if left untreated, especially in people with no or low immunity. Severe malaria is almost always fatal without treatment and patients may die within hours. Therefore, programs should ensure access to prompt diagnosis and effective treatments within 24–48 hours of the onset of malaria symptoms.

Consolidated key recommendations (2)

B: Combination therapy

- Preventing or delaying resistance is essential to the success of both national and global malaria control strategies. To help protect the current and future antimalarial medicines, all episodes of malaria should be treated with at least two antimalarials with different mechanisms of action (combination therapy). To improve adherence to treatment fixed-dose combinations are highly preferable to co-blistered or co-dispensed combinations.

C: Rational use of antimalarials

- To reduce the spread of drug resistance, limit wastage of precious artemisinin-based combination therapies and better identify other febrile illnesses in the context of changing malaria epidemiology, there is a strong need to dispense antimalarials only to those who truly have malaria and promote adherence to full treatment course.

Diagnosing malaria

- All people with suspected malaria should have a parasitological test to confirm the diagnosis.

Treating uncomplicated *P. falciparum* malaria

- Treat adults and children (including infants, pregnant women in their second and third trimesters, and breastfeeding women) with uncomplicated *P. falciparum* malaria with an ACT.
- The current recommended first or second-line ACT treatment options are:
- Artemether plus lumefantrine; Artesunate plus amodiaquine; Artesunate plus mefloquine; Dihydroartemisinin plus piperaquine; Artesunate plus sulfadoxine-pyrimethamine.

Strong recommendation, High quality evidence

Treating uncomplicated *P. falciparum* malaria

- All ACTs should contain at least three days treatment with an artemisinin-derivative.

  Strong recommendation, High quality evidence

- In low transmission areas, also provide a single dose of 0.25mg/kg primaquine to reduce onward transmission of P. falciparum, without the need for G6PD testing (excluding pregnant and breastfeeding women and infants aged < 1 year).

  Strong recommendation, Low quality evidence

Treating uncomplicated *P. Falciparum* malaria in special risk groups

- Treat pregnant women with uncomplicated *P. falciparum* or chloroquine resistant *P. vivax* malaria in the first trimester with seven days of quinine plus clindamycin (if unavailable use an ACT).

- Treat infants weighing less than 5 kg with uncomplicated *P. falciparum* malaria with an ACT dosed at the same mg/kg target as for children weighing 5 kg.

Conditional recommendation, Low quality evidence

Treating uncomplicated *P. falciparum* malaria in special risk groups

- In HIV positive people with uncomplicated *P. falciparum* malaria avoid AS+SP if on treatment with co-trimoxazole, and avoid AS+AQ if on treatment with efavirenz.
- Treat travellers returning to non-endemic settings with uncomplicated *P. falciparum* malaria with an ACT.
- People with *P. falciparum* hyperparasitaemia are at increased risk of death and require close monitoring in addition to an ACT.

Conditional recommendation, Low quality evidence

Treating uncomplicated non-falciparum malaria

- In areas with chloroquine susceptible *P. vivax*, treat adults and children with uncomplicated non-falciparum malaria using either an ACT or chloroquine.

  Strong recommendation, High quality evidence

- In areas with chloroquine resistant *P. vivax*, treat adults and children with uncomplicated *P. vivax* malaria with an ACT (including infants, lactating women, and pregnant women in their second and third trimesters).

  Strong recommendation, High quality evidence

- Treat adults and children with proven uncomplicated *P. ovale*, *P. malariae*, or *P. knowlesi* malaria with either a three-day course of an ACT known to be effective in the region or chloroquine.

Preventing relapse in *P. vivax* or *P. ovale* malaria

- In addition to the ACT or chloroquine treat people with *P. vivax* or *P. ovale* malaria (excluding pregnant or breastfeeding women, infants <6 months, and people with G6PD deficiency) with a 14-day course of primaquine to prevent future relapse.

  Strong recommendation, Moderate quality evidence

- In people with mild to moderate G6PD deficiency, consider relapse prevention with primaquine 0.75 mg base/kg once a week for 8 weeks.

  Conditional recommendation, Very low quality evidence

- In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding is complete, then treat with 14 days of primaquine to prevent future relapse.

  Conditional recommendation, Moderate quality evidence

Treatment of suspected severe malaria pending transfer to higher level facilities (Pre-referral treatment)

- Treatment of suspected severe malaria pending transfer to higher level facilities (Pre-referral treatment).

- In settings where complete treatment of severe malaria is not possible, but injections are available, give adults and children a single dose of intramuscular artesunate and refer to an appropriate facility for further care. Use artemether or quinine if artesunate is not available.

  Strong recommendation, Moderate quality evidence

- In settings where intramuscular injections are unavailable, treat children below the age of six years with a single dose of rectal artesunate and refer immediately to an appropriate facility for further care.

  Strong recommendation, Moderate quality evidence

Treating severe malaria

- Treat adults and children with severe malaria with intravenous or intramuscular artesunate for at least 24 hours (including infants, pregnant women in all trimesters, and lactating women).

  Strong recommendation, High quality evidence

- Children weighing less than 20 kg should receive a higher dose of artesunate (3 mg/kg/dose) than larger children and adults (2.4 mg/kg/dose) to ensure an equivalent drug exposure.

  Strong recommendation based on pharmacokinetic evaluation

- Once the patient has received at least 24 hours of parenteral therapy, AND is able to tolerate oral therapy, complete treatment with three-days of an ACT.

  Strong recommendation, High quality evidence

Treating severe malaria

Population Pharmacokinetics of Intramuscular Artesunate in African Children With Severe Malaria: Implications for a Practical Dosing Regimen

ICE Hendriksen[1,2], G Mtove[3], A Kent[4], S Gesase[5], H Reyburn[6], MM Lemnge[5], N Lindegardh[1,2], NPJ Day[1,2], L von Seidlein[7], NJ White[1,2], AM Dondorp[1,2] and J Tarning[1,2]

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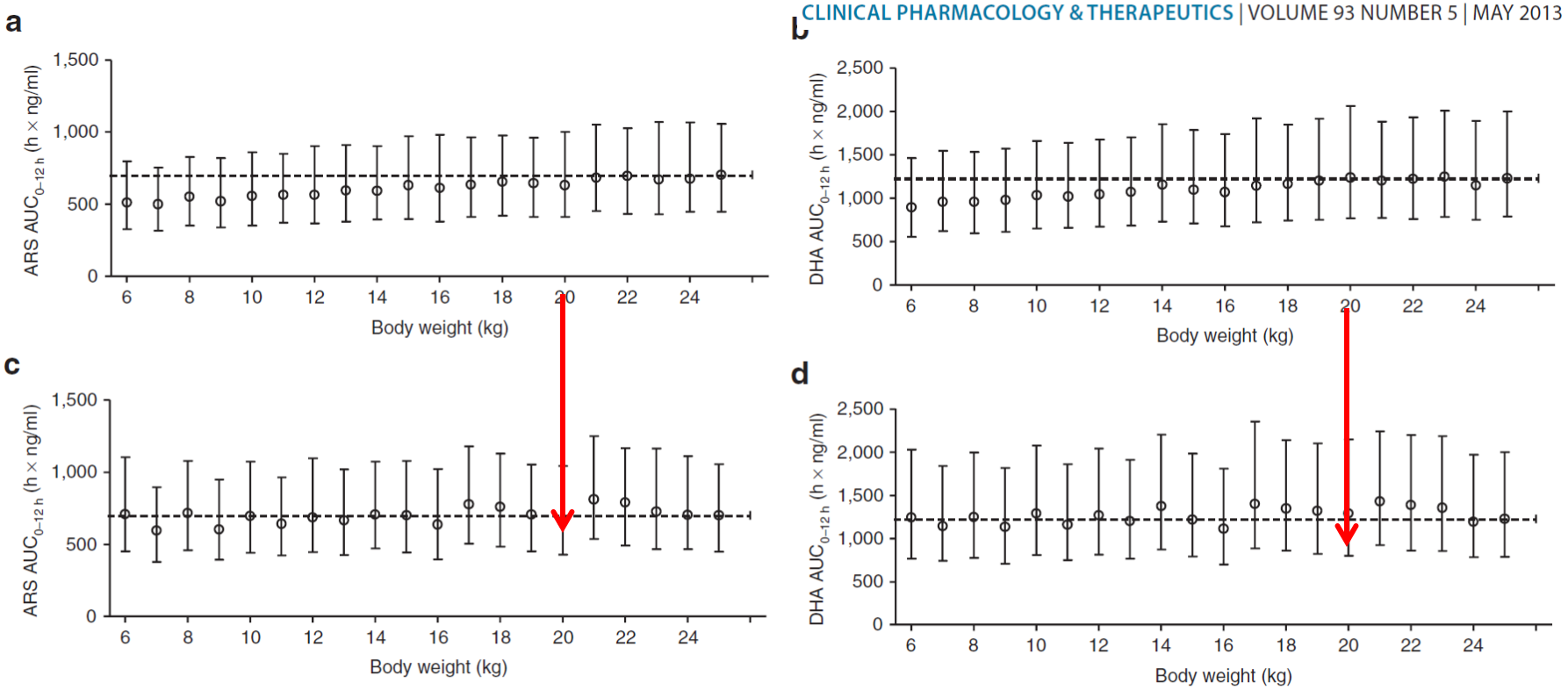


Figure 3 Simulated total first-dose exposure levels ($AUC_{0–12h}$) of (**a**) ARS and (**b**) DHA after the standard 2.4 mg/kg dosing in children at different body weights. Simulated total first-dose exposure levels ($AUC_{0–12h}$) of (**c**) ARS and (**d**) DHA after the suggested adjusted dose regimen (**Table 3**). Open circles represent median values, and bars indicate the 25th to 75th percentiles of simulations (1,000 simulations at each body weight). The broken line represents the median exposure for the largest weight group (i.e., 700 h × ng/ml and 1,230 h × ng/ml for ARS and DHA, respectively). ARS, artesunate; $AUC_{0–12h}$, area under the concentration–time curve from time point 0 to 12 h; DHA, dihydroartemisinin.

