Strategy Paper on

Management of Antimalarial Drug Resistance

for the

Roll Back Malaria (RBM) Board

17th Meeting, 2-4 December, 2009

Submitted by

The Global Malaria Programme (GMP)

World Health Organization

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Strategy Paper on Antimalarial Drug Resistance for the 17th Roll Back Malaria (RBM) Board Meeting

Background

Antimalarial drug resistance is one of the greatest threats to the achievement of the RBM targets. After increasing failure of earlier antimalarials, coinciding in some countries with increased child mortality, the development of artemisinin-based combination therapies (ACTs) offered a powerful new malaria control tool. ACTs were not only highly efficacious, but the combinations also protected drugs from development of resistance by *Plasmodium falciparum*. Once the major hurdle of making ACTs affordable to national programmes was overcome through lowered unit costs from manufacturers and increased availability of funding from a variety of sources, most countries rapidly adopted ACTs as the first line treatment. Serious problems still remain, however, in ensuring wide-scale access to ACTs. In the meantime, resistance to artemisinin has now been confirmed in Thailand and Cambodia, and there are indications that foci of artemisinin-resistance may be present elsewhere in the region.

Because of the constant battle with drug resistance, which began in the 1960s, WHO has established a strategy for dealing with antimalarial resistance, which has four key elements:

1. **Preventing the emergence of antimalarial drug resistance**
2. **Monitoring antimalarial drug efficacy, and when necessary confirming drug resistance**
3. **Ensuring a continuous pipeline of new antimalarial medicines**
4. **Containing the spread of antimalarial drug resistance once it has emerged.**

We are now at a highly vulnerable point: funds for malaria are at an all time high, and success in control has been demonstrated not just in Asia, Latin America and the margins of malaria distribution in Africa, but also in higher transmission settings of sub-Saharan Africa. Expectations are high, with political pressure to achieve the RBM targets in 2010 and aspirations to move towards elimination in many countries in the following decades. At the same time our strategies depend on highly efficacious tools, and there are no currently available medicines for nationwide use beyond ACTs. There is only a limited pipeline of non-ACT alternatives in the near future.

This paper has been developed for the 17th RBM Partnership Board meeting in response to the following decision at the 16th Board Meeting:

- The WHO will lead a consultative process involving the CMWG, the WIN WG, the HWG and other relevant stakeholders to develop a comprehensive strategy and management solutions for the RBM Partnership to use to address pharmaceutical and insecticide resistance
- A draft strategy should be available before the 17th Board meeting
- PMI and GFATM will consider funding once the requirements are determined in the strategy development process.

The purpose of the paper is to set out how the constituencies and mechanisms of the RBM Partnership can work together to mitigate the risk of emerging drug resistance which potentially undermines progress in malaria control.

1. Preventing the emergence of antimalarial drug resistance

The key elements of the strategy to prevent the emergence of drug resistance are:

a. Use of combination therapies
b. Halt the use of oral monotherapies[1]
c. Increase access to good quality combination medicines by:
   i) making efficacious ACTs affordable and widely accessible in both the public and private sectors
   ii) using medicines correctly, including in the private sector, by education of practitioners and patients.
d. Improve compliance with recommended treatment regimens by use of co-formulated (fixed dose) combination medicines
   i) supervising drug administration where possible to help to ensure adherence
e. Striving for universal parasitological confirmation of malaria by:
   i) reinforcing quality microscopy where available and increasing access to quality assured rapid diagnostic tests
   ii) using diagnostics correctly, including in the private sector, by education of practitioners
   iii) adhering to microscopy results, by educating both providers and patients.
f. Exclude poor quality and counterfeit drugs from markets
g. Reduce transmission rates to lower the malaria burden (size of the parasite population) and to reduce the use of antimalarial drugs (less drug pressure on parasites) by:
   i) vector control methods including insecticide treated mosquito nets and indoor residual spraying
   ii) reduction of the reservoir of infection (responsible for the spread of drug resistance) by improving therapeutic practice, in particular early diagnosis and effective treatment, and use of gametocytocidal medicines where safe and appropriate
   iii) deploying future vaccines and other proven transmission reduction tools as they become available.

2. Monitoring antimalarial drug efficacy and confirmation of drug resistance when it emerges

a. Routine monitoring of therapeutic efficacy of first and second-line medicines as an integral component of malaria control

This makes it possible to detect drug resistance early, and to be able to rapidly change drug policy when efficacy decreases (total treatment failure at day 28 > 10%) in order to avoid the further selection and spread of multidrug resistance. A standard element of these studies is the measurement of parasitemia on day 3 after enrolment. Failure to clear parasites by day 3 is an early indication of artemisinin resistance. Current guidance is to conduct additional confirmatory drug efficacy studies when the proportion of patients failing to clear parasitemia by day 3 exceeds 10%.

