



Evidence for antimalarial policy and access

TDR BUSINESS LINE 9

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Table of contents

Overview and highlights	5
1. Context, strategic objectives and framework	7
1.1 Context and rationale	7
1.2 Overall strategic objective	8
1.3 Specific objectives	8
1.4 Strategic framework	9
2. Key stakeholders, roles and responsibilities	12
3. Implementation plan 2008–2013 and progress	14
3.1 Plan, progress and key milestones	14
3.2 Implications of progress/delays and global context changes on 2008–2013 plans	16
4. BL leverage, synergies with TDR business lines and contributions to empowerment and stewardship	17
4.1 Leverage	17
4.2 Contribution to overall empowerment and stewardship objectives	17
4.3 Elements enhancing sustainability of BL outcome	18
4.4 Synergies with work of other TDR business lines	18
5. Critical issues and suggested solutions	19
6. Annexes	20
6.1 Publications resulting from BL or related activities	20
6.2 SAC membership	21
6.3 Detailed table of implementation plans and progress for 2008–2013 activities	22
6.4 Details of revision of business plan	26
6.5 Responses to specific JCB/STAC requests	26

List of abbreviations

ACT	Artemisinin Combination Therapy	GMP	Global Malaria Programme
ACT Initiative	Artemisinin Combination Therapy Initiative	HMM	Home Management of Malaria
ACTWatch	A consortium providing evidence for malaria policy (http://www.actwatch.info)	INESS Consortium	INDEPTH Efficacy and Safety Studies Consortium
AMFm	Affordable Medicine Facility for malaria	malERA	Consortium of research funders and scientists to eradicate malaria
CCM	Community Case Management	MDGs	Millennium Development Goals
CIDA	Canadian International Development Assistance	MMV	Medicines for Malaria Venture
DNDi	Drugs for Neglected Diseases Initiative	NGO	Non-governmental organization
ENTIS	European Network of Teratology Information Services	PSI	A nonprofit organization that delivers products/services to improve health
GFATM	Global Fund to Fight AIDS, TB and Malaria	SAC	Scientific Advisory Committee

Overview and highlights

Progress in reducing under-five mortality in sub-Saharan Africa can be achieved by increasing access to available effective and affordable tools. The over 1 million deaths from malaria that occur worldwide each year are avoidable, using effective treatment, and preventive strategies, but only 10% of malaria fevers are treated appropriately and prevention is not always the standard of care. Countries lack the evidence base to make appropriate antimalarial policy choices and for improving care delivery at the community level. To meet Millennium Development Goals, evidence that demonstrates what treatment packages can work to reduce mortality from malaria and other childhood fevers is required in communities where vulnerable groups live.

The malaria landscape is changing. Epidemiological studies show that in several areas malaria transmission and burden are decreasing, due to increased and combined use of efficacious tools. The number of partners working on delivery systems for antimalarial medicines is increasing, all with the aim of improving access to efficacious tools and medicines by underserved populations in disease-endemic areas. There is renewed interest in primary health care and community involvement. The newly developed Global Malaria Action Plan places emphasis on scaling up use of malaria control tools to reach the level of sustained control that is prerequisite to malaria elimination. Malaria elimination is within reach in several countries and a target in sight in many others. Malaria eradication has ceased to be a remote dream and has a well-defined research agenda supported by the donor community.

The research promoted by BL9 addresses the above context to focus on four objectives:

1. To provide stewardship and a convening platform that can facilitate assessment of the safety, effectiveness and access to antimalarial drugs in “real-life” conditions of use, at different levels of the health system;
2. To contribute to the assessment of the safety and effectiveness of antimalarial interventions and combined interventions in special groups and vulnerable populations;
3. To develop and assess an integrated implementation strategy, based on tools of proven efficacy, for the diagnosis and treatment of malaria episodes of various degrees of severity at the community level;
4. To develop an integrated case management strategy for malaria, pneumonia and other febrile illnesses to be delivered at the community level and to measure its public health impact.

The research will generate evidence for policy, defining the type of interventions that are best suited for different countries with different epidemiological, socio-economic and cultural contexts. and develop approaches for reaching hard-to-reach populations. These interventions will be developed in a context in which tools for the prevention of malaria, such as impregnated bednets, are the standard of care. The long-term goal is to use the evidence to support the adoption and implementation of appropriate policies and public health practices in disease-endemic countries.

Research undertaken during 2008 has laid the groundwork for the coming two years of work. Evidence has been produced that artemisinin-based combination therapy (ACT) can be integrated into community-level malaria treatment strategies and

that pre-referral rectal artesunate is a life-saving form of treatment in children who are distant from clinics. Policy-makers in some countries are already using this evidence to revise their malaria control strategies. Protocols for assessing the safety of ACTs in pregnant women are being piloted and research protocols have been developed to provide the evidence on how different diagnostic and therapeutic tools can best be combined effectively to reduce the malaria burden. While this BL is on track in delivering expected research results, there is an urgent need to inject adequate, fresh resources in order to maintain momentum and reinforce TDR's position in the malaria research landscape.