Treating severe malaria

Population Pharmacokinetics of intra-venous artesunate: a pooled analysis of individual data from patients with severe malaria

Sophie G Zaloumis[1,#]

Joel Tarning[2] (joel@tropmedres.ac)

Sanjeev Krishna[4] (sgjf100@sgul.ac.uk)

Ric N Price[3] (ricprice99@gmail.com)

Nicholas J White[2,5] (nickwdt@tropmedres.ac)

Tim Davis[6] (tim.davis@uwa.edu.au)

James M McCaw[1] (jamesm@unimelb.edu.au)

Piero Olliaro[5,7] (olliarop@who.int)

Richard J Maude[2,8] (Richard@tropmedres.ac)

Peter Kremsner[9,10] (peter.kremsner@uni-tuebingen.de)

Arjen Dondorp[5,11] (arjen@tropmedres.ac)

Melba Gomes[7] (gomesm@who.int)

Karen Barnes[12] (Karen.Barnes@uct.ac.za)

Julie A Simpson[1] (julieas@unimelb.edu.au)

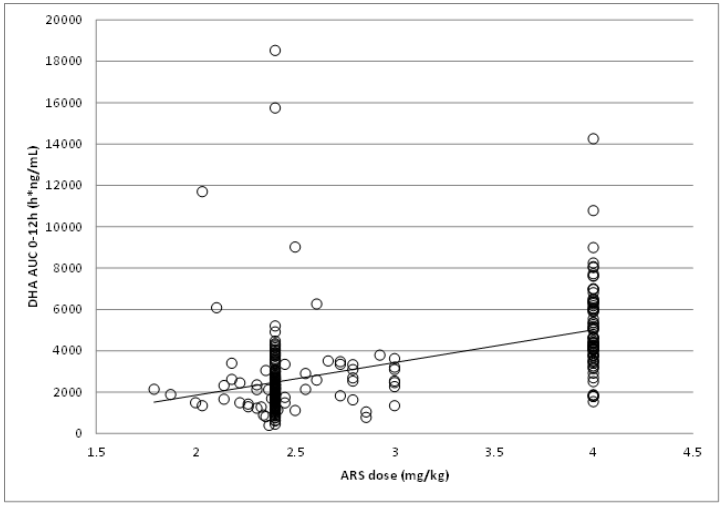


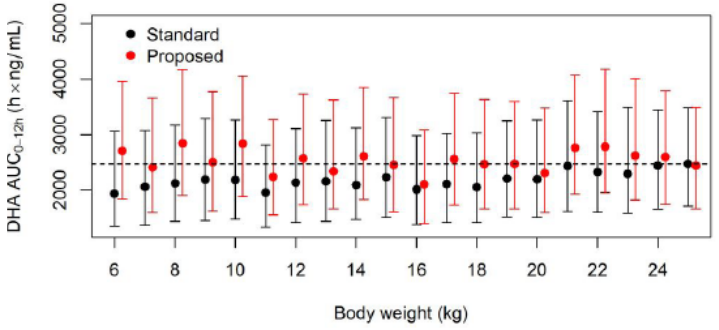
Table 4: Study site, number of patients, study population, study design and ARS dosing scheme(s) for all routes of ARS administration (i.e. intravenously (IV), intrarectally (IR) and intramuscularly (IM)) and each study contributing data to the pooled analysis.

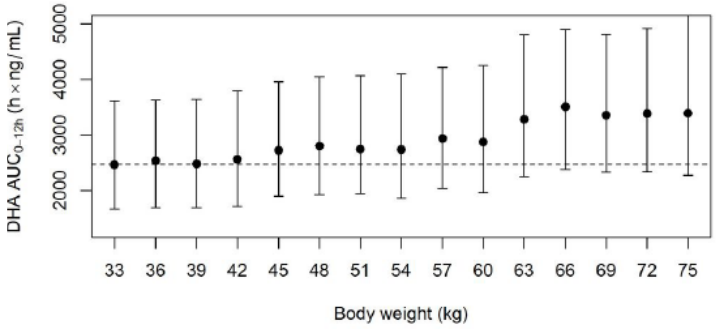
Research team	Study site	No. of patients[1]	Study population	Study design	Dosing scheme
Kremsner et al.	Gabon, Malawi	ITT[2] – 182 PP[3] – 177	Children with severe malaria	Randomised Controlled Trial	I – 2.4 mg/kg at 0, 12, 24, 48, 72 hrs II – 4 mg/kg at 0, 24, 48 hrs
Krishna et al.	Ghana	34	Children with moderately severe malaria	Cross-over Trial	I – 10 mg/kg IR at 0 hrs, 2.4 mg/kg IV at 12 hrs II – 20 mg/kg IR at 0 hrs, 2.4 mg/kg IV at 12 hrs III – 2.4 mg/kg IV at 0 hrs, 20 mg/kg IR at 12 hrs
Nealon et al.	Gabon	28	Children with severe malaria	Cross-over Trial	I – 2.4 mg/kg IV at 0 hrs, 1.2 mg/kg IM at 12 hrs II – 2.4 mg/kg IM at 0 hrs, 1.2 mg/kg IV at 12 hrs
Maude et al.	Bangladesh	21	Adults with severe malaria	Clinical Study	2.4 mg/kg at 0, 12, 24, 48 hrs etc
WHO	Bangkok, Thailand	48	Adults with moderately severe malaria	Cross-over Trial	I – 2.4 mg/kg IV at 0 hrs, 10 mg/kg IR at 12 hrs II – 10 mg/kg IR at 0 hrs, 2.4 mg/kg IV at 12 hrs III – 2.4 mg/kg IV at 0 hrs, 20 mg/kg IR at 12 hrs IV – 20 mg/kg IR at 0 hrs, 2.4 mg/kg IV at 12 hrs
Davis et al.	Vietnam	30	Adults with either severe or moderately severe malaria	Phase 1– Clinical Study Phase 2 – Randomised Controlled Trial	Phase 1 – 120 mg/kg IV at 0 hrs Phase 2 I – 120 mg/kg IV at 0 and 4 hrs II – 240 mg/kg IV infusion over 4 hrs at 0 hrs

[1]Number reported in published paper or internal WHO report; [2]ITT – intention to treat; [3]PP – per protocol

Population Pharmacokinetics of Intramuscular Artesunate in African Children With Severe Malaria: Implications for a Practical Dosing Regimen

ICE Hendriksen[1,2], G Mtove[3], A Kent[4], S Gesase[5], H Reyburn[6], MM Lemnge[5], N Lindegardh[1,2], NPJ Day[1,2], L von Seidlein[7], NJ White[1,2], AM Dondorp[1,2] and J Tarning[1,2]