[1] It should be noted that the use of rectal and parenteral artemisinin monotherapy for the initial treatment of severe malaria is appropriate and recommended. All such patients should eventually receive after the initial treatment a full treatment course with ACTs.

Guidance on the conduct of these studies (including a standard protocol) is available in the WHO Global Malaria Programme document "Methods for surveillance of antimalarial drug efficacy" (http://apps.who.int/malaria/docs/drugresistance/Protocol2009.pdf). This monitoring should be conducted every two years at sentinel sites.

Monitoring antimalarial drug efficacy is mandatory to allow for proper case management and for early detection of changing patterns of drug efficacy in order to revise national malaria treatment policies.

b. Research to confirm presence of resistance using in vitro, molecular markers or pharmacokinetic data, and to validate new tools.

Confirmation of drug resistance by these methods should not delay appropriate antimalarial policy change. These tools can help to clarify or complement the results of antimalarial drug efficacy monitoring but need not be conducted routinely by National Malaria Control Programmes.

3. Ensuring a continuous pipeline of new antimalarial medicines

a. Develop and register new antimalarial combination medicines with different targets of action and in accordance with the recommended target product profiles, and ensure a steady development pipeline.

Given the long lead time needed to develop novel antimalarial medicines, the development of new chemical agents with different modes of action to broaden therapeutic options is crucial. By analogy with the treatment of other infectious diseases such as tuberculosis and human immunodeficiency virus infection, the antimalarial treatment strategy to overcome multidrug resistance is to use medicines in combination. Combinations are usually more effective than monotherapy, and they also help to avoid or at least delay the emergence of resistance. The probability of a malaria parasite emerging that is resistant to two drugs with different modes of action is markedly reduced when they are used in combination. Therefore, the medicine pipeline needs to include potential partner medicines with different modes of action and with transmission blocking effects.

4. Containing the spread of antimalarial drug resistance

Key elements of the strategy to contain the spread of drug resistance once it has emerged are:

a. Intensify implementation of all the previous strategies listed under 1, to avoid the further spread of drug resistance
   i) in particular halt the use of oral monotherapies.
b. Change antimalarial treatment policy to remove selection pressure on the parasites by medicines to which the parasites are resistant
   i) vigorous efforts to limit exposure to the drug to only that necessary for treatment (control of private sector practice, increased use of parasitological diagnosis).
c. Eliminate the foci of resistant malaria
   i) rapid detection and full treatment of cases which may be carrying resistant parasites through intensified surveillance and response
   ii) detection and treatment of asymptomatic parasite carriers by screening appropriate populations using rapid and highly sensitive diagnostic tools (e.g. high throughput PCR or other methods)

iii) focus on detecting and protecting priority population groups - i.e. people most likely to carry and spread resistant parasites (eg., mobile and migrant populations). Protection will include rapid access to standard treatment and prevention measures, as well as tailored personal protection, such as mosquito repellents

iv) adopting measures to prevent the export of parasites to other areas where possible

v) cross-border and regional collaboration among countries to implement the above.

d. Operational research to:

i) determine the specificities in the local situation

ii) map accurately the geographical extent of resistance

iii) determine potential route and mechanisms of spread

iv) test the feasibility and effectiveness of systems to implement new strategies (such as screening, surveillance and response, accessing mobile populations).

Role of the partnership

The contributions to be made by each of the seven RBM constituencies and by the RBM partnership mechanisms are outlined in the following table.

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Proposed Contributions of RBM Constituency and RBM Mechanisms to Managing Antimalarial Resistance

1. Preventing the emergence of antimalarial drug resistance (1)

a. Use of combination therapies
b. Halt the use of oral monotherapies
c. Increase access to good quality medicines by:
   i) making efficacious ACTs affordable and widely accessible in both the public and private sectors
   ii) using medicines correctly, including in the private sector, by education of practitioners and patients.
d. Improve compliance with recommended treatment regimens by use of co-formulated (fixed dose) combination medicines
   i) supervising drug administration where possible to help to ensure adherence.