1. Context, strategic objectives and framework

1.1. Context and rationale

Malaria is a preventable disease that causes more than 1 million deaths a year. There are good drug treatments and diagnostics, but they are not being used extensively enough in many disease-endemic countries (DECs), and only 10% of fevers are treated appropriately. Substantial progress in reducing under-five mortality in sub-Saharan Africa can be achieved by increasing access to available effective and affordable tools — rapid diagnostic tools, artemisinin-based combination therapies (ACTs) and appropriate case management. However, countries often lack the evidence base to make appropriate antimalarial policy choices and to improve care delivery at the community level. To meet Millennium Development Goals, evidence that guides malaria treatment policy with proven malaria treatment packages and other childhood fevers is required in communities where vulnerable groups live.

There is now a call to eliminate and eventually eradicate the disease, with increased political commitment to scale up interventions in several sub-Saharan African countries where the burden of malaria is greatest. There is consensus on the need to expand research beyond drug registration to develop integrated and sustainable delivery strategies for the treatment of malaria and other childhood fevers as early as possible.

Supporting this, there has been a substantial increase in international funding for malaria control during the past five years through major international financing mechanisms such as the Global Fund to Fight HIV, TB and Malaria, the US President's Malaria Initiative and the World Bank's Booster Programme, as well as NGOs and programmes focused on drug development and access like the Medicines for Malaria Venture (MMV) and Drugs for Neglected Diseases initiative (DNDi).

The newly developed Global Malaria Action Plan places emphasis on scaling up use of malaria control tools to reach the level of sustained control that is prerequisite to malaria elimination. Malaria elimination is within reach in several countries and a target in sight in many others. Malaria eradication has ceased to be a remote dream and has a well-defined research agenda supported by the donor community.

The aim of the malaria business line is to use this current momentum to demonstrate the impact of integrated treatment interventions on the burden of disease. At the same time, evidence on the safety of treatment interventions in populations where safety has not yet been demonstrated will also be obtained. To accelerate translation to strategies and policy advice for countries, this business line will also provide consortia and research groups with forums for sharing research methods and approaches and for pooling and synthesizing related evidence. The stewardship function related to artemisinin-combination treatment (ACT) safety and effectiveness will be managed within the framework of Business Line 9.

1.2. Overall strategic objective

The overall strategic objective is to provide evidence for policy and practice by (i) developing strategies for improved access to effective treatment for malaria and other childhood fevers at all levels of the health system (ii) by assessing safety in specific populations or with specific treatments and (iii) accomplishing both these objectives by training the next generation of public health specialists in collaboration with BL2.

1.3. Specific objectives

Specific objectives were revised by the BL9 Strategic Advisory Committee (SAC) in June 2008, including the recommendations to include a new objective (objective 1 below) to fulfill a stewardship role, and slightly revising the wording of objectives 2, 3 and 4 (see Annex 6.4) to fill the need for a platform for discussing and coordinating research carried out by many researchers and consortia in ACT safety and effectiveness. TDR can facilitate collaboration, coherence and provision of evidence for policy among overlapping initiatives.

Specific objectives are to:

1. Provide stewardship and a convening platform that can facilitate the assessment of safety, effectiveness and access to antimalarial drugs in “real-life” conditions of use, at different levels of the health system;
2. Contribute to assessment of the safety and effectiveness of antimalarial interventions in special groups and vulnerable populations;
3. Develop and assess an integrated implementation strategy, based on tools of proven efficacy, for the diagnosis and treatment of malaria episodes of various degrees of severity at the community level;
4. Develop an integrated case management strategy for malaria, pneumonia and other febrile illnesses to be delivered at the community level, and measure its public health impact.

1.4. Strategic framework

The business line operates in close collaboration with WHO's Global Malaria Programme (GMP), thus combining TDR's R&D strength with GMP's disease control mandate. Activities draw upon the technical advice of a Strategic Advisory Committee (SAC) comprising international experts with different areas of expertise, policy-makers and implementers from disease-endemic countries (DECs) and members from civil society. The model is based on continuous review and update of priority research areas, competitive selection of proposals to be funded, provision of technical support to research teams, monitoring by the secretariat and SAC, and

prompt analysis and dissemination of research results. Particular importance is given to training individuals in the conduct of intervention research; integrating community-based research into broader efforts to strengthen the health system; and working with participating countries to facilitate adoption of research results by policy makers and scale-up successful implementation strategies

Fig. 1 illustrates schematically the strategic framework by objectives, end-products and outcomes.

Indicators to measure end-products delivery and outcomes have been developed and are presented in Table 1 (see next page).