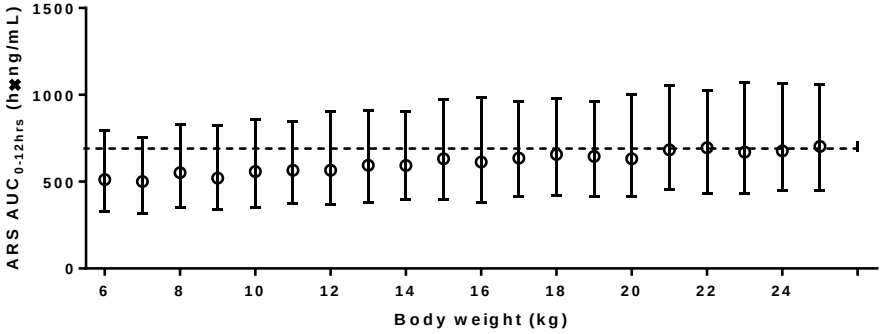


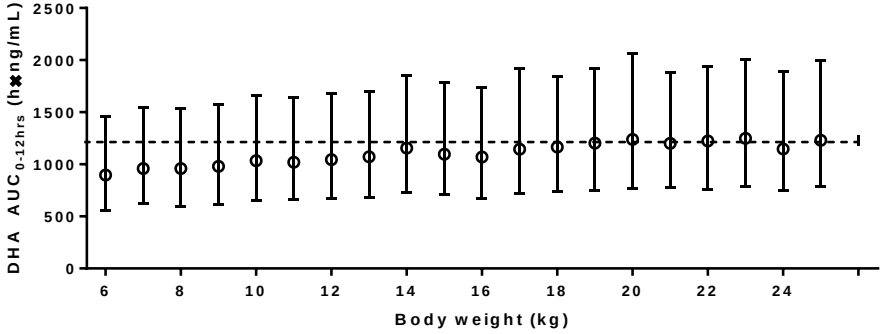


Treating severe malaria

OLD

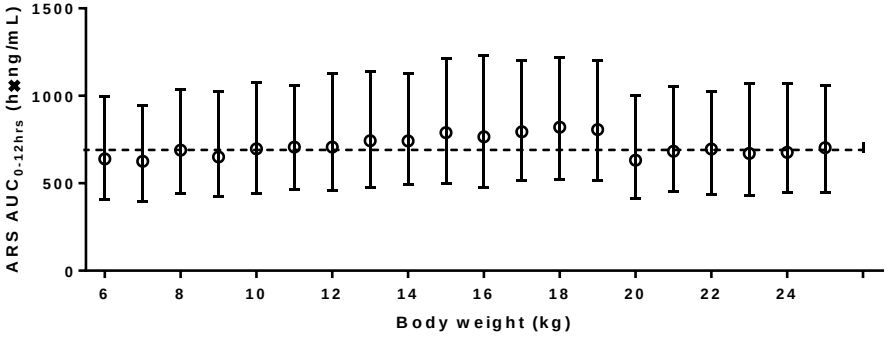
2.4 mg/kg

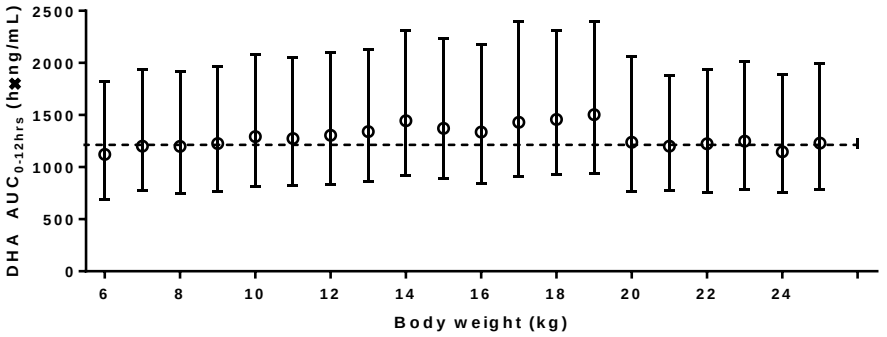




NEW

<20 kg: 3.0 mg/kg





Chemoprevention for special risk groups

- In areas with highly seasonal malaria transmission, provide seasonal malaria chemoprevention with monthly AQ+SP for all children below the age of six years during each transmission season.

  Strong recommendation, High quality evidence

- In areas of moderate to high malaria transmission where SP is still effective, provide intermittent preventive treatment of infants with SP (SP-IPTi) alongside DTP2, DTP3, and measles vaccinations.

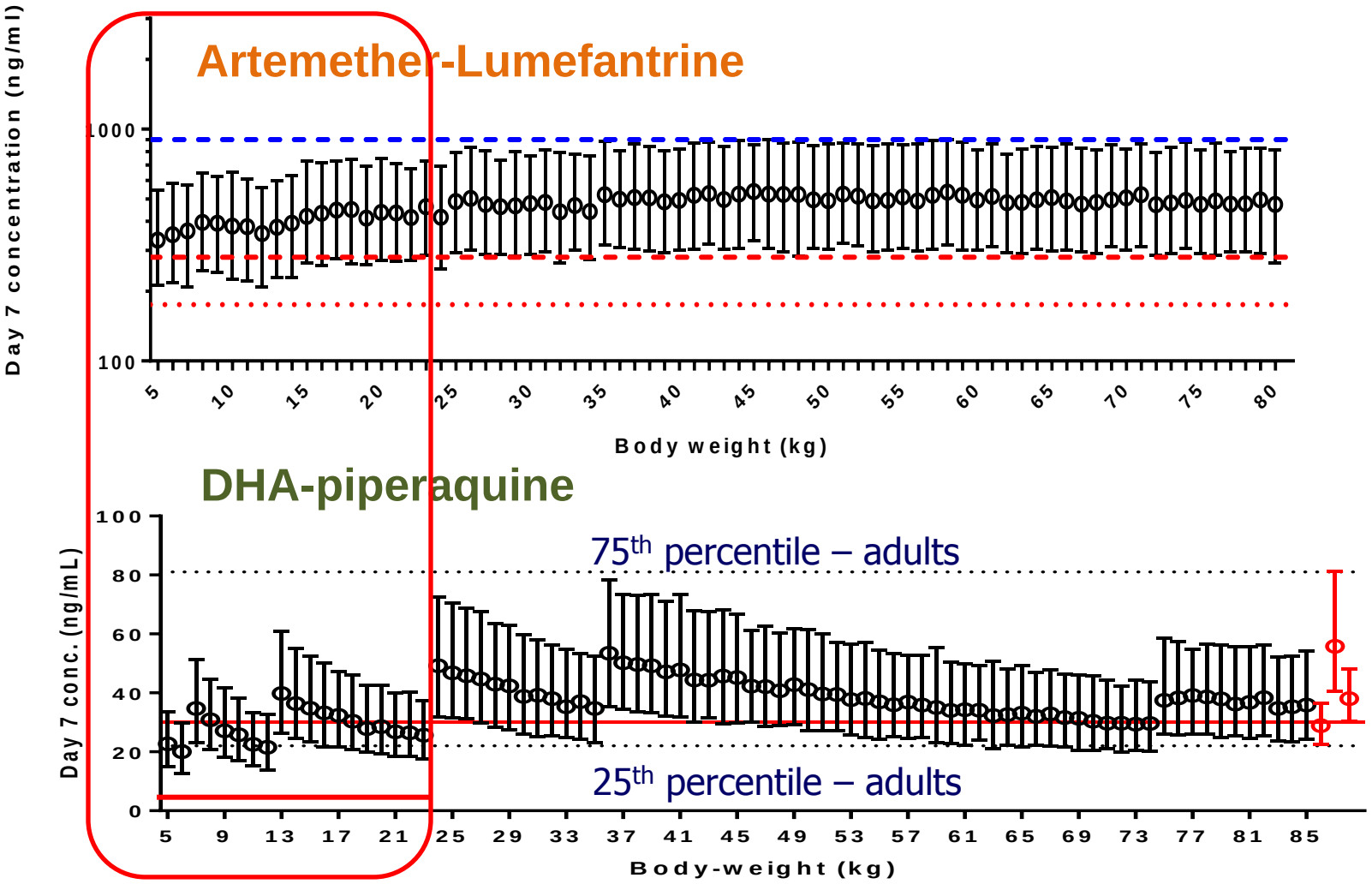
  Evidence not graded

- In malaria endemic areas, give Intermittent Preventive Treatment with SP to all pregnant women in their first or second pregnancies at every scheduled antenatal visit commencing at the start of the second trimester. Each SP dose should be given at least one month apart.

  Strong recommendation, High quality evidence

Dosing

All patients deserve an equal chance of being cured



Dosing

Drug	Exposure in young children	Predictable relationship between dosing and exposure?	Dose increase?
Lumefantrine	Reduced	No	No
Piperaquine	Reduced	Yes	Yes

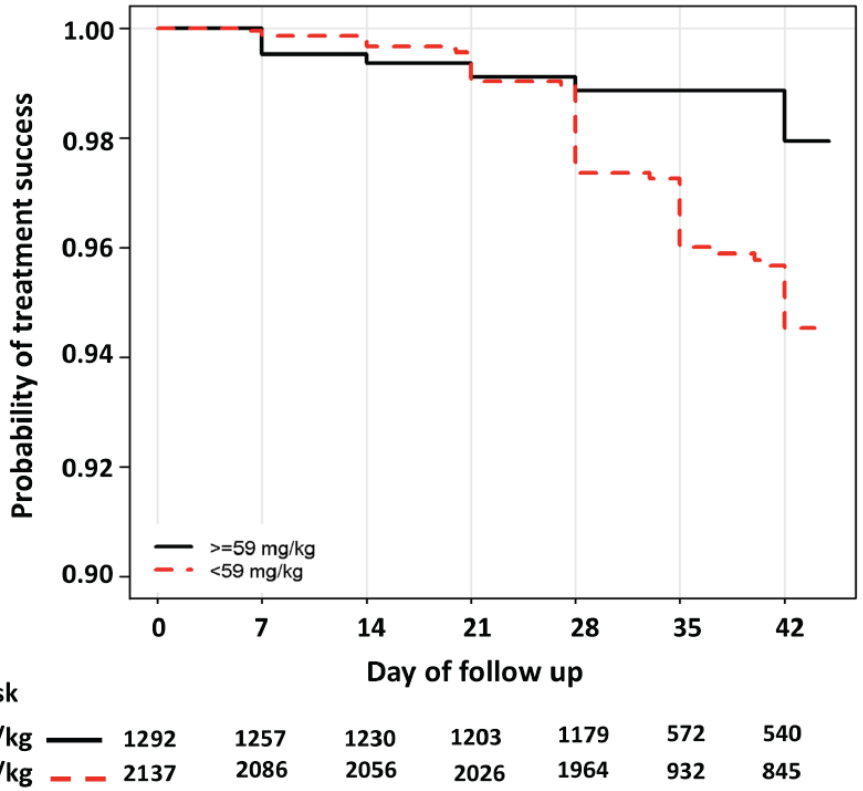
Piperaquine dose response

Recrudescence	N (n)	Adjusted HR	95% CI	P-value
Total PIP dose (every 5 mg/kg increase)	**7,070 [127]**	**0.87**	**[0.79–0.95]**	**0.002**
Parasitaemia (Log10)	7,070 [127]	1.23	[1.08–1.41]	0.003
Age (ref ≥12 years)				
< 1 year	439 [7]	2.36	[0.79–7.06]	0.200
1-<5 years	**3,429[9]**	**3.71**	**[1.66–8.26]**	**0.002**
5-<12 years	943 [7]	1.48	[0.56–3.91]	0.610

Risk of recrudescence in 1–4y olds, by dose

By day 42, the risk of recrudescence in patients receiving a PIP dose below 59 mg/kg was 5.5% (95% CI 4.2–6.7) compared to 2.1% (95%: 1.1–3.0) in patients receiving a higher dose, [p < 0.001].

