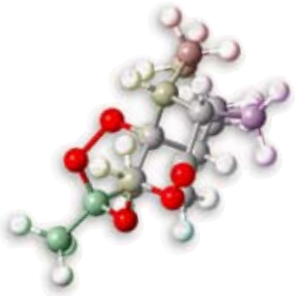
THE ARTEMISININ ENTERPRISE

Exploring new sources of artemisinin

REPORT of the 2008 Artemisinin Enterprise Conference October 8-10 York UK

Meeting the Malaria Treatment Challenge: Effective introduction of new technologies for a sustainable supply of ACTs



Roll Back Malaria

RBM

ROLL BACK MALARIA PARTNERSHIP

iOWH

Institute for OneWorld Health

Medicines for Malaria Venture

THE UNIVERSITY of York

Department of Biology

CNAP

CENTRE FOR NOVEL AGRICULTURAL PRODUCTS

BIOLOGY TO BENEFIT SOCIETY

BILL & MELINDA GATES foundation

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“Almost every death from malaria is a wholly avoidable tragedy.”

Professor Christopher Whitty, Chair of International Health,
London School of Hygiene and Tropical Medicine

image: © CNAP.

Executive Summary

The World Malaria Report 2008 highlights that in 2006 there were between 189 and 327 million cases of malaria annually with over 880,000 deaths, 85% of which are children in sub-Saharan Africa. In the face of increasing parasite resistance to antimalarial drugs such as chloroquine, 75 countries have adopted the 2001 WHO recommendation to switch to using artemisinin combination therapies (ACTs) for the first-line treatment of uncomplicated malaria caused by the *P. falciparum* parasite. There is now increasing global investment for ACT treatments to underpin the call for malaria eradication and an unparalleled opportunity for effective and sustained progress. A massive scaling-up of activity is forecast.

This window of opportunity is finite due to the ever-present threat of the development of resistance to the only effective drugs available - ACTs. The influential report "Saving Lives, Buying Time" (Institute of Medicine, 2004) warned that access to effective treatment with ACTs must be expanded in the fight against malaria but this must be accompanied by measures to preserve their effectiveness, such as eliminating the use of artemisinin monotherapies.

Against this background there is growing concern that the current global supply chain will be unable to produce consistent, affordable and high quality artemisinin in the quantities that will be required for the projected demand for ACTs.

The Artemisinin Enterprise (AE) comprises the Centre for Novel Agricultural Products at the University of York, UK; the Institute for OneWorld Health, USA; and the Medicines for Malaria Venture, Switzerland. Supported by the Bill & Melinda Gates Foundation, the AE projects have a collective aim of rapidly improving the production technologies of artemisinin and developing a more stable, rapidly acting, fully synthetic artemisinin-like compound.

The three projects of the AE represent a portfolio approach to address the need for affordable and reliable sources of ACTs, with complementary technologies that work in different ways and at different points in the supply chain.

CNAP	Fast-track breeding of *Artemisia annua* to increase yields of plant-derived artemisinin and develop new high-yielding varieties
iOWH	Artemisinin derived by microbial fermentation in yeast with subsequent chemical conversion
MMV	Development of a novel class of compounds for their incorporation into antimalarial drug combinations

The third annual Artemisinin Enterprise (AE) Conference was co-sponsored by the Bill & Melinda Gates Foundation and the Roll Back Malaria partnership (RBM) and convened at the University of York, UK in October 2008. It built on the experience and gains from earlier AE meetings and broadened participation to include researchers, growers, policymakers, regulatory experts, Product Development Partnerships (PDPs) and industry representatives. The objective was to update the malaria community on project progress and work with stakeholders to ensure a complementary deployment of the new technologies to meet the projected global demand for ACTs. The stakeholders were invited to assess the impact of the three new technologies on the ACT supply chain and provide a series of recommendations on how best to ensure smooth and effective integration of products derived from the new technologies into the supply chain so that they contribute to the envisaged growth in demand for ACTs.

Assessment of the impact of the AE technologies by the stakeholders

The three new AE technologies should:

- increase the supply of high quality artemisinin to meet projected needs;
- lower the cost of artemisinin production with sustainable technologies;
- remove volatility in artemisinin prices by improving the reliability of and diversifying artemisinin supply;
- develop novel synthetic artemisinin-like compounds.

Stakeholders agreed that the technologies of the three AE partners have the potential to contribute to the rapid acceleration in the manufacture and use of ACTs that will be essential to meet the targets of the Global Malaria Action Plan, drawn up by the Roll Back Malaria Partnership. Through underpinning the consistent supply of quality ACTs, the AE technologies will play an important role in mitigating the risk of parasite resistance. The stakeholders confirmed that the outputs from all three AE technologies will be essential to satisfy the projected global demand for malaria treatments.

Recommendations for the Artemisinin Enterprise

The recommendations of the Conference are set out in detail in the report. Those organisations tasked with progressing the issues are identified.

For all AE partners:

The Conference considered it important that the outputs from the AE technologies should be used only for the manufacture of high quality ACTs. A mechanism should be developed in collaboration with RBM Procurement and Supply Chain Management Working Group (RBM PSM) and other relevant stakeholders to ensure that outputs are not diverted to the manufacture of other products.

An effective, joined-up communication strategy should be developed by the AE partnership that provides regular updates to the wider malaria community on progress, approximate timelines for delivery and likely impact on artemisinin and ACT prices. As part of this activity it will be important to address the impact of artemisinin production through fermentation and the development of synthetic peroxides on farmer confidence, particularly given the continuing role of plant-derived artemisinin in the supply chain for the coming years.

In order to ensure that there is a high level of awareness of the work of the AE partners, a regular forum for stakeholders should be established to maintain active discussion on key topics relating to the development and deployment of the AE technologies. There should be recognition of the ongoing requirement for all three of the emerging technologies for the foreseeable future of global ACT use and malaria eradication.