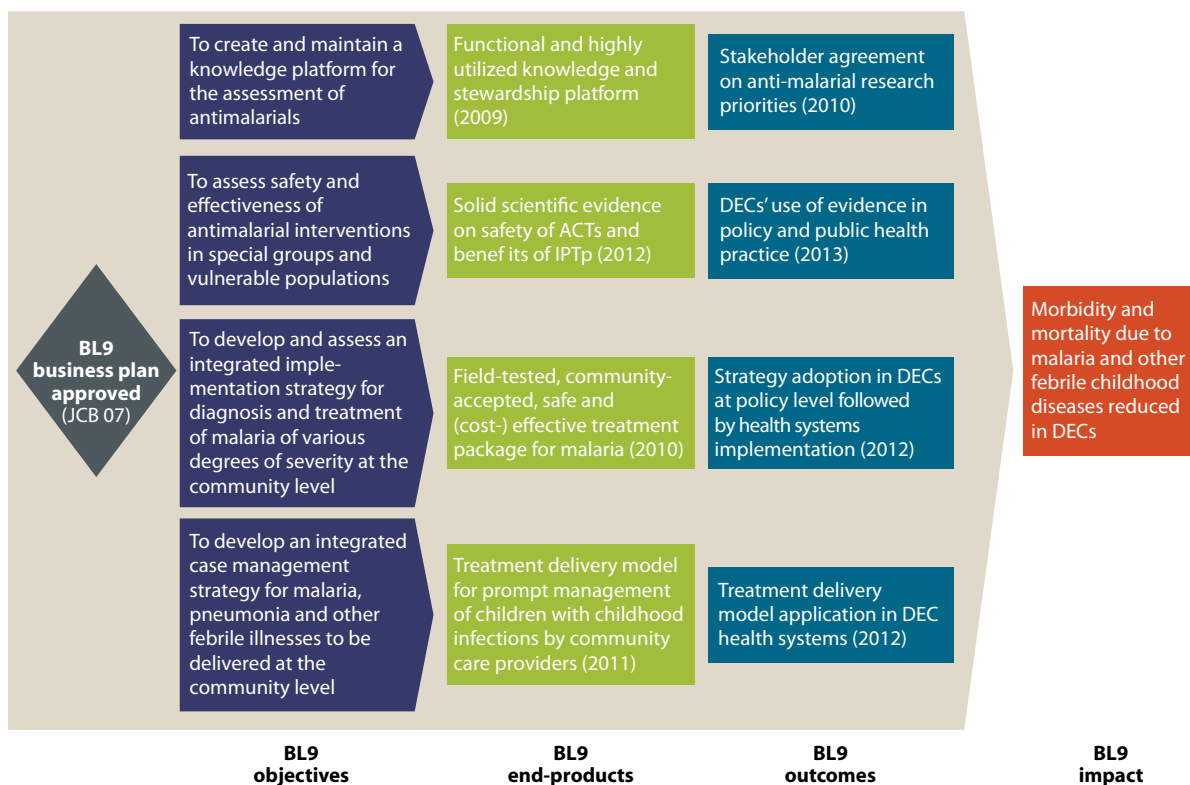


Fig. 1. Evidence for antimalarial policy and access: strategic approach

TABLE 1. INDICATORS FOR END-PRODUCTS AND OUTCOMES

BL9 objectives	End-products (by 2013)	Indicators for end-products	Expected outcomes	Indicators for expected outcomes
1. To provide a stewardship and convening platform that can facilitate the assessment of the safety, effectiveness and access to antimalarial drugs in “real-life” conditions of use at different levels of the health system	Functional and highly utilized knowledge and stewardship platform available by 2009	SharePoint established on TropIKA.net and maintained (up-to-date mapping of stakeholders’ involvement, roles and responsibilities) SharePoint utilized by increasing number of stakeholders	Stakeholder agreement on antimalarial research priorities and respective roles and responsibilities from 2010 onwards	Common plan available from 2010 onwards
2. To contribute to the assessment of the safety and effectiveness of antimalarial interventions in special groups and vulnerable populations	Registration of rectal artesunate. Evidence of strategies for wide uptake in communities including follow-up with ACTs by 2013 Solid scientific evidence on safety of ACTs and benefit of intermittent preventive treatment (IPTp) by 2012	Marketing authorization report and scientific publications by 2012 Evidence dissemination meetings held with national policy-makers by 2012	DECs use of evidence in policy and public health practice by 2013	Number of countries incorporating the research results into their policies
3. To develop and assess an integrated implementation strategy, based on tools of proven efficacy, for the diagnosis and treatment of malaria episodes of various degrees of severity at the community level	Field-tested, community-accepted, safe and cost-effective treatment package for malaria by 2010	Report and publications of study results on feasibility, acceptability, cost-effectiveness of the treatment package for malaria (Malawi, Uganda, Nigeria and Burkina Faso) by 2010	Strategy adoption in DECs at policy level allowed by health systems implementation by 2012	Number of countries adopting the strategy

TABLE 1. INDICATORS FOR END-PRODUCTS AND OUTCOMES (CONTINUED)

BL9 objectives	End-products (by 2013)	Indicators for end-products	Expected outcomes	Indicators for expected outcomes
4. To develop an integrated case management strategy for malaria, pneumonia and other febrile illnesses to be delivered at the community level, and to measure its public health impact	Treatment delivery model for prompt management of children with childhood fevers by community care providers by 2011	Report and publications of study results on feasibility, acceptability and cost-effectiveness of the treatment delivery model for malaria (Uganda, Ghana and Burkina Faso) by 2011	Treatment delivery model application in DEC health systems by 2012.	Number of countries adopting the strategy

The four objectives are synergised to achieve the overall goal of improving access to effective treatment for malaria and other childhood fevers to reduce overall childhood mortality. TDR is generally recognized as an institution able to provide the appropriate overarching architecture for partners of different natures to share experiences and develop common research methodologies with respect to pharmacovigilance and effectiveness of and access to antimalarial medicines. Objectives 2, 3 and 4 constitute a research continuum in which evidence-

based guidance on antimalarial drug policy forms the basis for the development of a diagnostic and treatment package for malaria case management at the community level. This in turn can be further expanded to integrate malaria treatment into the broader context of case management of childhood fevers due to different causes. The anticipated outcome is the adoption by disease-endemic countries (DECs) of a sound antimalarial drug policy in the context of an efficient and integrated treatment delivery model.