Raising the target minimum dose of PIP in this age group to **59 mg/kg would halve the risk of treatment failure** and ensure cure of at least 95% of young children.

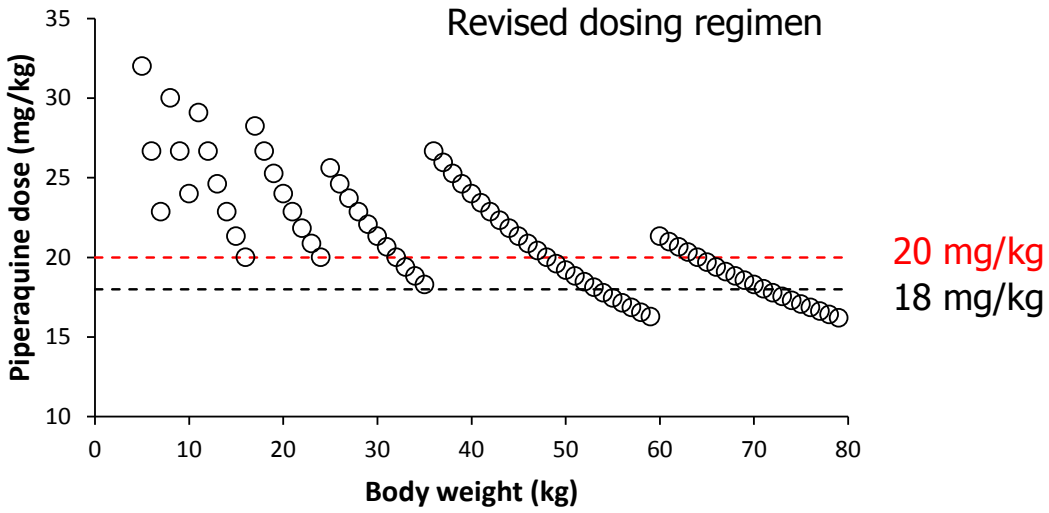


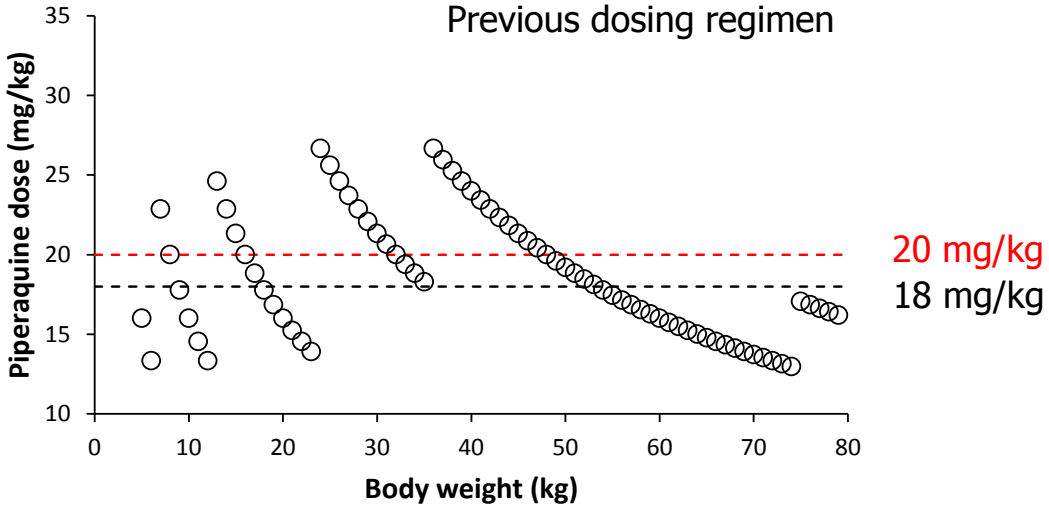
Dihydroartemisinin-Piperaquine

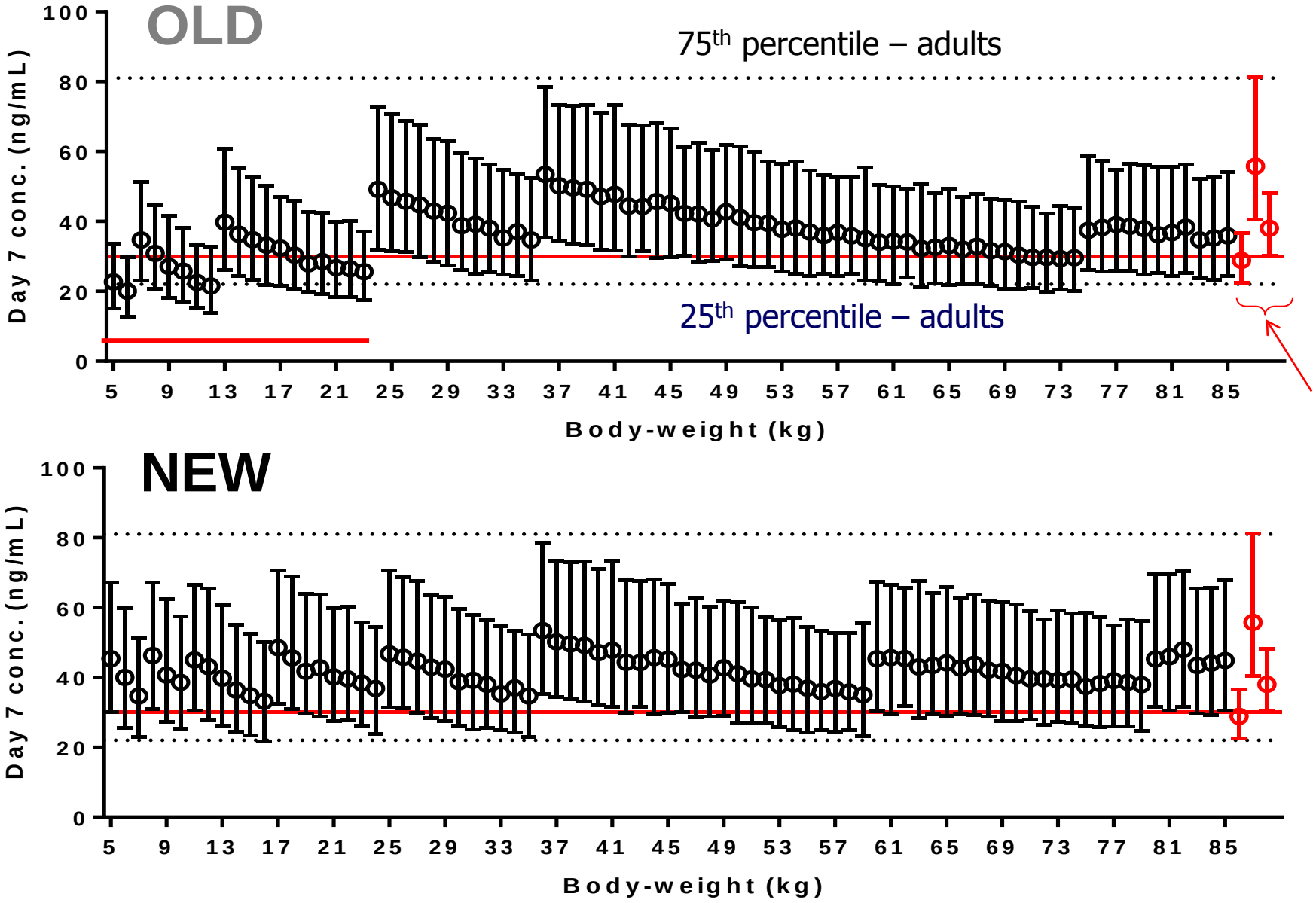
Body weight	DHA/PPQ dose given daily for 3 days	DHA mg/kg dose range, given daily for 3 days	Piperaquine mg/kg dose range, given daily for 3 days
5 – 7 kg	1 x 20 / 160 mg	2.9 – 4.0 mg/kg	23 - 32 mg/kg
8 - 10 kg	1.5 x 20 / 160 mg	3.0 – 3.8 mg/kg	24 - 30 mg/kg
11 - 16 kg	1 x 40 / 320 mg	2.5 - 3.6 mg/kg	20 - 29 mg/kg
17 - 24 kg	1.5 x 40 / 320 mg	2.5 – 3.5 mg/kg	20 - 28 mg/kg
25 - 35 kg	2 x 40 / 320 mg	2.3 – 3.2 mg/kg	18 - 26 mg/kg
36 - 59 kg	3 x 40 / 320 mg	2.0 – 3.3 mg/kg	16 - 27 mg/kg
60 - 79 kg	4 x 40 / 320 mg	2 – 2.6 mg/kg	16 - 21 mg/kg
≥80 kg	5 x 40 / 320 mg	2* – 2.5 mg/kg	16* - 20 mg/kg