For CNAP:

New communication networks should be developed to ensure the wider community, as well as growers and extractors in major growing locations of Africa and Asia, is aware of progress and regional developments in field trialling the new high-yielding varieties. Experience gained in different environmental and climatic conditions of cultivation should be widely communicated.

Farmer and extractor knowledge, confidence and participation are essential to the successful uptake of the outputs of the CNAP work. These key elements should be developed by the early engagement of farmers and extractors in field trialling, training and transfer of good agricultural practice through extension services - all of which are components that need to be delivered as part of an effective global roll out.

As the development of new varieties could impact on artemisinin extraction including impurity profiles, this aspect should be assessed early through interactions with extractors, derivatisers and ACT manufacturers.

For iOWH:

As the iOWH project develops, forward-looking communications about the project will be essential and should provide updates on target price and volume estimates in order to enable growers and other stakeholders to adjust to the changing artemisinin landscape.

For MMV:

The new synthetic endoperoxide under development by MMV is subject to all the risks associated with drug research and development. Stakeholders should be kept aware of progress at each stage of the lengthy development process.

Recommendations for the wider malaria community

The Conference noted the essential need for accurate demand forecasting. RBM and UNITAID should develop an agreed set of planning assumptions to support demand forecasting. A single set of demand forecasts, universally available and regularly updated, should inform the wider community and ACT manufacturers.

Supply/demand mismatches have had a major negative impact on the supply chain for artemisinin in recent years. RBM PSM Working Group and relevant

stakeholders should consider mechanisms and design an action plan to mitigate future supply/demand mismatches. Suggested ways forward included: buffer stocks, fair trade/price arrangements, farmer incentives, financial risk sharing, the development of grower cooperatives and off-take arrangements. An open and transparent options analysis should be carried out within a year, to assess the relative merits of these suggestions.

The significant scale-up of the use of rapid diagnostic tests for malaria recommended by the Global Malaria Action Plan was noted. This scale-up should be integrated into the therapy mix in parallel with the development of a strategy for the treatment of patients who do not have malaria.

RBM PSM, working closely with other stakeholders including the MMV Access team, should consider how regulatory and health guidance mechanisms can be used to minimize the use of counterfeit drugs, monotherapies and Artemisia teas thereby maximizing benefits of the new AE technologies.

The Conference considered it important to work to achieve consensus that, from a regulatory perspective, artemisinin should be considered to be a starting material rather than an API. A full regulatory and cost analysis of this area should be undertaken by at least one major regulatory body, and preferably more, within a year to avoid the risk of differential decisions in this area by different regulatory bodies. The RBM PSM Quality Assurance workstream should work together with ACT and API manufacturers to consider and clarify whether and how changing the source of artemisinin may impact existing registrations. This will involve assessing detailed information on specification, manufacturing process and related issues held in registration files.

During the Conference, the desire that malaria-endemic countries have local production of antimalarial treatments at international quality standards was highlighted. Donors and international regulatory bodies should consider pathways to promote sustainable and appropriate development of regulatory and pharmaceutical capacity in these countries that is sustainable.

The lack of detailed information on current capacity in the extraction and derivatisation sector was noted. RBM PSM Working Group should review the current capability to extract artemisinin from plant material by undertaking a quantitative economic study and assessment of current global extractor/derivatiser capacity.

The innovations of the Artemisinin Enterprise provide important opportunities to improve significantly the ACT supply chain. If the three new AE technologies are implemented effectively and in a timely manner, benefits can include increased stability in artemisinin supply, reduction in artemisinin production costs and improved quality of end products. Communication and transparency are all-important to create the much needed stability and stakeholder confidence to realize the full potential of the new technologies for the treatment of malaria.

Artemisia harvesting, Kenya, © CNAP

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"We are at a point in time with an unprecedented window of opportunity. Funding is already in place for phenomenal quantities of ACT."

Alan Court, Senior Adviser to the Office of the Secretary General's Special Envoy for Malaria, United Nations

image: © CNAP.

Introduction to the 2008 Artemisinin Enterprise Conference

In the face of increasing parasite resistance to antimalarial drugs such as chloroquine, 75 countries have adopted the 2001 WHO recommendation to switch to using artemisinin combination therapies (ACTs) for the first-line treatment of uncomplicated malaria caused by the *P. falciparum* parasite. The influential report "Saving Lives, Buying Time" (Institute of Medicine, 2004) warned that access to effective treatment with ACTs must be expanded in the fight against malaria, but this must be accompanied by measures to preserve their effectiveness, such as eliminating the use of artemisinin monotherapies. There is an ever-present threat of the development of resistance to ACTs and a growing concern about the global supply chain of artemisinin. It is recognized that there is a finite timeline within which to eradicate malaria. Given the substantial financial investment now available, it is imperative that there is a consistent, affordable and high quality artemisinin supply in the quantities that will be required for the projected demand for ACTs.

Supported by the Bill & Melinda Gates Foundation, the Artemisinin Enterprise (AE) comprises three projects with the aim of rapidly improving the production technologies of artemisinin and developing a more stable, rapidly acting, fully synthetic artemisinin-like compound.

In June 2007 the Artemisinin Enterprise met with selected ACT manufacturers and Artemisia growers and extractors to discuss the goals, plans and timing for low cost alternative supplies of artemisinin. The meeting was widely considered as highly useful. The discussions focused the thoughts of the Artemisinin Enterprise partners on the wider issues of project roll-out.

The AE Conference 2008 provided an update of progress for the malaria community on the three projects and went on to consider the impacts and opportunities of introducing the AE technologies into existing supply chains. The Conference brought together high-level stakeholders from the fields of global health, policymaking, industry, agriculture, economics, access and delivery. Discussions benefited from the expertise and experience of these stakeholders who were invited in breakout groups to make recommendations on how best to integrate the new AE technologies. The conference was supported with funding from the Bill and Melinda Gates Foundation. The Roll Back Malaria Partnership joined the Artemisinin Enterprise as co-sponsors and their expertise was crucial in helping to devise and plan the event.