2. Key stakeholders, roles and responsibilities

A number of new stakeholders have entered the arena, both as donors, e.g. the Bill & Melinda Gates Foundation and the Global Fund to Fight AIDS, Tuberculosis and Malaria, and as implementers of programmes in the field and policy arena.

Some implementing programmes are led by public-private partnerships (PPPs) such as the Medicines for Malaria Venture (MMV) and Drugs for Neglected Diseases initiative (DNDi), or consortia of PPPs and other governmental or non-governmental agencies.

Some consortia, such as the ACT Consortium and the INESS Consortium, have a strong research perspective, while others focus mainly on market expansion and monitoring (e.g. the Affordable Medicines Facility for malaria initiative (AMFm), ACTwatch, the MMV Access Initiative and the EU-funded ACT Initiative).

Still other consortia are focused on efficacy and safety of different strategies for improving control — for example the Malaria in Pregnancy consortium. Other important initiatives are being undertaken by the Malaria Consortium, Médecins sans Frontières, Population Services International, and the Clinton Foundation; these address both operational research and programme implementation. All consortia aim to improve access to ACTs, including through collaborations with the private sector, formal or informal, and influence malaria control policy in disease-endemic countries.

As the malaria research landscape has become more crowded, the BL will focus on its role as an independent broker and convener — objective 1 in this BL. In relation to other objectives, TDR will work closely with consortia and other organizations named above, insofar as they provide value added to the objectives in this workplan.

As part of WHO, TDR works closely in a coordinated fashion with other WHO departments involved in malaria control, childhood health and disease treatment policy (e.g. WHO's Department of Child and Adolescent Health, Making Pregnancy Safer, Department of Procurement and Supply Management and the WHO Regional Office for Africa as well as the Global Malaria Programme); UN agencies such as UNICEF and the Global Fund for AIDS, TB and Malaria (GFATM); malaria control programmes in disease-endemic countries; regulatory authorities, drug development agencies and various other partners.

TDR and GFATM have recently developed a framework for implementation research in health and disease control programmes. This includes the standardization of operations research across the international health community and the stimulation of the integration of operations research into health programmes. TDR co-leads a group of partners interested in operational research to develop community case management (CCM) of malaria, pneumonia and diarrhoea. This group comprises developing country research institutions such as Makerere University, Uganda; Université Cheikh Anta Diop, Senegal; the Health Research Unit, Ghana; and the Centre National de Recherche et Formation sur le Paludisme (CNRFP) in Burkina Faso, as well as developed-country institutions such as Sweden's Karolinska Institute and Boston University, USA.

In terms of the UN system, WHO's Child and Adolescent Health Department and the Global Malaria Programme are key stakeholders, as are other UN agencies such as UNICEF. Bilateral aid agencies, e.g. USAID, and NGOs such as Save the Children and the International Rescue Committee also play a role. Furthermore, TDR's BL9 is contributing its research experience in Africa

to several major ongoing initiatives on access to antimalarial medicines. These include the AMFm initiative led by Roll Back Malaria and the GFATM, the multi-disciplinary global R&D initiative malERA, the MMV access group, and the RBM-led Global Action Plan for Malaria.

TDR, through BL9, is also part of the WHO-MMV-AMFm-GFATM initiative on active pharmacovigilance studies with a special focus on questions of safety of ACTs distributed in the context of the AMFm. Departments in the WHO (Making Pregnancy Safer, Global Malaria Programme, Quality and Safety of Medicines and TDR-BL9) have led the development of a global pregnancy register for medicines including ACTs. This is an activity not covered by the Malaria in Pregnancy Consortium (MiP), but common membership of committees contributes to sharing of information between the WHO Pregnancy Register and the MiP. Finally, TDR-BL9 is involved in studies on the use of rapid diagnostic tests (RDTs) at the community level to optimize deployment of ACTs and guide treatment for malaria and other illnesses that have fever as the main symptom.

The specific roles and responsibilities of all partners are being analysed and developed under activities related to objective 1 (see table in Annex 6.3).

3. Implementation plan 2008–2013 and progress

3.1. Plan, progress and key milestones

The list of activities presented to STAC in 2008 is detailed in Annex 6.3. Progress and specific highlights of this are:

- Landscaping work on the safety and efficacy of ACT deployment.** A consultant has been competitively selected to produce a document landscaping the activities and roles of research partners working on safety, real-life effectiveness and access to antimalarial medicines. The document will help identify gaps and priorities so that TDR can bring groups together in March 2009 to discuss and develop workplans. The consultant will also assist in structuring the SharePoint platform provided by the Tropika.net web site to support this group's work.
- Rectal artesunate.** A TDR-supported large randomized controlled trial has established that the administration of a single rectal artesunate suppository substantially reduced the risk of death or disability in patients in rural villages with severe malaria who could not take oral medication and could not access antimalarial injections for several hours. The trial undertaken in malaria-endemic areas of Bangladesh, Ghana and the United Republic of Tanzania is the largest randomized controlled study in severe malaria and assesses the value of rectal artesunate in remote community-based settings. TDR-generated evidence from hospital-based studies has already been used in support of the WHO recommendation of rectal artemisinins for pre-referral treatment. Evidence from the large-scale trial further supports treatment recommendations by the Malaria Treatment Guidelines Committee. Hospital studies to examine the benefit of single-dose and sequential treatment in very young children are under way in Ghana and the United Republic of Tanzania.
- Making rectal artesunate available in “real-life” conditions through community health workers.** A multi-country deployment study in Ghana, Guinée Bissau, United Republic of Tanzania and Uganda assessing the advantage of mother-coordinators has concluded and data are being analysed; publication is planned in 2009. The trial answers outstanding questions: What is the coverage achieved by different dispensers providing near-home rectal artesunate treatment in real-life settings? How should community personnel be trained and supported to make the drug available? Will patients and guardians feel that hospital referral can be deferred after their child has received a suppository or will they adhere to advice to go to the hospital?
- Pregnancy registry on safety of ACTs in pregnancy and in HIV-infected subjects.** TDR/WHO's leadership in revealing that there are some adverse events in preclinical studies and insufficient evidence on safety in human pregnancy has united research consortia and malaria and reproductive health programmes in a joint and global effort to obtain large-scale evidence on the safety of artemisinins in pregnancy and to source complementary funding for work by WHO and academic research programmes. A protocol to examine any increased risk of congenital abnormalities consequent to exposure to antimalarial medicines in resource-poor settings where more than one-fifth of women can be HIV-positive has been developed for global application; large-scale evidence will only be derived from wide application at antenatal care centres through a centralised repository for managing and analysing

the data. Countries for global implementation of the protocol have been identified with GMP, HIV and Make Pregnancy Safer departments. Funds for implementation are being sought with technical support provided by WHO's Making Pregnancy Safer, HIV, Global Malaria Program and Safety of Medicine departments and by relevant consortia. The European Network of Teratology Information Services (ENTIS) and the US Organization of Teratology Information Specialists have offered to develop training programmes to support clinical assessment of newborn children, thereby improving the reliability of data on congenital abnormalities in resource-poor settings.

- **Feasibility, acceptability, effectiveness of ACT use at the community level.** New evidence has been generated through multi-country studies and published in peer-reviewed journals. These results now contribute to national policy decisions, e.g. Ghana and Uganda, to allow use of ACTs at the community level and to declassify ACTs from prescription-only to over-the-counter medicines.
- **Improving access to ACTs through the private sector.** The results of a study carried out in Kenya evaluating the distribution of ACTs through private shops operating with a franchising system has contributed to a paper prepared to inform the Affordable Medicine Facility for malaria (AMFm).
- **Home management of malaria (HMM) for uncomplicated malaria.** The studies launched in 2005 to adapt the HMM strategy to urban settings have continued, as have studies launched in 2006 to establish the role of rapid diagnostic tests (RDTs) within HMM. These are all on track in several sub-Saharan African (SSA) countries and are anticipated to be completed by the end of 2009.
- **Home management of malaria (HMM) for uncomplicated and severe malaria.** The original HMM concept has been expanded to include RDTs and rectal artesunate for severe malaria. Eight research teams from SSA countries participated in a proposal development workshop, with the four best proposals approved for funding and implementation in 2009. These proposals will establish the feasibility, acceptability and cost-effectiveness of this new concept.
- **Integrated management of fevers.** There are three randomized controlled trials to establish the benefit of integrated treatment of malaria and pneumonia, two of which are anticipated to be completed by the end of 2009.

3.2. Implications of progress/ delays and global context changes on 2008–2013 plans

The malaria world is experiencing an unprecedented momentum of new initiatives targeting malaria elimination and — in the long run — eradication, which require packaging and scaling-up of effective interventions, evidence on how combined interventions can be used at different levels of the health system, and information on safety of treatment where information is lacking. The research priorities of this BL are consistent with the new initiatives and elimination goals. They inform policy through a focus on 1) testing delivery systems to improve access to antimalarial treatment by hard-to-reach and vulnerable populations, 2) investigations on how to scale up interventions, and 3) studies on how to integrate malaria diagnosis and care into systems that also manage other illnesses of fever.

These and other areas of work on safety and benefit of treatment in vulnerable populations have been jointly developed with WHO's Global Malaria Programme so that the research is responsive to WHO's research priorities both in countries that still have relatively high malaria prevalence as well as those that have been able to substantially reduce malaria, but where a new mix of tools may be required to make further progress. These research areas greatly contribute to the goal of universal coverage with effective tools that the recently developed Global Malaria Action Plan defines as a prerequisite to malaria elimination. In areas with low malaria transmission, TDR will be working closely with the Global Malaria Department and the relevant WHO regional offices to identify the research relevant to choice of strategies for elimination.

In the context of attaining the Millennium Development Goals (MDGs), there is now renewed interest from donors in the upscaling of integrated community case management of the three main childhood killer diseases — malaria, pneumonia and diarrhoea. This represents an area of research led by TDR since 2000. As mentioned in section 2 of this report, an operational research group co-chaired by TDR and the Karolinska Institute, and including the Child and Adolescent Health department in the WHO, several NGOs and other research institutions, has linked to a community case management task force headed by UNICEF to advance work on this issue. Funding is being sought for a number of identified key research priorities, and if this is successful, will impact on the workplan.