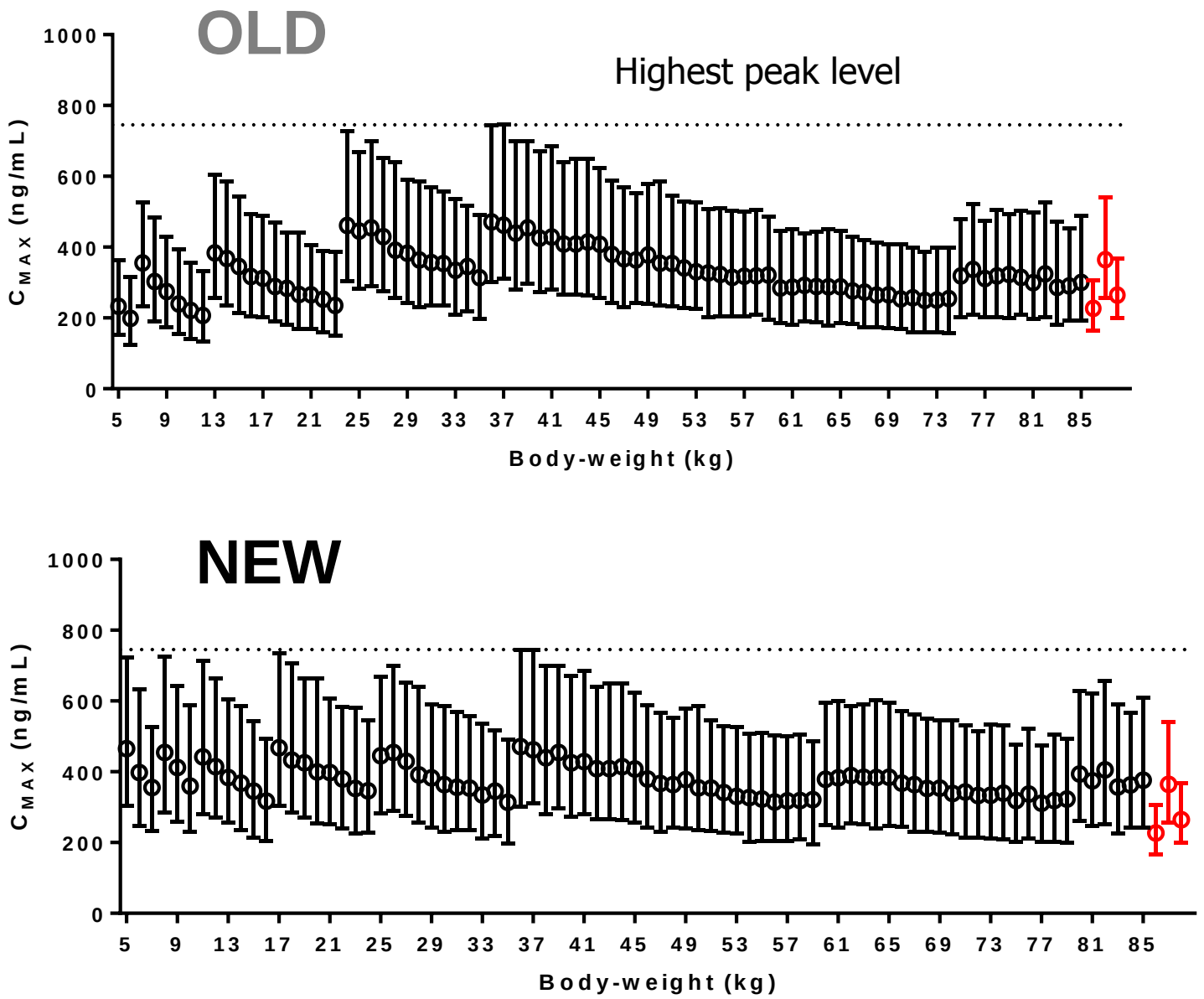
*Weight adjusted dose range assumes a maximum weight of 100kg

Dihydroartemisinin-Piperaquine





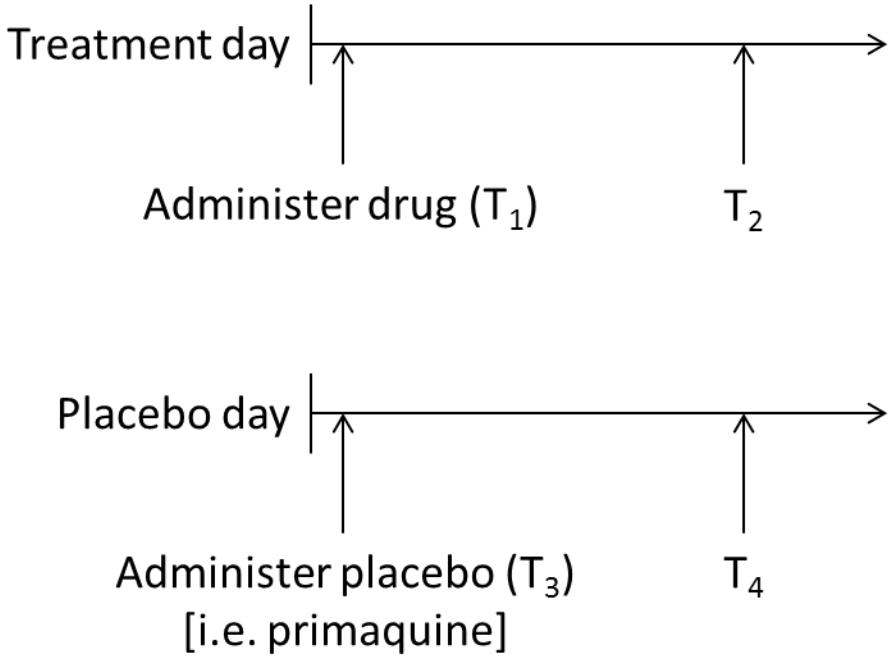

OLD
75th percentile – adults
25th percentile – adults
Day 7 conc. (ng/mL)
Body-weight (kg)
NEW
Day 7 conc. (ng/mL)
Body-weight (kg)


OLD
Highest peak level
1000
800
600
400
200
0
C_{MAX} (ng/mL)
5 9 13 17 21 25 29 33 37 41 45 49 53 57 61 65 69 73 77 81 85
Body-weight (kg)
NEW
1000
800
600
400
200
0
C_{MAX} (ng/mL)
5 9 13 17 21 25 29 33 37 41 45 49 53 57 61 65 69 73 77 81 85
Body-weight (kg)

Review process and timelines

- **September 2014** Approval from MPAC.
- **Q4 2014** Compilation, external review, proofing (October).
- **Q4 2014** Final clearance through the WHO GRC and other WHO in-house processes.
- **Q1 2015** Release and launching, web publication, translations and dissemination.

Definition of ΔΔQTc



$$\Delta\Delta QTc = \Delta QTc_{Treatment} - \Delta QTc_{Placebo}$$

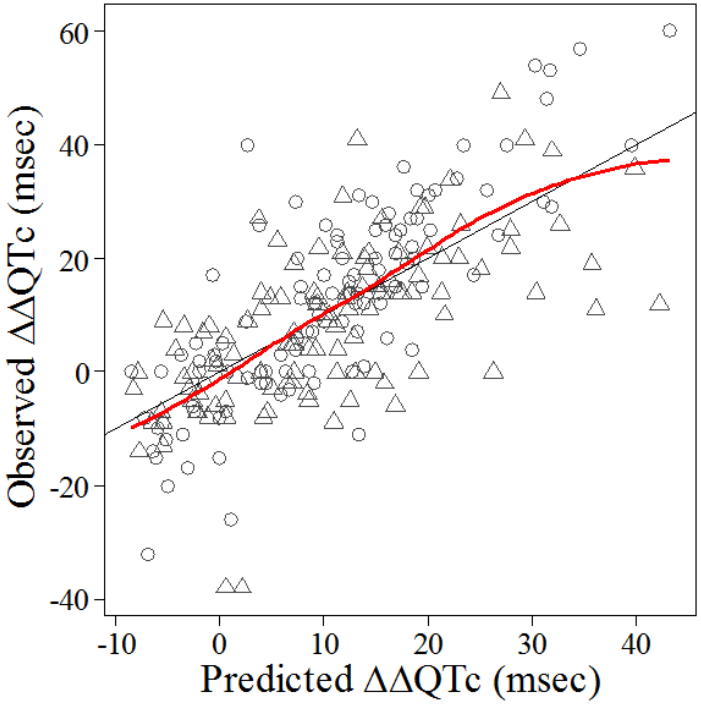
$$\Delta\Delta QTc = [QTc(T_2) - QTc(T_1)] - [QTc(T_4) - QTc(T_3)]$$

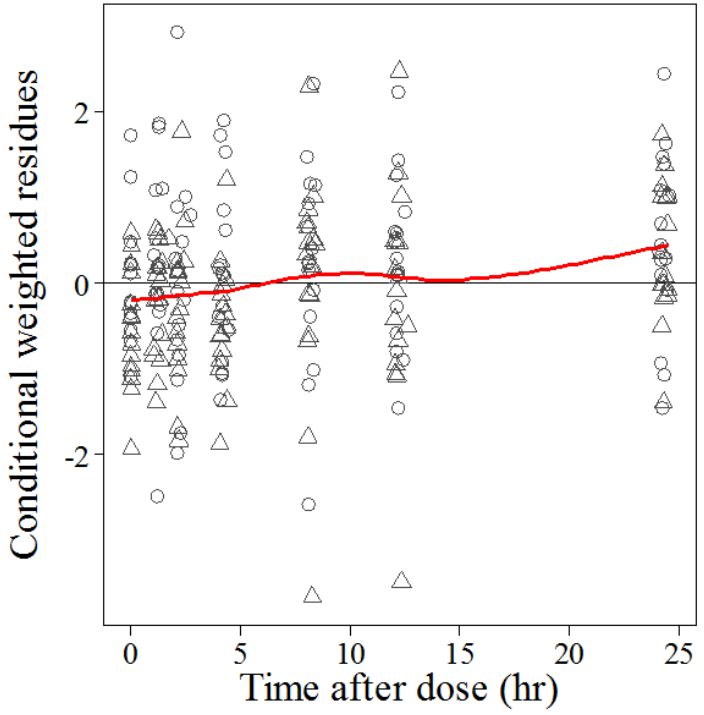
T_2 and T_4 is the same clock time.