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“The Artemisinin Enterprise is meant as a portfolio approach - we have to attack this broadly because we have such a tremendous threat - not only the loss of lives but the threat of resistance.”

Dr Tom Brewer, Senior Program Officer,
Bill and Melinda Gates Foundation

image: © Bill & Melinda Gates Foundation/ Liz Gilbert.

The Artemisinin Enterprise Partners

The projects in the Artemisinin Enterprise share the ultimate goal of making high quality ACTs less expensive and more accessible to the people who need them.

The Artemisinin Enterprise comprises three complementary scientific projects with support from the Bill & Melinda Gates Foundation. The aim of the Enterprise is to improve artemisinin production technologies, which should:

- diversify the sources of high quality artemisinin;
- lower the cost of artemisinin production;
- stabilize supplies, preventing cyclical fluctuations in artemisinin prices;
- provide new antimalarial combinations;
- make high quality ACTs less expensive and therefore more accessible.

All three approaches are needed to satisfy projected global demand for ACTs. The projects are collaborating for maximum impact on ACT supply chains and to ensure the new technologies do not enter substandard drug or monotherapy supply chains. Successful delivery of the Artemisinin Enterprise projects will make an important contribution to the provision of affordable ACTs and new malaria therapeutic options, whilst providing incentives for existing Artemisia growers and artemisinin manufacturers to remain in the market.

3.1 The CNAP Artemisia Research Project

Introduction to the project

This project aims to produce high-yielding varieties of *Artemisia annua* using fast track molecular breeding technologies. The new varieties will:

- help to reduce the cost of artemisinin production and secure sustainable supplies;
- incentivise existing growers and producers to stay in production by improving crop quality and increasing returns;
- bring environmental benefits in terms of reduced transport requirements, waste generation and the amount of solvent used for extraction.

The project represents a step change in the plant breeding of a pharmaceutical crop both in terms of scale of programme and in the sophistication of the technologies involved. It is based at the Centre for Novel Agricultural Products (CNAP). This centre, which is part of the University of York, specializes in gene discovery with plant-based applications. The project's research team is led by Professor Dianna Bowles and Professor Ian Graham and comprises over twenty scientists with expertise in plant breeding, plant phenotyping and molecular biology, as well as administrative and outreach staff.

The Artemisia plant

The aromatic herb Artemisia is currently the sole source of the vital antimalarial drug artemisinin and will continue to be essential to supplies for the foreseeable future. However, the yield of artemisinin from the plant is very low, making production expensive. Relatively little has been done to develop this plant from a wild

weed into a fully domesticated crop so there is much scope for improvement.

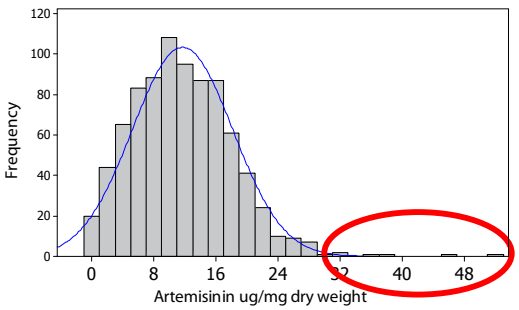
The plant makes and stores artemisinin in specialised groups of cells known as glandular trichomes, which are found on the leaves, stems and flowers. Yields might be increased by:

- increasing the number of leaves on a plant;
- increasing the number of trichomes on a leaf;
- increasing the productivity of the trichomes.

Searching for high-yielding plants

A seed treatment widely used in plant breeding has been applied to an existing Artemisia cultivar (Artemis) in order to boost the genetic diversity within the population. Many thousands of plants grown from this treated seed are being screened for useful features. For example, rapid high-throughput analytical tests enable exact measurement of artemisinin and other key plant metabolites to be performed on thousands of individual plants. Many plant lines have been identified with artemisinin contents significantly higher than that of the existing variety Artemis and these are now being tested for their field performance and heritability.

Frequency distribution of artemisinin content in batch of screened plants. Ringed individuals are worthy of further study.



Useful genetic diversity does not always show up in plant features so plants are also being screened at the DNA level. A range of approaches is being used to identify genes with the potential to impact artemisinin yields. A technique known as “heteroduplex mapping“ is used to hunt through the genome and pick out plants with variations in these target genes. The effect of this genetic variation on artemisinin yield is then assessed. Genetic modification (GM) is used as a laboratory tool for the identification of target genes but not in the production of crop plants: the plant varieties produced will be non-GM.

A variety of molecular tools are being used to examine the natural genetic diversity present in Artemisia. Genetic mapping of the Artemisia plant is helping us understand which genes underlie good agricultural performance. We are also developing molecular markers - genetic sequences that are associated with high-performing plants. These markers will help us to recognize valuable individuals whilst they are still young plants, greatly speeding up the breeding process.

Development of high-yielding varieties

Once promising plants have been identified, molecular markers and further trait and DNA screening speeds up their conversion from promising individuals to agriculturally viable crop varieties. Throughout the development of new varieties, the plants are field-trialled at several sites to test their performance in different growing regions of the world. The Swiss not-for-profit organisation, Mediplant (breeders of the Artemis variety), is working with us on classical plant breeding and plant husbandry aspects of the project.

To ensure that the project meets the requirements of the supply chain and stays relevant in the face of

new developments, the project regularly consults with industry representatives including growers, extractors, processors and pharmaceutical companies.