4. BL leverage, synergies with TDR business lines and contributions to empowerment and stewardship

4.1. Leverage

Successful TDR home management of malaria (HMM) research has led to CIDA funding to evaluate the impact on childhood mortality of large-scale HMM programmes to be implemented by Population Services International (PSI) in three sub-Saharan African countries. The evaluation project starts in early 2009 and has been funded with a grant of US\$ 2.5 million.

4.2. Contribution to overall empowerment and stewardship objectives

The Antimalarial Policy/Access business line participates fully with TDR's Stewardship Function. Further to its specific stewardship role described under objective 1, it is also providing input into the development and running of the malaria disease reference group, whose findings will be used for a global report on infectious diseases coordinated by TDR's overall Stewardship Function.

The principle of empowerment permeates the strategic approach of BL9. The very nature of its research — oriented to inform policy — implies the need to move beyond simple collaboration with partners in disease-endemic countries and towards full engagement of policy-makers in those countries. Empowerment of caregivers is a critical element in community-level management of malaria. Gender issues and inequities affect access to and uptake of malaria-related interventions at the community level. This BL places emphasis on empowering and

recognizing the role of mothers in society, as they bear the children and are the principal providers for them. When they can be taught to recognize illness in their children and treat it early, mothers play a crucial role in the community-level treatment of malaria and other acute childhood fevers.

The overall Empowerment Function in TDR also provides key support in the development and implementation of BL9-funded studies. It provides critical input into development of proposals and finalization of study protocols, as well as into the clinical monitoring of funded studies (Fig. 2).

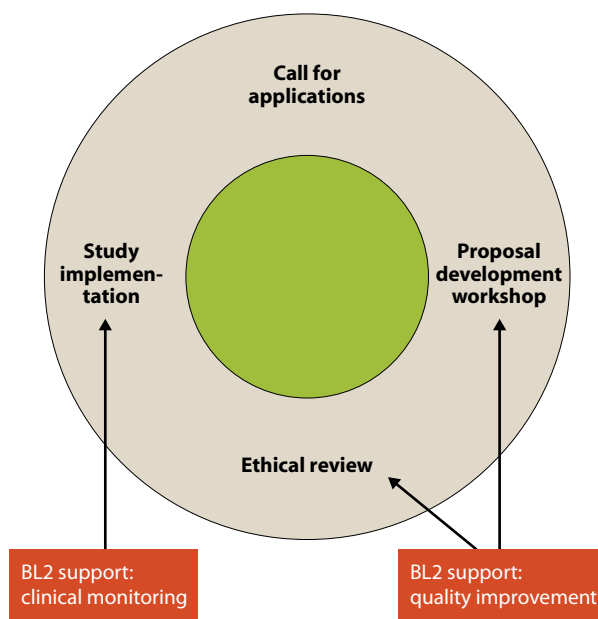


Fig. 2. BL9 project cycle

4.3. Elements enhancing sustainability of BL outcome

The ultimate aim of the research promoted by the Antimalarial Access/Policy Business Line is to inform malaria control policy in DECs. This will be pursued in three different and synergistic ways: (i) at the planning stage, when research axes are identified and discussed with WHO's Global Malaria Programme and Child and Adolescent Health department and the African regional office to ensure consistency with research priorities in DECs; (ii) engagement of local policy-makers in the research teams; and (iii) dissemination of results through publications, workshops and meetings.

4.4. Synergies with work of other TDR business lines

The Antimalarial Access/Policy business line has links to several other business lines, including Innovative Vector Control Interventions (BL5), Accessible Quality-assured Diagnostics (BL7) and Integrated Community-based Interventions (BL11). Results of studies supported by BL9 — e.g. relative to RDT or rectal artesunate use within the context of Home Management of Malaria — will feed into, and possibly be incorporated in, the package of community-directed interventions developed by BL11. Furthermore, BL9 and BL11 will have a synergistic approach to common research areas, such as the development of community-level intervention models in urban areas and research on incentives and motivating factors for community agents to ensure sustainability of activities. BL7 and BL9 also have developed some joint research protocols, e.g. to elucidate clinical and parasitological outcome of malaria patients with negative rapid diagnostic test (RDT) results. The research on RDT use at community level will also contribute to the assessment of RDT performance under real-life conditions of use.

5. Critical issues and suggested solutions

Many of the issues being addressed by research in this business line are pressing and require rapid answers; both countries and donors need quick results. However, there is a risk related to the complexity of the environment and of players involved in the research. To be accepted by all players as an independent convening platform for information sharing, this business line needs to operate as an honest broker between all sectors and organizations involved. The credibility and legitimacy of this business line will be jeopardized if it fails to present itself as an independent body and to develop true partnerships.

This BL is intended to provide support to the global effort of the malaria research community towards malaria elimination; as such it will need to be receptive to the needs related to the changing epidemiological context of malaria and flexible enough to quickly address them.

At the same time, research in this BL needs to fit into the broader context of health system research and contribute to the overall strengthening of the health system. It is critical that research is conducted within the context of country programmes and as a concerted effort with all relevant stakeholders.