ΔΔQTc modelling

Direct response model:

$$\Delta\Delta QTc = (\theta_1 + \eta_1) + \theta_2 \cdot CP(t) + \varepsilon_i$$

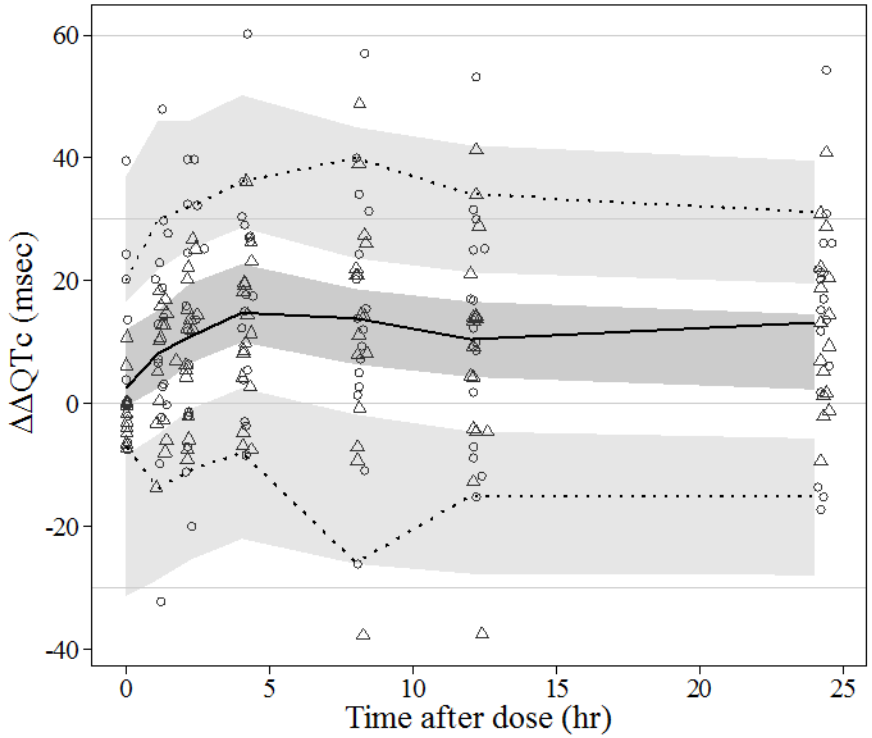




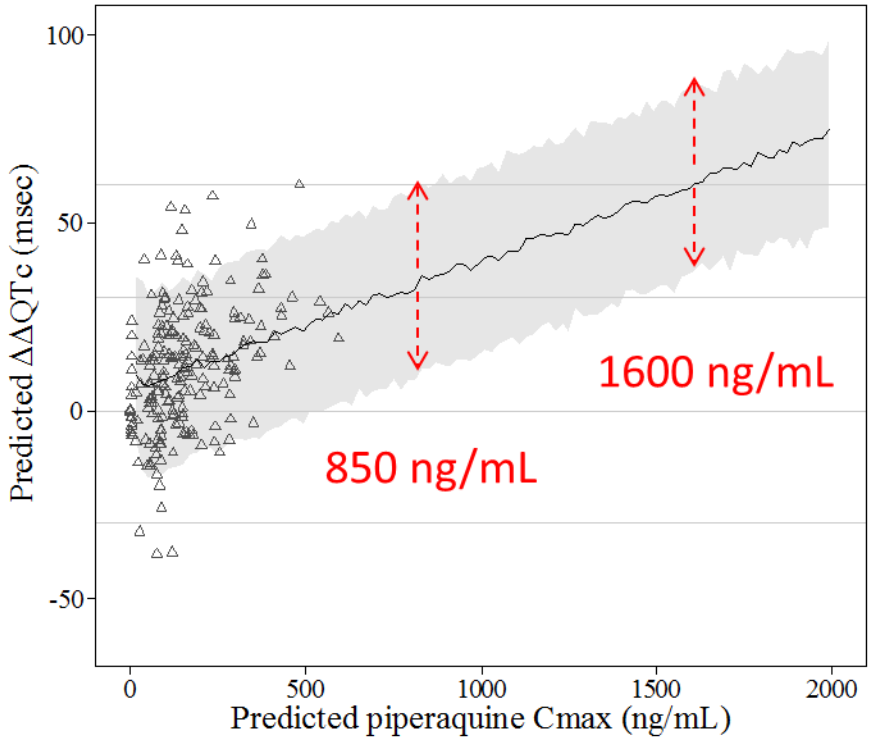
θ_1 = Baseline ΔΔQTc

θ_1 = Slope, concentration-effect relationship

VPC (n=1,000)



Simulation



Final parameter estimates:

Parameter	Population estimate	%RSE
θ_1, Baseline ΔΔQTc (msec)	5.39	51%
θ_2, Slope (msec/(ng/mL))	0.0352	21%
η_1, IIV of Baseline ΔΔQTc (msec)	9.48	40%
σ, Additive error (msec)	10.6	10%

Conclusion: 95% of patients will be below 60 msec QTc at 850 ng/mL

Piperaquine has effects ≤ to chloroquine on the QTc interval

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PLoS CLINICAL TRIALS

Randomized Dose-Ranging Controlled Trial of AQ-13, a Candidate Antimalarial, and Chloroquine in Healthy Volunteers

Fawaz Mzayek[1,2,3], Haiyan Deng[1,3], Frances J. Mather[4], Elizabeth C. Wasilevich[1,2,3,a¤], Huayin Liu[1,3‡], Christiane M. Hadi[5], David H. Chansolme[5,b¤], Holly A. Murphy[1,3,5], Bekir H. Melek[5], Alan N. Tenaglia[5,c¤], David M. Mushatt[1,3,5], Albert W. Dreisbach[5,6,7,d¤], Juan J. L. Lertora[5,6,7,e¤], Donald J. Krogstad[1,3,5,7*]

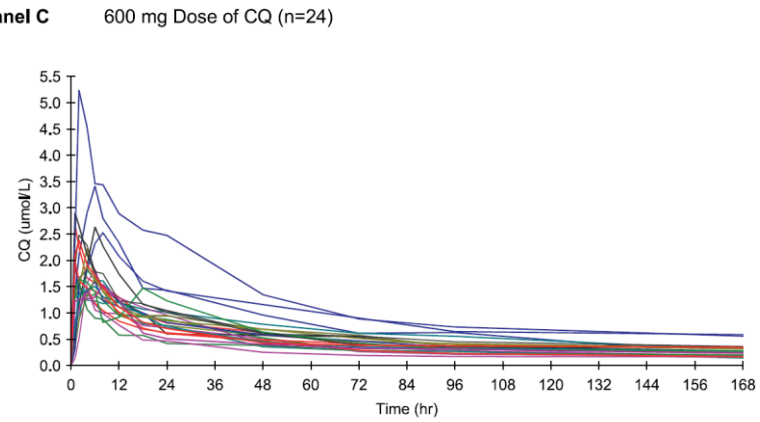


Figure 3. Pharmacokinetics of AQ-13 and CQ at Doses Equivalent to 600 and 700 mg CQ Base

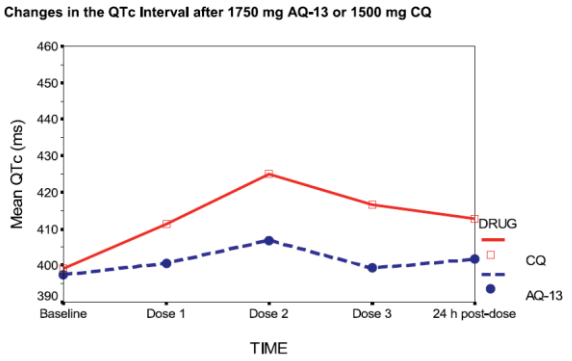


Figure 4. Changes in the QTc Interval after 1,750 mg AQ-13 or 1,500 mg CQ

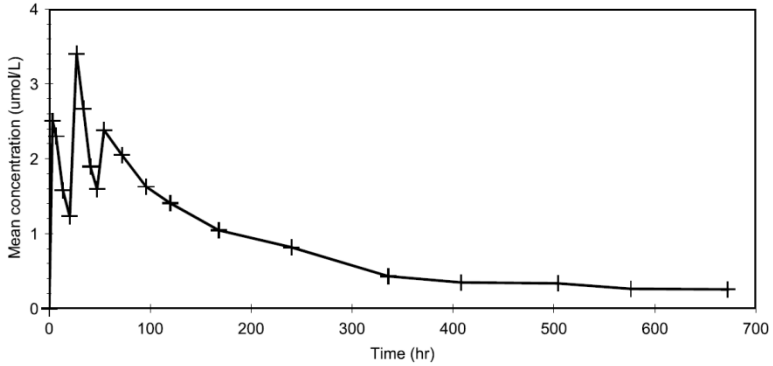


Figure 6. Modeled Concentration–Time Data (1,500 mg CQ Therapeutic Dose)