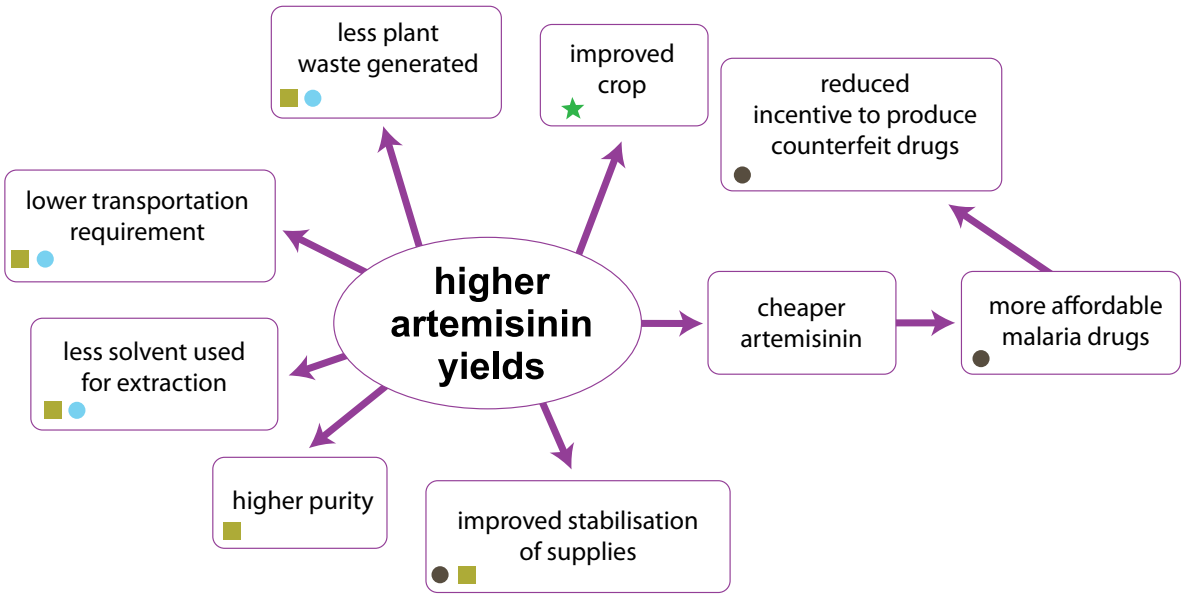
Access to the new varieties

We are developing a global access plan that aims to deliver sufficient seed of the new varieties in quantity at cost to the ACT supply chain. By improving the supply of artemisinin for ACTs, this project - along with the other projects in the Artemisinin Enterprise - aims to contribute towards making effective malaria treatments more accessible to those who need them.

For more information on the project visit:
http://www.york.ac.uk/org/cnap/artemisiaproject/index.htm

For regular updates on project progress email:
CNAP-artemisia@york.ac.uk

Benefits of new high-yielding varieties of *Artemisia annua*

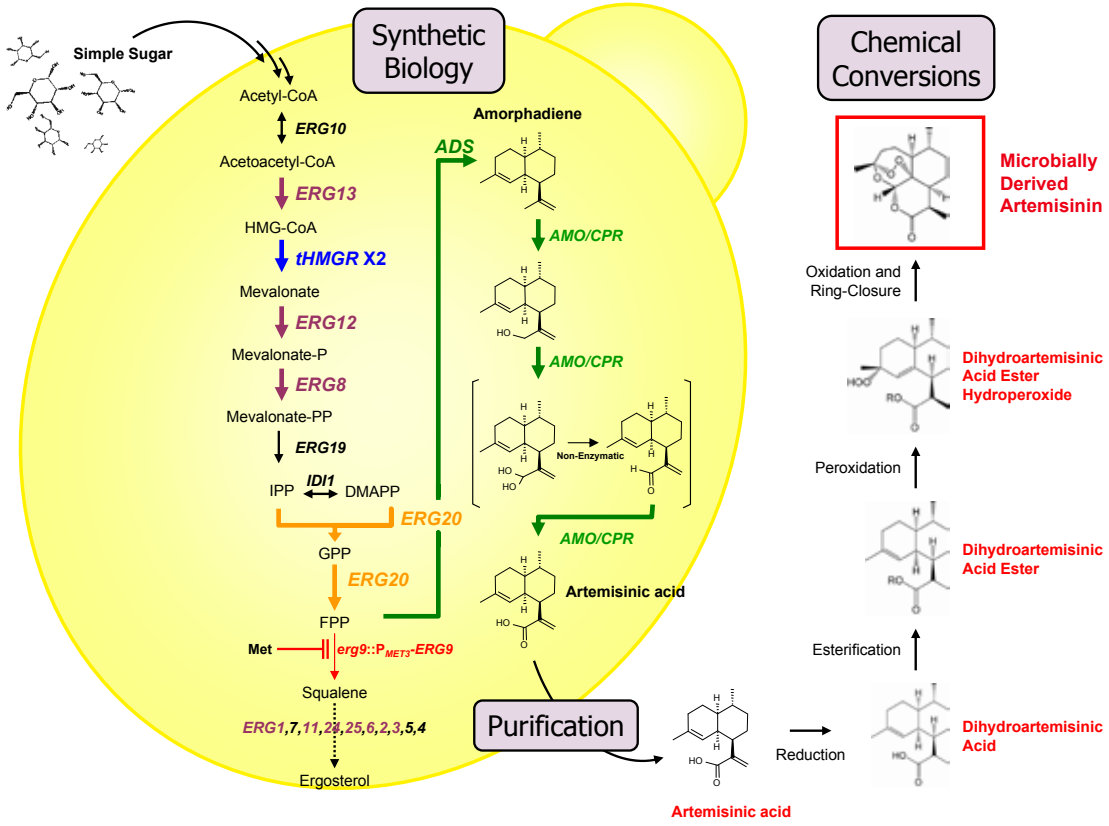


3.2 The iOWH Semisynthetic Artemisinin Project

Introduction

The Artemisinin Project will establish and validate a new manufacturing process to make semisynthetic artemisinin, and from that, artemisinin-based combination therapies (ACTs). ACTs need to be accessible and affordable for those who suffer from malaria, particularly those living at or below poverty levels in developing countries of the world. To meet this goal, the project is applying scientific and drug development expertise in a unique public / private partnership of diverse groups with critical knowledge and skills that can pool talents to address this major global health problem.