There is an understandable lag time between initiating research and producing research results, but technical and other support should be provided to projects to minimize this time lag. Furthermore, to be relevant, these activities should start or be scaled up very soon, and research should be conducted within the context of country programmes and as a concerted effort with relevant stakeholders.

6. Annexes

6.1. Publications resulting from BL or related activities

1. Ajayi I et al. Feasibility and acceptability of artemisinin-based combination therapy for the home management of malaria in four African sites. *Malaria Journal*, 2008, 7:6 10.1186/1475-2875-7-6. PMID:18182114.
2. Ajayi I et al. Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: a report from three study sites in sub-Saharan Africa. *Malaria Journal*, 2008, 7:190 10.1186/1475-2875-7-190. PMID:18822170.
3. Ajayi I et al. A qualitative study of the feasibility and community perception on the effectiveness of artemether-lumefantrine use in the context of home management of malaria in south-west Nigeria. *BMC Health Services Research*, 2008, 8:119. PMID:18513447.
4. Gomes M et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet*, 8 December 2008, 8: 10.1016/S0140-6736(08)61734-1.
5. Gomes M et al. Rectal artemisinins for malaria: a review of efficacy and safety from individual patient data in clinical studies. *BMC Infectious Diseases*, 2008, 8:39:1471-2334.
6. Pagnoni F. Treatment for malaria: no place like home. *Trends in Parasitology*. In press.
7. Sabot O et al. *Distribution of artemisinin-based combination therapies through private sector channels: lessons from four country case studies*. Paper presented at the presented at the Consultative Forum on the Affordable Medicines Facility for malaria (AMFm), Washington, 25-26 September 2008. In press.
8. Tiono A et al. Implementation of home-based management of malaria in children reduces the work load for peripheral health facilities in a rural district of Burkina Faso. *Malaria Journal*, 2008, 7:201. PMID:18834504.

6.2. SAC membership

	Proposed member	Area of expertise	DEC	Non-DEC	M	F
1	Don De Savigny (chair)	Health systems research		✓	✓	
2	Kaendi Munguti	Social sciences, medical anthropology	✓			✓
3	Peter Brown	Medical anthropology		✓	✓	
4	Catherine Goodman	Health economics		✓		✓
5	Karen Barnes	Epidemiology, drug resistance		✓		✓
6	Umberto d'Alessandro	Epidemiology, malaria control		✓	✓	
7	Patrick Kachur	Epidemiology, malaria control		✓	✓	
8	Alex Dodoo	Pharmacovigilance	✓		✓	
9	Miriam Chipimo	Malaria in pregnancy	✓			✓
10	K. Corine (NMCP manager, Rwanda)	Malaria control	✓			✓
11	George Amofah (deputy director general, GHS)	Malaria control policy	✓		✓	
12	Stefan Peterson	Integrated management of childhood fevers		✓	✓	
13	WHO AFRO malaria regulations advisor	Malaria control				
14	Medécins Sans Frontières (Martin De Smet)	Malaria control, partnership				
15	UNICEF (Alexandra de Sousa)	Malaria control, partnership				
16	Malaria Consortium (Sylvia Meek)	Malaria control, partnership				
Total			5	7	7	5

6.3. Detailed table of implementation plans and progress for 2008-2013 activities

ANNEX 6.3. BL9 WORKPLAN, 2008–2013, BY OBJECTIVE

Objectives/ research areas	Proposed activities	Milestones	Deliverables and respective impact
1. To provide the stewardship and convening platform to facilitate the assessment of the safety, effectiveness and access to antimalarial drugs in “real-life” conditions of use, at different levels of the health system	<ol style="list-style-type: none"> 1. Commission the work of cataloguing all of the projects, actors, methods and tools of all ACT safety, effectiveness and access studies 2. Structure the SharePoint and keep it up to date 3. Convene meetings of stakeholders in safety, effectiveness and access on specific needs, e.g. methods development 4. Analysis and publication on the state, trends and needs of ACT safety, effectiveness and access research and experience <p>Periodic synthesis of collective experiences with a view towards contributing evidence to strategies and policy</p>	<p>Catalogue of projects, actors, methods and tools, Q4 2008</p> <p>Stakeholders’ meeting involving all players in ACT phase IV, safety and access, Q1 2009</p> <p>Collection and evaluation of the safety of ACT following switch from POM to OTC, ongoing</p>	

Objectives/ research areas	Proposed activities	Milestones	Deliverables and respective impact
<p>2. To contribute to the assessment of the safety and effectiveness of antimalarial interventions in special groups and vulnerable populations</p>	<ol style="list-style-type: none"> 1. Continue and consolidate the development of a core protocol for pregnancy registries 2. Extract evidence from country experiences with the protocol to provide evidence of safety of ACTs in pregnancy and in HIV-infected subjects 3. Establish additional evidence on the effectiveness of antimalarial drugs for treatment and prevention in special situations as required for policy (e.g. SP-based IPTp in the current malaria control environment) 4. Establish the factors affecting treatment response in different populations and at different levels of the health system 5. Completion of hospital studies to establish benefit of sequential treatment with rectal artesunate in infants 	<ol style="list-style-type: none"> 1.1 Development of core protocol in collaboration with other interested parties (1Q 2008) 1.2 Pregnancy register: testing of tools and implementation in sentinel sites by 4Q 2008 1.3 Examine country experiences with the registry (4Q 2010) 2.1 Research questions identified, study design defined, & protocol completed, Q4 2008 2.2 Studies launched, Q2 2009 4.1 Research questions identified, study design defined for completion of protocol, Q1 2010 4.2. Studies launched, Q2 2010 5.1 Intake completed, end 2010 	<ol style="list-style-type: none"> 1.1 Evidence on safety of ACTs in pregnant women and HIV-infected subjects available 3.1 Evidence available on benefit of intermittent preventive treatment (IPTp) in different settings 4.1 Evidence available on treatment response at different levels of health system 5.1 Evidence on sequential treatment of <i>non per os</i> young children available