RBM Board Constituencies[1]	**MEC:** Ensure policies promote universal access and use, mobilize resources, manage public sector procurement, distribution and programmatic use, stewardship of private sector.
	MLD: Develop and promote strategies to ensure appropriate use, support guidelines, develop national capacity, oversee monitoring, promote research. Advocate for enforcement of ban on oral artemisinin monotherapies
	NGO: Increase reach to inaccessible populations, field test strategies, collect information, advocate for support, develop capacity.
	OECD & FDN: Provide resources, advocate for full implementation of strategies, promote harmonization of contributions.
	PVT: Identify and meet needs for R&D, promote good practice in private sector, support better forecasting and avoidance of supply shortages. Peer pressure on pharmaceutical sector to observe best practice.
	RES: Studying the effectiveness of multiple first line therapies in preventing the emergence of drug resistance. Systems research to improve delivery.
RBM Partnership Mechanisms[2]	**CMWG:** Resistance Workstream to coordinate further strategy development, analyse previous containment efforts, disseminate lessons. Develop an operational framework for implementing a partnership strategic plan to manage resistance.
	CMWG: Access to Treatment/Service Delivery Workstream to gain consensus on strategies for rapid scale-up of better access to full and effective treatment including community case management, referral and facility treatment. Identify bottlenecks, communicate through RBM partnership and advise on approaches to solution.
	SEC, MAWG: Develop and disseminate messages on the importance of rational drug use and on resources needed to prolong useful life of ACTs.
	MERG: Support monitoring of coverage of effective diagnosis and treatment.
	HWG: Coordinate partnership inputs to resource mobilization and technical assistance. Ensure that applications to GFATM have appropriate resources and activities to ensure universal access to parasitological diagnosis and appropriate treatment with ACTs at all levels of the health care system, including training and supervision of HCWs as well as BCC and IEC activities at the community level.
	RWG: Contribute to resource mobilization strategies for timely and adequate response.
	SRNs: Work with countries to assess and respond to TA needs.

[1] **MEC**=Malaria Endemic Countries, **OECD**=OECD countries, **MLD**=Multilateral Development Agencies, **RES**=Research and Academic, **PVT**=Private Sector, **NGO**=Non-Governmental Organizations, **FDN**=Foundations.
[2] **SRN**=Subregional RBM Network, **SEC**=RBM Secretariat, **CMWG**=Case Management Working Group, **PSM**=Procurement and Supply Management WG, **MERG**=Monitoring and Evaluation Reference Group, **MAWG**=Malaria Advocacy Working Group, **HWG**=Harmonization Working Group. **RWG**=Financing and Resources Working Group, **WIN**=Vector Control Working Group.

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Proposed Contributions of RBM Constituency and RBM Mechanisms to Managing Antimalarial Resistance (continued)

1. Preventing the emergence of antimalarial drug resistance (2)

e. Striving for universal parasitological confirmation of malaria by:
   i) reinforcing quality microscopy where available and increasing access to quality assured rapid diagnostic tests
   ii) using diagnostics correctly, including in the private sector, by education of practitioners
   iii) adhering to microscopy results, by educating both providers and patients.

RBM Board Constituencies[1]	**MEC:** Clarify diagnosis policies, implement scale-up of parasitological diagnosis. **MLD:** Promote new strategy of universal parasitological diagnosis. Provide operational guidance to countries on scale up of parasite based diagnosis. Support quality assurance systems for products and their use. **NGO:** Support roll-out of diagnostics, implementation research. **OECD & FDN:** Develop funding mechanism for universal access to parasitological diagnosis in public and private sector. **PVT:** Improve quality of affordable RDTs, promote private sector uptake. **RES:** Socio-economic research on use of diagnosis, testing of new tools.
RBM Partnership Mechanisms[2]	**CMWG:** Diagnosis Task Force to formulate scaling up strategies. **SRNs:** Work with countries to assess and respond to TA needs.

f. Exclude poor quality and counterfeit drugs from markets.

RBM Board Constituencies[1]	**MEC:** Enforce legislation, strengthen enforcement capacity. **MLD:** Coordinate international efforts to drive out fake and substandard drugs; technical support to national drug regulatory authorities. **NGO:** Advocacy; technical support to national drug regulatory authorities. **OECD & FDN:** Financial and strategy support, influence on source countries. **PVT:** Influence on manufacturers and distributors, improved quality control and packaging. **RES:** Surveillance for substandard drugs, development of less expensive and more easily usable tests.
RBM Partnership Mechanisms[2]	**PSM, CMWG:** Contribute as needed. **MAWG:** Awareness raising.