The project is a collaboration between The Institute for OneWorld Health (iOWH), Dr. Jay Keasling and the University of California at Berkeley, Amyris Biotechnologies, and sanofi-aventis. The goal is to develop a manufacturing process using microbial "factories" to produce artemisinic acid, a key precursor to artemisinin. This precursor will be chemically converted to artemisinin via novel chemical processes. The major objective of the project is to produce a non-seasonal complementary supply of artemisinin, of consistent quality and cost, thus stabilizing the price of ACTs. It is anticipated that artemisinin will be a highly purified starting material. This will enable the synthesis of artemisinin derivatives as an Active Pharmaceutical Ingredient (API) that meets all existing compendial specifications, allowing a transparent substitution into ACTs.



The process

Artemisinin, the starting material for the derivatives used in ACTs, is currently extracted from *Artemisia annua*, an annual, very labour-intensive crop with a lengthy growing cycle (12-18 months). The plant's artemisinin content is quite sensitive to genetic backgrounds as well as cultivation conditions and harvesting periods. The Artemisinin Project team is creating semisynthetic artemisinin by engineering microorganisms (in this case, yeast) to produce large amounts artemisinic acid. Specifically, the yeast has been engineered to alter its metabolism and incorporate genes from the plant *A. annua* for high level production of artemisinic acid. Standard chemistry techniques are then used to complete the synthesis to artemisinin.

The partnership

The Artemisinin Project brings together academia, small business, large pharma and a non-profit PDP to address a critical need in global health. iOWH's role in this collaboration is to be the engine that drives the technology from the bench to commercialization. Our expertise is to integrate basic science, pharmaceutical best practices, project management communications and advocacy with the goal of introducing a new source of artemisinin into the supply chain. It is this unique combination of basic research, PDP experience, and large pharma processes that allows us to tackle a global problem on such a large scale.

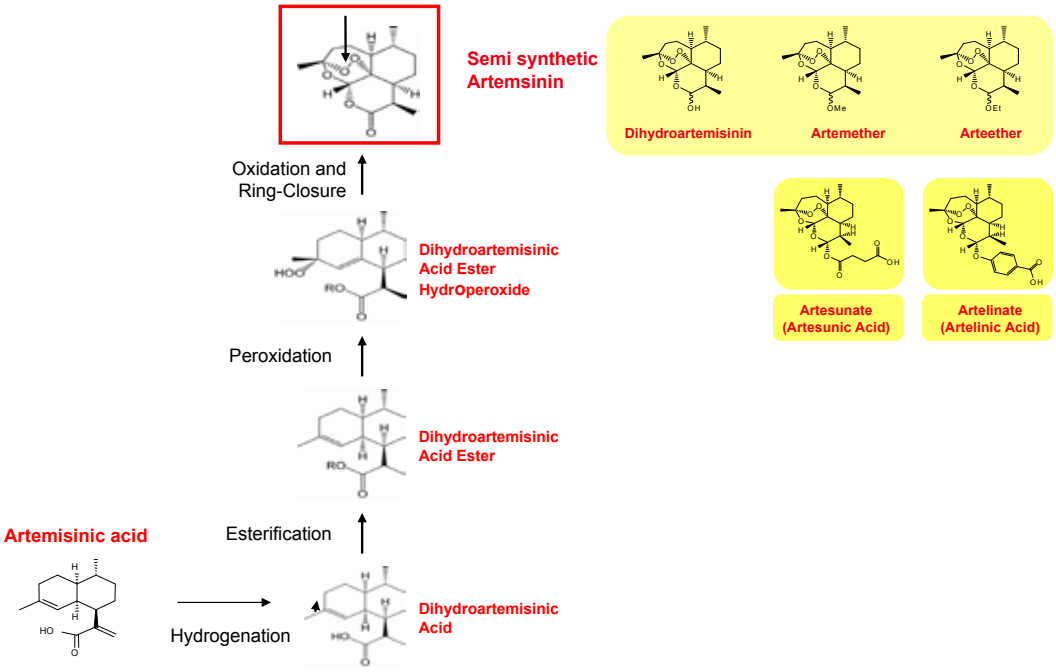
Partnership has been a key component to our successes thus far. Dr Jay Keasling pioneered the synthetic biology process behind the project; UC Berkeley provided breakthrough technology to produce artemisinic acid in microbial systems in the laboratory. Amyris Biotechnologies engineered and optimized the microbial strain so that it can be utilized for pilot and ultimately commercial-scale fermentation. Amyris also developed scalable processes for the fermentation of artemisinic acid and the chemical conversion of artemisinic acid to artemisinin. Sanofi-aventis is reproducing the Amyris processes and will further optimize the laboratory-scale process for eventual pilot and commercial scale-up.

Supplementing the supply chain

The goal of the project is to develop a low cost, non-seasonal, high quality, commercial-scale manufacturing process to produce semisynthetic artemisinin using the tools of synthetic biology, fermentation and chemistry to the highest industrial standards. Since this process has a shorter lead time than traditional artemisinin from plants, we aim to be a part of a variety of endeavours that seek to supplement and stabilize the supply of artemisinin. We anticipate that our technology will stabilize supply and shorten production times, resulting in a low cost, high quality source of artemisinin that will then be made available to drug manufacturers who will synthesize the various artemisinin derivatives and introduce into the ACTs for the end user.