Table 6. Effects of AQ-13 and CQ on the QTc Interval

Time of QTc Measurement	600/700 mg AQ-13, 600 mg CQ		1,750 mg AQ-13, 1,500 mg CQ	
	AQ-13 (n = 25)	CQ (n = 24)	AQ-13 (n = 13)	CQ (n = 14)
Baseline	403 ± 17	406 ± 19	397 ± 16	396 ± 21
4–5 h post-dose (day 1)	414 ± 17	421 ± 20	401 ± 14	412 ± 22
4–5 h post-dose (day 2)	NA	NA	407 ± 11	424 ± 18
4–5 h post-dose (day 3)	NA	NA	400 ± 11	417 ± 21
2 wk follow-up	405 ± 18	403 ± 15	402 ± 13	412 ± 13

All data are presented in milliseconds as mean ± standard deviation. Data presented in columns 3 and 4 are for 12 volunteers randomized to AQ-13 at the 600 mg dose, plus an additional 13 volunteers who received 700 mg AQ-13; for 12 volunteers randomized to 600 mg CQ as capsules and an additional 12 volunteers randomized to 600 mg CQ as the commercially available Sanofi-Winthrop tablets (Aralen). Data in columns 4 and 5 are for 13 volunteers randomized to 1,750 mg AQ-13 and 13 volunteers randomized to 1,500 mg CQ.
NA, not applicable.

doi:10.1371/journal.pctr.0020006.t006

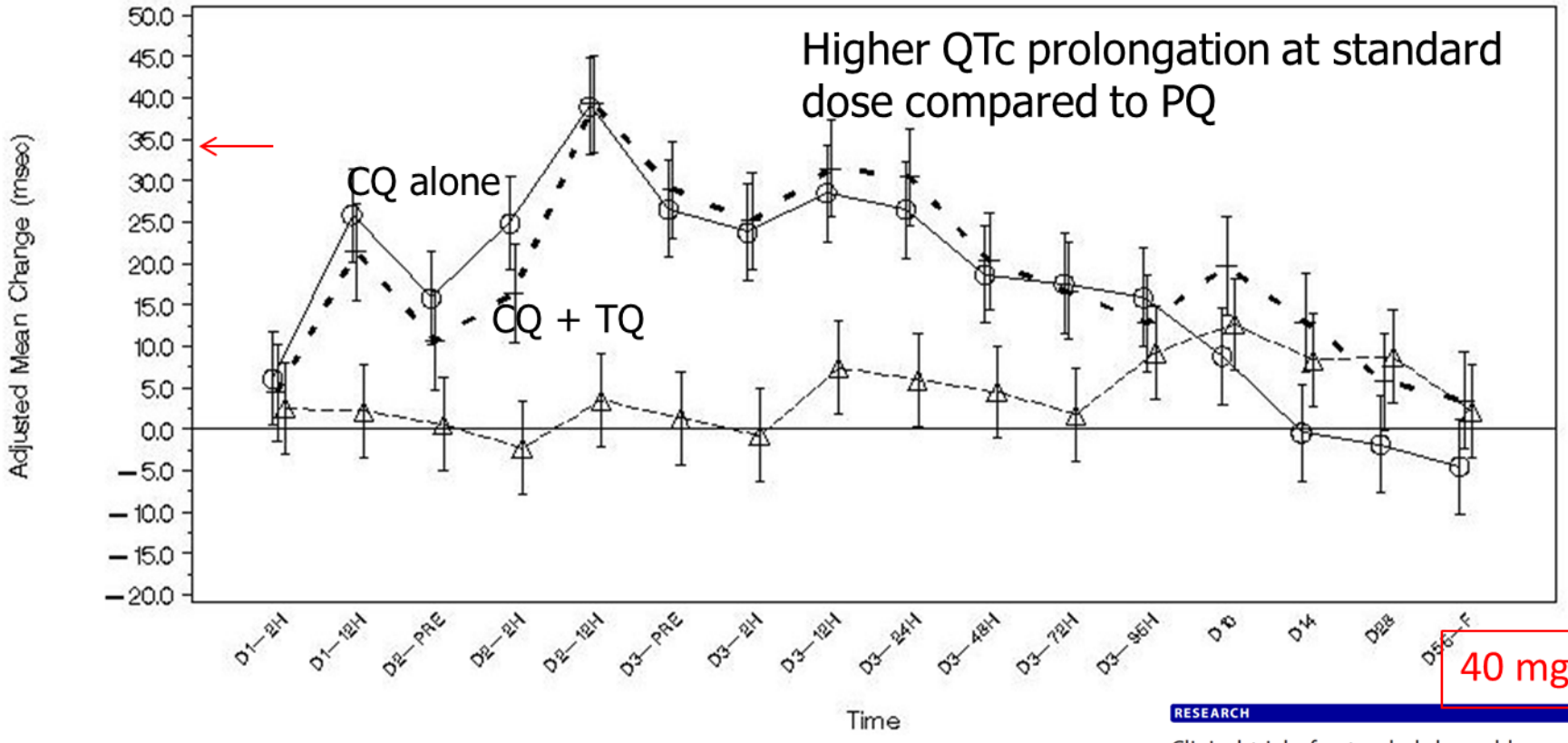
GLOBAL MALARIA PROGRAMME

Pharmacokinetic Interactions and Safety Evaluations of Coadministered Tafenoquine and Chloroquine in Healthy Subjects

Ann K. Miller, PhD, Emma Harrell, BSc, Li Ye, MS, Sharon Baptiste-Brown, MSN, Jőrg-Peter Kleim, PhD, Colin Ohrt, MD, MPH, Stephan Duparc, MD, Jörg J. Möhrle, PhD, Alison Webster, MD, Sandra Stinnett, MS, Arlene Hughes, PhD, Sandy Griffith, PharmD, Andrew P. Beelen, MD

Chloroquine (25 mg/kg)

Day 1	Day 2	Day 3
600 mg CQ	600 mg CQ	300 mg CQ



40 mg/kg

RESEARCH Open Access

Clinical trial of extended-dose chloroquine for treatment of resistant falciparum malaria among Afghan refugees in Pakistan

Natasha Howard[1*], Naeem Durrani[2], Sanda Sanda[1], Khalid Beshir[1], Rachel Hallett[1] and Mark Rowland[1,2]

Updating the WHO Guidelines for the Treatment of Malaria (MTGs)[*]

Dr. P. Olumese

1. INTRODUCTION

The WHO Guidelines for the Treatment of Malaria (MTGs), provides comprehensible, global and evidence-based guidelines for the formulation of policies and national guidelines for the treatment of malaria. It was first published in 2006 and the 2nd edition was published in 2010. The MTGs have been produced under the guidance of the Technical Expert Group (TEG) on Malaria Chemotherapy.

A draft plan for revision and update of the 2nd edition was presented and endorsed at the meeting of the Malaria Policy Advisory Committee (MPAC) in September 2012, and updates of the review process presented to the MPAC at the March 2013 and March 2014 meetings.

The recommendations in the third edition of the these guidelines as in previous editions, aim to provide recommendations on malaria treatment, including a new section on intermittent preventive treatment based on the latest scientific evidence of in vitro antimalarial susceptibility, safety, and the pharmacokinetic and pharmaco-dynamic properties of the different antimalarial medicines. It takes into account areas where levels of drug resistance and background immunity vary as well as operational and feasibility aspects even in severely resource-constrained settings.

An online survey was carried out to obtain feedback from end-users of the current edition (2nd edition) of the Guidelines for the treatment of malaria with the main objective to assess satisfaction of the end-users with the document's scope, content and suitability for their needs, and sought input and specific suggestions regarding the format, presentation, content, accessibility, and overall user-friendliness of the MTGs. The main target audience for the survey included policy makers in ministries of health, public health and policy specialists, and health professionals, clinicians and managers of health services in endemic countries, who have consulted and used the WHO MTGs.

Overall, respondents expressed satisfaction with the current scope, content and format of the MTGs. All sections of the guidelines were considered very important, and it was considered equally important to retain evidence for existing recommendations in future editions of the guidelines. GRADE tables and key references were regarded the most useful format for presenting evidence. The respondents however suggested expansion on certain topics (such as antimalarial resistance and chemoprophylaxis)and the inclusion of more visual aids, graphs and images and a different colour scheme, Based on this results of the survey, the overall format of presentation of the MTG has been retained as in the past editions.

The recommendations of the updated MTGs (3rd edition) have been finalised at the last malaria chemotherapy TEG held in June 2014 and are presented to MPAC for ratification.

2. CONSOLIDATED KEY RECOMMENDATIONS

The following set of core principles, held by the guideline panel, form the foundation for the recommendations.

[*] This document was prepared as a pre-read for the September 2014 meeting of the Malaria Policy Advisory Committee (MPAC) and is not an official document of the World Health Organization.

A. Prompt diagnosis and effective treatment

Universal access to parasitological diagnosis of malaria beyond the reach of quality controlled microscopy, is possible with deployment of quality assured rapid diagnostic tests (RDTs), appropriate for use in primary healthcare and community settings.