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Proposed Contributions of RBM Constituency and RBM Mechanisms to Managing Antimalarial Resistance (continued)

1. Preventing the emergence of antimalarial drug resistance (3)

g. Reduce transmission rates to lower the malaria burden (size of the parasite population) and to reduce the use of antimalarial drugs (less drug pressure on parasites) by:

i) vector control methods including insecticide treated mosquito nets and indoor residual spraying

ii) reduction of the reservoir of infection (responsible for the spread of drug resistance) by improving therapeutic practice, in particular early diagnosis and effective treatment, and use of gametocytocidal medicines where safe and appropriate

iii) deploying future vaccines and other proven transmission reduction tools as they become available.

RBM Board Constituencies[1]	**MEC:** implement scale-up of vector control strategies **MLD: (WHO)** clear policy recommendations on use of transmission blocking medicines and strategies; support scaling-up of proven vector control methods, and evaluation of evidence for new vector control tools as they are developed. **NGO:** Support scale up of vector control methods, particularly ITNs **OECD & FDN:** Develop funding mechanism for scaling up, and sustaining coverage with vector control methods. **PVT:** Development and registration of new and improved vector control tools and promote uptake; develop and register vaccines. **RES:** Research on gametocyctocidal medicines; Phase III research on first generation vaccines; upstream and development research on second generation malaria vaccines; research on novel insecticides for existing vector control approaches, and development of novel vector control tools.
RBM Partnership Mechanisms[2]	**WIN:** WIN Task Force to formulate strategies for scaling up and sustaining coverage with recommended vector control interventions. **SRNs:** Work with countries to assess and respond to TA needs.

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Proposed Contributions of RBM Constituency and RBM Mechanisms to Managing Antimalarial Resistance (continued)

2. Monitoring antimalarial drug efficacy, and when necessary confirming drug resistance

a. Routine monitoring of therapeutic efficacy of first and second-line medicines as an integral component of malaria control.

RBM Board Constituencies[1]	**MEC:** Conduct routine therapeutic efficacy studies in sentinel sites as an integral component of malaria control; actively participate in regional and sub-regional therapeutic efficacy networks. **MLD: (WHO)** Coordinate data collection, analysis, dissemination and capacity building. Provide to countries, standardized methodologies and tools for therapeutic efficacy monitoring; provide technical assistance to countries and sub-regional networks. Make publicly available global data on drug efficacy and resistance. **NGO:** Support countries to conduct surveillance on therapeutic efficacy, and to run sentinel sites. **OECD & FDN:** Coordinated and predictable financial support for therapeutic efficacy monitoring and ensure that such funding is an integral component of malaria control package. **PVT:** support therapeutic efficacy studies in countries of existing and new medicines. **RES:** Develop and validate new tools for early detection of drug resistance. Engage national research institutions and NMCPs to ensure quality data, support global databases of efficacy data.
RBM Partnership Mechanisms[2]	**CMWG:** Support WHO efforts and countries in routine surveillance for therapeutic efficacy. HWG: Ensure that applications to GFATM have appropriate resources and activities for routine malaria surveillance as well as routine conduct of *in vivo* drug efficacy studies. **SRNs:** Work with countries on TA needs. **RES:** develop and validate new tools.

b. Research to confirm presence of resistance using in vitro, molecular markers or pharmacokinetic data, & to validate new tools.

RBM Board Constituencies[1]	**MEC:** Develop priority research agenda and coordinate country activities. Collaborate with research institutions. **MLD:** Provide standardized protocols and standard operating procedures. Coordinate and promote priority research. Synthesise and disseminate results. **NGO:** Undertake country level research, engage in PDPs. Implement field research. **OECD & FDN:** Support priority research and capacity development for research. **PVT:** Ensure manufacturers monitor efficacy of own products. **RES:** Design and implement research plans.
RBM Partnership Mechanisms[2]	**CMWG:** Identify implementation systems and collaborate on design of research to test strategies.

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Proposed Contributions of RBM Constituency and RBM Mechanisms to Managing Antimalarial Resistance (continued)

3. Ensuring a continuous pipeline of new antimalarial medicines

a. Develop and register new antimalarial combination medicines with different targets of action and in accordance with the recommended target product profiles, and ensure a steady development pipeline.