This unique technology, among others in the Artemisinin Project, is part of a larger array of solutions aimed at treating and ultimately eradicating malaria worldwide.

Synthesis of Artemisinin



For more information on the Semisynthetic Artemisinin project, visit:
http://www.artemisininproject.org/ or http://www.oneworldhealth.org

3.3 MMV - Synthetic Peroxides: A Viable Alternative to Artemisinin

Background

Artemisinin-based Combination Therapies (ACT) form the mainstay in treatments for malaria. Within such combination products there is a heavy reliance on the artemisinin component due to its ability to act rapidly and show high efficacy against both *P. falciparum* and *P. vivax*. However, artemisinin derivatives are rapidly cleared and so they are used in combination with a longer-acting partner drug.

Despite the successes of artemisinin there are issues of natural sourcing, supply and cost. Furthermore, were resistance to develop it would challenge the whole position of ACTs in frontline therapy.

Synthetic peroxides

The first synthetic peroxide project or OZ (an abbreviation of ozonide, which is the peroxide functional group and antimalarial "warhead" within the structures) was begun on the premise that a new class of peroxides could be identified that would show greater potency in reducing parasite burden than the best artemisinin derivatives, such that a 3-day treatment, in combination, could be realised. In addition, due to its being fully synthetic *via* a simple synthesis, the drug would be available at low cost and without potential supply issues. The fruit of the first project was OZ277 or RBx11160 (*Figure 1, ozonide* "warhead" highlighted with a box).

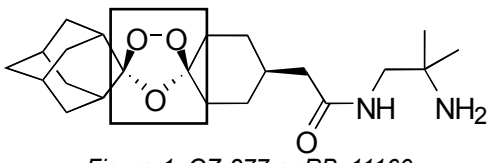


Figure 1. OZ-277 or RBx11160

The second generation OZ project extended these goals to include also the provision in combination of a single-dose oral cure for patients with uncomplicated *P. falciparum* malaria (and possibly *P. vivax*) and the potential for prophylactic treatment and intermittent preventative treatment in pregnant women and infants (IPTp and IPTi).

RBx11160 itself was shown to be more active than chloroquine, mefloquine, and artemisinin derivatives against *P. falciparum in vitro*, and *P. berghei* in mice. It had good physicochemical and pharmacokinetic profile in rats and dogs, though with a short half-life. The safety profile in rats, dogs and humans was excellent and pharmacokinetic studies in healthy volunteers were reproducible with excellent exposure at doses of 100mg or above. However, the pharmacokinetic studies in malaria patients demonstrated a significant reduction in the drug plasma concentration which was pinned down to greater clearance due to reduced stability in parasite-infected whole blood.

It was postulated that Fe(II)-mediated cleavage was likely to be a significant contributor to the *in vivo* clearance of RBx11160 and thus increasing the stability in infected blood became the medicinal chemistry focus of the second generation OZ project. The follow-up to RBx11160, Next Generation OZ, is significantly more stable in whole blood *in vitro* (both healthy and infected blood - see Figure 2) than its predecessor and this increased stability contributes to better exposure, a longer half-life and increased biological activity

From studies in *P. berghei*-infected mice, compounds from the second generation OZ project have demonstrated 100% survival out to 30 days, and single-dose cures following oral doses of 30mg/kg. Furthermore, several compounds demonstrate 100% prophylaxis and superiority to mefloquine (Lariam®).

The Next Generation OZ will shortly be going into healthy volunteers with the hope for launch at the end of 2015.