Uncomplicated malaria can progress rapidly to severe forms of the disease if left untreated, especially in people with no or low immunity. Severe malaria is almost always fatal without treatment and patients may die within hours. Therefore, programs should ensure access to prompt diagnosis and effective treatments within 24–48 hours of the onset of malaria symptoms.

B. Combination therapy

Preventing or delaying resistance is essential to the success of both national and global malaria control strategies. To help protect the current and future antimalarial medicines, all episodes of malaria should be treated with at least two antimalarials with different mechanisms of action (combination therapy). To improve adherence to treatment fixed-dose combinations are highly preferable to co-blistered or co-dispensed combinations.

C. Rational use of antimalarials

To reduce the spread of drug resistance, limit wastage of precious artemisinin-based combination therapies and better identify other febrile illnesses in the context of changing malaria epidemiology, there is a strong need to dispense antimalarials only to those who truly have malaria and promote adherence to full treatment course.

2.1 Summary of key recommendations

Diagnosing malaria
All people with suspected malaria should have a parasitological test to confirm the diagnosis.
Treating uncomplicated *P. falciparum* malaria
Treat adults and children (including infants, pregnant women in their second and third trimesters, and breastfeeding women) with uncomplicated *P. falciparum* malaria with an ACT. The current recommended first or second-line ACT treatment options are: • Artemether plus lumefantrine; Artesunate plus amodiaquine; Artesunate plus mefloquine; Dihydroartemisinin plus piperaquine; Artesunate plus sulfadoxine-pyrimethamine. *Strong recommendation, High quality evidence* All ACTs should contain at least three days treatment with an artemisinin-derivative. *Strong recommendation, High quality evidence* In low transmission areas, also provide a single dose of 0.25mg/kg primaquine to reduce onward transmission of *P. falciparum*, without the need for G6PD testing (excluding pregnant and breastfeeding women and infants aged < 1 year). *Strong recommendation, Low quality evidence*

Treating uncomplicated *P. falciparum* malaria in special risk groups

- Treat pregnant women with uncomplicated *P. falciparum* or chloroquine resistant *P.vivax* malaria in the first trimester with seven days of quinine plus clindamycin (if unavailable use an ACT).
- Treat infants weighing less than 5 kg with uncomplicated *P. falciparum* malaria with an ACT dosed at the same mg/kg target as for children weighing 5 kg.
- In HIV positive people with uncomplicated *P. falciparum* malaria avoid AS+SP if on treatment with co-trimoxazole, and avoid AS+AQ if on treatment with efavirenz.
- Treat travellers returning to non-endemic settings with uncomplicated *P. falciparum* malaria with an ACT.
- People with *P. falciparum* hyperparasitemia are at increased risk of death and require close monitoring in addition to an ACT.

Conditional recommendation, Low quality evidence

Treating uncomplicated non-falciparum malaria

In areas with chloroquine susceptible *P. vivax*, treat adults and children with uncomplicated *non-falciparum* malaria using either chloroquine or an ACT.

Strong recommendation, High quality evidence

In areas with chloroquine resistant *P. vivax*, treat adults and children with uncomplicated *P. vivax* malaria with an ACT (including infants, lactating women, and pregnant women in their second and third trimesters).

Strong recommendation, High quality evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria

To prevent future relapse, treat people (excluding pregnant or breastfeeding women, and people with G6PD deficiency) with *P. vivax* or *P. ovale* malaria with a 14-day course of primaquine.

Strong recommendation, Moderate quality evidence

In people with mild to moderate G6PD deficiency, consider relapse prevention with primaquine 0.75 mg base/kg once a week for 8 weeks.

Conditional recommendation, Very low quality evidence

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding is complete, then treat with 14 days of primaquine to prevent future relapse.

Conditional recommendation, Moderate quality evidence

Treatment of suspected severe malaria pending transfer to higher level facilities (Pre-referral treatment)

In settings where complete treatment of severe malaria is not possible, but injections are available, give adults and children a single dose of intramuscular artesunate and refer to an appropriate facility for further care. Use artemether or quinine if artesunate is not available

Strong recommendation, Moderate quality evidence

In settings where intramuscular injections are unavailable, treat children below the age of six years with a single dose of rectal artesunate and refer immediately to an appropriate facility for further care. *Strong recommendation, Moderate quality evidence*
Treating severe malaria
Treat adults and children with severe malaria with intravenous or intramuscular artesunate for at least 24 hours (including infants, pregnant women in all trimesters, and lactating women). *Strong recommendation, High quality evidence* Children weighing less than 20 kg should receive a higher dose of artesunate (3 mg/kg/dose) than larger children and adults (2.4 mg/kg/dose) to ensure an equivalent drug exposure. *Strong recommendation based on pharmacokinetic evaluation* Once the patient has received at least 24 hours of parenteral therapy, AND is able to tolerate oral therapy, complete treatment with three-days of an ACT *Strong recommendation, High quality evidence*
Chemoprevention for special risk groups
In areas with highly seasonal malaria transmission, provide seasonal malaria chemoprevention with monthly AQ+SP for all children below the age of six years during each transmission season. *Strong recommendation, High quality evidence* In areas of moderate to high malaria transmission where SP is still effective, provide intermittent preventive treatment of infants with SP (SP-IPTi) alongside DTP2, DTP3, and measles vaccinations. *Evidence not graded* In malaria endemic areas, give Intermittent Preventive Treatment with SP to all pregnant women in their first or second pregnancies at every scheduled antenatal visit commencing at the start of the second trimester. Each SP dose should be given at least one month apart. *Strong recommendation, High quality evidence*

3. ADDITIONAL RECOMMENDATION / CHANGES IN THE REVISED EDITION

3.1 Dosage Recommendations

Identification of the dose regimens of each antimalarial that provide the best balance between tolerability, safety and efficacy (therapeutic ratio) is a main objective of the development of this guidelines. Under-dosing is dangerous both for the patient and the community; it increases the individual risk of treatment failure and it accelerates the spread of resistance. The randomised controlled trials which are the basis for efficacy and safety evaluation and drug registration typically provide clinical data for a single dose regimen, and often do not provide enough information on important sub-groups such as young children and pregnant women. The application of target dose and

therapeutic ranges derived from these studies, in some cases has resulted in dose recommendations which were too low for specific groups at risk.

The therapeutic objective of treatment is to ensure adequate and optimal antimalarial drug exposures across all patient groups. Based on pharmacokinetic studies and modelling, if a sub-group of patients is found to have consistently lower drug blood levels than in main sub-groups in whom the dose has been established, then provided there is no safety concern, these guidelines have recommended dose adjustment to achieve comparable antimalarial drug exposure.

Principles underlying the recommendations on dosing of antimalarial medicines

- In all patients, malaria parasites need to be exposed to therapeutic antimalarial drug blood levels.
- ACT regimens should be deployed using optimal dosing strategies that prolong the useful therapeutic life, i.e. maximize the likelihood of rapid clinical and parasitological cure and retard drug resistance, including transmission of resistant strains.
- While age-based dosing may be more practical, it carries the risk of potentially under-dosing or over-dosing unless region-specific weight-for-age databases are available to guide dosing in specific regions.

The dosage recommendations in the MTGs are derived from the dose response and the drug exposure profiles (pharmacokinetic and pharmacodynamics data) of recommended drugs – in all target populations, and awareness of dose related toxicity. Based on the review of this data for all main antimalarials, the new guidelines propose a change in the dosing schedule recommended target doses of two specific antimalarials for small children to ensure the recommended target doses and thus adequate drug blood levels is achieved. This change was necessary and made for:

- Dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria,
    - Though the overall cure rates achieved with the manufacturers' dosing recommendations are generally high (> 95%), a sub-analysis shows that these doses are sub-optimal in children aged 1 to 4 years who are at a three-fold increased risk of treatment failure. This is attributed to many young children currently being dosed below the minimum recommended targeted piperaquine dose of 16 mg/kg per day. Also pharmacokinetic differences resulting in this age group having significantly lower drug concentrations than older children and adults given the same mg/kg dose. This means that these young children require a higher mg/kg dose of at least 54–59 mg/kg (i.e. 18-20 mg/kg per day) to achieve the recommended target dose.
- Artesunate injection for the treatment of severe malaria.
    - Pharmacokinetic studies in children with severe malaria receiving intramuscular artesunate suggest that there is underexposure relative to older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin (DHA) in young children. Body weight has also been identified as a significant covariate in studies of oral and rectal artesunate pharmacokinetics. As absorption of intramuscular artesunate is rapid and reliable this suggests that young children have a larger apparent volume of distribution for both compounds, and therefore need a slightly higher dose of parenteral artesunate to achieve comparable exposures to older children and adults. The recommendation was thus modified as
        - In children ≤20Kg give 3mg/kg/dose of injectable at 0,12 and 24 hours and continue once daily until oral administration is feasible

- In children with weight >20Kg and adults give 2.4mg/kg/dose injectable artesunate at 0,12 and 24 hours and continue once daily until oral administration is feasible

3.2 New Sections included in the 3rd Edition of the Malaria Treatment Guidelines

- Intermittent Preventive Treatment in pregnancy
- Intermittent preventive Treatment in infants
- Seasonal Malaria Chemoprevention

Review process and timelines

September 2014	Approval from MPAC.
Q4 2014	Final clearance through the WHO GRC and other WHO in-house processes.
Q1 2015	Release and Launching, Web Publication, translations and dissemination.