RBM Board Constituencies[1]	**MEC:** Support in country research institutions to conduct research and development on new antimalarial medicines, and develop clinical trial sites for their evaluation. **MLD:** (WHO) Define target product profiles of new medicines, and co-operate and support drug development agencies and institutions, by identifying and advocating for needs, opportunities and partnerships; (TDR) capacity development on drug development, and developing partnerships. **NGO:** Support field studies on new medicines, including and specially Phase IV studies, and advocacy, and nurture product development partnerships. **OECD & FDN:** Coordinated and predictable financial support and investment for new medicines development. **PVT:** develop quality medicines in accordance with TPPs and in compliance with prequalification standards. Commitment through CSR programmes. **RES:** laboratory and clinical research on new medicines for malaria through all phases including Phase IV (PMS).
RBM Partnership Mechanisms[2]	**CMWG:** Support clinical trial sites. **SRNs:** Work with countries to support clinical testing of new medicines. **RES:** develop and test new medicines. **SEC & MAWG:** Advocate for resources for new drug development.

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Proposed Contributions of RBM Constituency and RBM Mechanisms to Managing Antimalarial Resistance (continued)

4. Containing the spread of antimalarial drug resistance (1)

a. Intensify implementation of all previous strategies listed under #1, to avoid the further spread of drug resistance

i) in particular halt the use of oral monotherapies.

RBM Board Constituencies[1]

MEC: Develop national containment preparedness, communicate to country partnership.

MLD: Develop, disseminate and advocate clear strategies.

NGO: Support implementation of containment strategies, advocate for resource, develop and test surveillance systems, private sector strategies and work with marginalised and mobile populations.

OECD & FDN: Develop mechanisms for more rapid resource mobilization where resistance is strongly suspected, allocate sufficient resources.

PVT: Contribute to emergency efforts through donations, rapid processing of orders, communication.

RES: Measure spread and impact of resistance and strategies to contain it. Evaluate strategies for containment in mobile populations.

RBM Partnership Mechanisms[2]

As in (1) above.

b. Change antimalarial treatment policy to remove selection pressure on the parasites by medicines to which the parasites are resistant

i) vigorous efforts to limit exposure to the drug to only that necessary for treatment (control of private sector practice, increased use of parasitological diagnosis).

RBM Board Constituencies[1]

MEC: Enforce oral monotherapy bans, stewardship of private sector, improve public sector access.

MLD: International advocacy for evidence-based strategies, global monitoring and report of spread.

NGO: Support testing, implementation and monitoring of strategies, assist resource mobilization.

OECD & FDN: International influence on best practice, rapid resource mobilization.

PVT: Peer pressure on pharmaceutical sector to observe best practice.

RES: Test new strategies, assess role of mass drug administration.

RBM Partnership Mechanisms[2]

As in (1) above.

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Proposed Contributions of RBM Constituency and RBM Mechanisms to Managing Antimalarial Resistance (continued)

4. Containing the spread of drug resistance (2)

c. Eliminate foci of drug resistant malaria by:

i) rapid detection and full treatment of cases which may be carrying resistant parasites through intensified surveillance and response
ii) detection and treatment of asymptomatic parasite carriers by screening appropriate populations using highly sensitive diagnostic tools
iii) focus on detecting and protecting priority population groups
iv) adopt measures to prevent export of resistant parasites
v) cross border and regional collaboration on implementing strategies.

RBM Board Constituencies[1]	**MEC:** re-programme malaria control efforts to include elimination efforts in foci as a high priority. **MLD: (WHO)** support countries to co-ordinate partnership action in support of focal elimination; co-ordinate and support intercountry cross border planning and implementation. **NGO:** Support implementation of elimination efforts and assist resource mobilization. **OECD & FDN:** Investment of resources on an emergency basis. **PVT:** Support high priority elimination efforts in country with resources - both financial and in kind. **RES:** Conduct monitoring and evaluation of elimination programmes.
RBM Partnership Mechanisms[2]	**CMWG:** Support WHO efforts on strategy implementation. **SEC, MAWG:** Advocate for resources for elimination efforts. Awareness raising. **PSM:** Contribute as necessary, especially in fast tracking procurement of supplies.

d. Operational research to:

i) determine the specificities of the local situation
ii) spatially map extent of resistance
iii) determine potential routes and mechanisms of spread
iv) test feasibility and effectiveness of new strategies to contain the spread of resistance.

RBM Board Constituencies[1]	**MEC:** Develop priority research agenda and coordinate country activities. Collaborate with research institutions. **MLD:** Coordinate and promote priority research. Synthesize and disseminate results. **NGO:** Undertake country level research, engage in PDPs. Implement field research. **OECD&FDN:** Support priority research and capacity development for research. **PVT:** Ensure manufacturers monitor efficacy of own products. **RES:** Design and implement research plans.
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