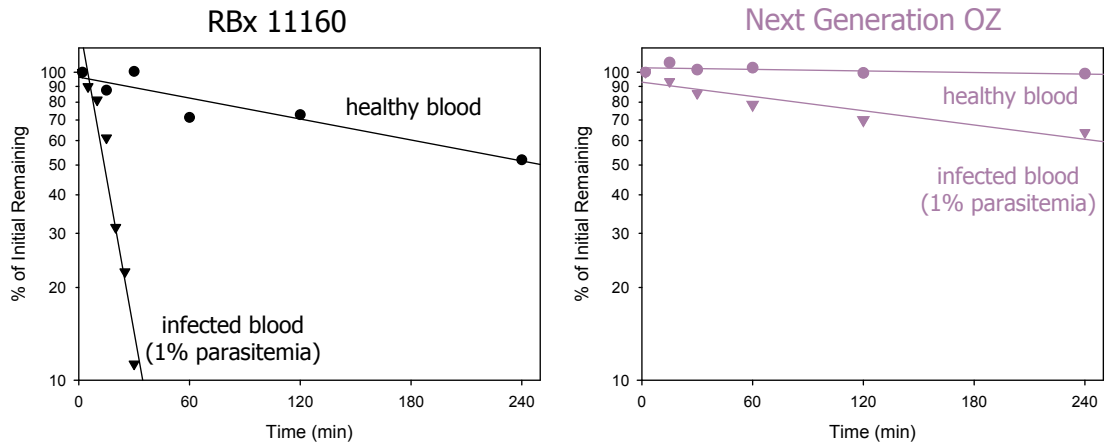
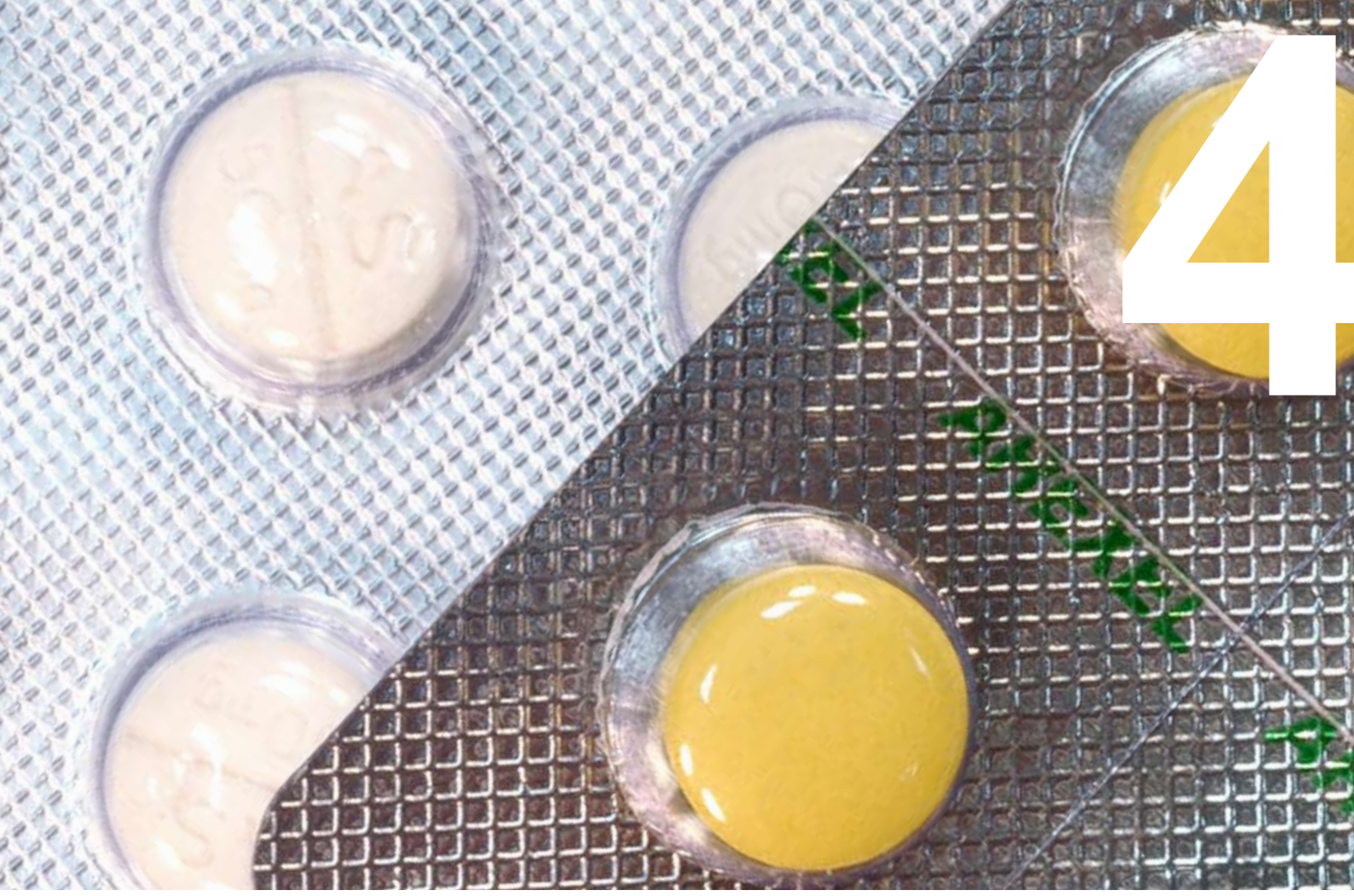


Figure 2. Comparison of the stability of first and second generation OZ compounds in healthy and parasite-infected blood



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“Even without taking the AMFm into consideration, demand for ACTs will increase by 60% over the next few years”

Inder Singh, Director of Drug Access,
CHAI/Clinton Foundation

image: © CNAP.

The malaria context

Burden of malaria

The World Malaria Report 2008 highlights that in 2006 there were between 189 and 327 million cases of malaria annually leading to at least 880,000 deaths, 85% of which are children in Sub-Saharan Africa. Children under five, pregnant women, malnourished people or others with compromised or underdeveloped immune systems are at the greatest risk of acquiring severe malaria and succumbing to the disease. The immunity of populations, including adults, where malaria strikes only every so many years falls back to very low levels or to zero, making them extremely vulnerable each time again, leading to murderous epidemics. It is estimated that a child dies from malaria every thirty seconds. In sub-Saharan Africa malaria is responsible for nearly one in five deaths in children under five.

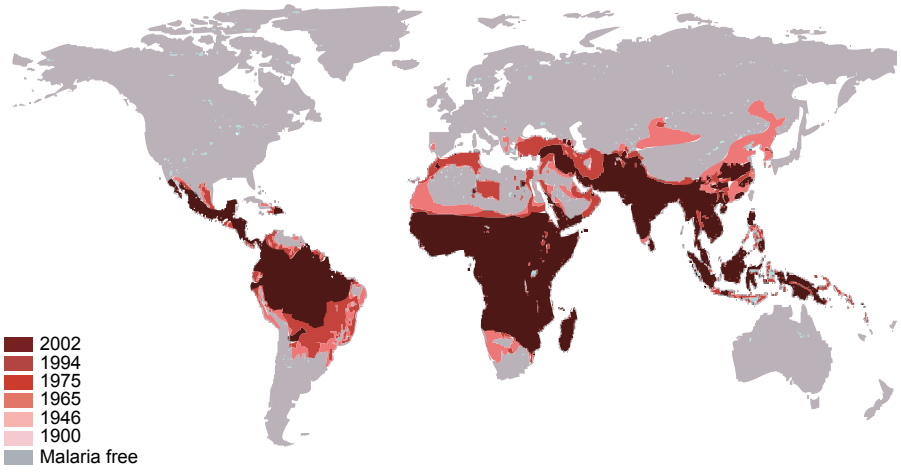
In addition to its impact on health care, the malaria burden extends to the economies and families of the poorest countries. Malaria is estimated to cost sub-Saharan Africa approximately 1.3% of its Gross Domestic Product (GDP), or about USD 12 billion in direct losses each year resulting from illness, treatment and premature death[1]. If malaria had been eliminated from sub-Saharan Africa before 1980, the region's GDP in 2000 would likely have been 32% higher, or an increase from some USD 300 to USD 400 billion[2].