ANNEX 6.3 CONT. BL9 WORKPLAN, 2008–2013, BY OBJECTIVE

Objectives/ research areas	Proposed activities	Milestones	Deliverables and respective impact
<p>3. To develop and assess an integrated implementation strategy based on tools of proven efficacy for the diagnosis and treatment of malaria episodes of various degrees of severity at the community level</p>	<ol style="list-style-type: none"> 1. Conclude ongoing preparatory research in 12 sub-Saharan African countries on feasibility, acceptability and effectiveness of ACT, RA and RDT use at community level 2. Initiate one multi-country study (3-4 countries) to develop an adequate delivery strategy for the comprehensive package 3. Initiate one large-scale multi-country study (3-4 countries) to establish the cost-effectiveness, public health impact and optimal approach to implementation of a comprehensive package 4. Provide guidance required by national health systems to scale up to the community level with an effective package 	<ol style="list-style-type: none"> 1.1 Results from preparatory research available by June 2009 2.1 Research questions identified, study design defined, protocol completed, Q3 2008 2.2 Studies launched Q1 2009; e.g. product stability studies 3.1 Multi-country studies on cost-effectiveness and impact initiated by the end of 2009 3.2 Findings on cost-effectiveness and impact of the treatment package available and disseminated by the end of 2012 	<ol style="list-style-type: none"> 1.1 Evidence from preparatory research available 2.1 A field-tested, community-accepted, safe and effective treatment package for malaria episodes of various degrees of severity at the community level is available 3.1 Evidence of the cost-effectiveness and impact of the comprehensive diagnostic and treatment package to reduce severe malaria morbidity and mortality

Objectives/ research areas	Proposed activities	Milestones	Deliverables and respective impact
<p>4. To develop an integrated case management strategy for malaria, pneumonia and other febrile illnesses to be delivered at the community level, and to measure its public health impact</p>	<ol style="list-style-type: none"> 1. Conclude ongoing preparatory research in three sub-Saharan African countries to develop a treatment delivery model for prompt management of children with uncomplicated malaria and pneumonia by community care providers 2. Initiate a multi-country study to generate evidence on the benefit-to-risk ratio, behaviour, public health and health system impacts, cost and cost-effectiveness of an integrated intervention for malaria, pneumonia and other febrile illnesses 3. Provide guidance required by national health systems to scale up to the community level with an effective package 	<ol style="list-style-type: none"> 1.1 Two preparatory studies completed by June 2009 (Ghana, Uganda) 1.2 One additional preparatory study completed by December 2010 2.1 Research questions identified, study design defined, protocol completed, Q4 2008 2.2 Studies launched, end Q1 2009 2.3 Evidence available by 2012 	<ol style="list-style-type: none"> 1.1 A treatment delivery model for prompt management of children with childhood fevers by community care providers is available 2.1 Evidence on the effectiveness of the combined intervention is available for use by countries in sub-Saharan Africa

6.4. Details of revision of business plan

Revisions of the business plan introduced by BL9 SAC, June 2008:

- A new objective has been added (Objective 1): *To provide a stewardship and convening platform that can facilitate the assessment of the safety, effectiveness and access to antimalarial drugs in “real-life” conditions of use, at different levels of the health system.*
- Objectives 3 and 4 have been slightly reworded:
 - To develop and assess an integrated implementation strategy, based on tools of proven efficacy, for the diagnosis and treatment of malaria episodes of various degrees of severity at the community level.
 - To develop an integrated case management strategy for malaria, pneumonia and other febrile illnesses to be delivered at the community level, and measure its public health impact.
- Section 2 (Needs and opportunities) and 3 (TDR comparative advantage) have been revised to address STAC recommendations.
- The workplan has been revised to reflect changes in objectives and update milestones.

6.5. Responses to specific JCB/STAC requests

Recommendation STAC 2007

Objectives and activities to be more clearly defined in relation to ongoing/forthcoming major national/international initiatives on malaria research and control to i) maintain profile and niches; ii) achieve best possible synergies

Response: the recommendation was addressed in collaboration with the BL9 SAC. A new objective has been added and objectives 3 and 4 have been slightly reworded, as noted above, while Section 2 (Key stakeholders, roles and responsibilities) was completely revised.

Recommendations JCB 2007

1. *Importance of efforts by TDR and JCB participants at political level for strengthening national institutions and research at international level.* Response: this was addressed in a revised section 4: BL leverage, synergies with other BLs, and contributions to empowerment and stewardship.
2. *Pay attention to research on impact of climate change on tropical and vector borne diseases.* Response: see revised section 1 (Context).



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