4.1 Roadmap to malaria eradication

History of malaria control

Malaria has been a scourge on humanity for thousands of years and has influenced the outcomes of wars and the decline of empires around the world. The disease has long been linked with a self-perpetuating cycle of poverty that continues today.

Malaria Global Distribution (1900-2002)



Redrawn from: Hay, S.I. & Snow, R.W. "The Malaria Atlas Project: developing global maps of malaria risk." PLoS Med., 3(12):e473.(2006)

Conventional attack on the disease focused on two fronts: vector control through the spraying of DDT and swamp drainage; and the widespread utilization of chloroquine to treat infection and break the cycle of transmission. DDT use declined significantly because mosquitoes developed resistance and because concerns increased about potential toxicity to the environment. Chloroquine also became less effective as the malaria parasites developed resistance. Given these problems, the global fight against malaria was left with few options.

The Roll Back Malaria Partnership (RBM) was launched in 1998, with the objective of reducing the global burden of malaria in half by 2010.[3] In addition to improving the communication and coordination of malaria control activities among the several key actors, the RBM called for the development of new technologies that would aid in their effort to achieve the target. The RBM advocated the development and effective delivery of vaccines, preventative tools, and more effective and novel antimalarial drugs.

Global targets and tools

The Global Malaria Action Plan (GMAP) 2008 outlines the RBM Partnership's vision for a substantial and sustained reduction in the burden of malaria in the near and mid-term, and the eventual global eradication of malaria in the long-term, when new tools make eradication possible. To reach this vision, the targets of the GMAP are to:*

- achieve universal coverage, as recently called for by the UN Secretary-General, for all populations at risk with locally appropriate interventions for prevention and case management by 2010 and sustain universal coverage until local field research suggests that coverage can gradually be targeted to high risk areas and seasons only, without risk of a generalized resurgence;
- reduce global malaria cases from 2000 levels by 50% in 2010 and by 75% in 2015;
- reduce global malaria deaths from 2000 levels by 50% in 2010 and to near zero preventable deaths in 2015;
- eliminate malaria in 8-10 countries by 2015 and afterwards in all countries in the pre-elimination phase today;
- in the long-term, eradicate malaria worldwide by reducing the global incidence to zero through progressive elimination in countries.

During the first five years, the RBM made notable progress in significantly increasing the amount of funding and resources available to combat malaria. Additionally, improvements in coordinating efforts and developing multi-pronged interventions were promising. However, its overall success was limited by shortcomings in the final delivery of curative and preventative tools to the target populations, particularly those in sub-Saharan Africa where malaria-induced morbidity and mortality remained high. It has become increasingly clear in recent years that new tools and interventions, which had previously encountered challenges in reaching those in need, could demonstrate a positive impact when implemented effectively.

The main strategies for effective malaria control now include:

(1) Distribution of long-lasting insecticidal bed nets (LLINs)
(2) Indoor residual spraying (IRS) with insecticides
(3) Use of rapid diagnostic tests (RDTs)
(4) The widespread and controlled use of a new, highly

* Exerpted from RBM Partnership's Global Malaria Action Plan

effective treatment for malaria known as artemisinin combination therapy (ACT)

(5) Intermittent presumptive therapy for malaria in pregnancy (IPTp)

The WHO and the Global Fund to fight AIDS, Tuberculosis, and Malaria (GFATM) published results that showed that Rwanda and Ethiopia had reduced under-five mortality from malaria by more than 50% due to increased funding and the effective implementation of control strategies.[4] Other countries including Zambia registered significant progress although challenges related to sustaining these efforts remain in all three countries.

During his Keynote address to the AE conference, Mr. Alan Court, Senior Adviser to the Office of the Secretary General's Special Envoy for Malaria, United Nations, acknowledged that there was, "a massive unmet demand for effective treatment". This was in spite of the fact that, "the accelerated scale-up of the use of [LLINs] and [IRS] will prevent many new cases from occurring, and new and improved rapid diagnostic testing [RDT] will also reduce the numbers of presumptive treatments given to patients with fevers not caused by malaria, there is, right now, a massive unmet demand for effective treatment." He stated that the AE has an "unprecedented window of opportunity" to address this unmet demand for effective malaria treatments.

4.2 Artemisinin and ACTs

Development of resistance to early antimalarials

By 1990, significant levels of resistance to chloroquine had been reported throughout sub-Saharan Africa, as well as across Asia and Latin America. Despite rampant resistance, its use remained widespread because it was inexpensive and relatively easy to access. Some new antimalarials, such as sulfadoxine-pyrimethamine (SP) and mefloquine, were developed to counter this resistance to chloroquine but they rapidly suffered similar fates. Resistance to SP was reported in much of South East Asia within five years after it was introduced in the late 1970s and had spread to sub-Saharan Africa by the 1990s.[5] Mefloquine resistance was found in Thailand and by 1994, only 50% of infections were responsive to treatment. At this time, many pharmaceutical companies could not see an incentive to undertake R&D into new antimalarial drugs that might be able to replace the failing drugs, because of both the threat of rapid resistance and the fact that they would be unable to recoup their costs because the affected population could not afford the medications. With mefloquine, SP and chloroquine resistance widespread, the outlook for malaria control was bleak. Significantly, the RBM partnership recognized the need for the development of new technologies to aid malaria treatment and combat resistance. ACTs offer the ability to delay resistance for a much longer time period, and since artemisinin derivatives are the most potent of the antimalarial drugs, they offer faster cure rates. For this reason they were chosen as partner drugs in antimalarial combination therapies.

The development of Artemisinin Combination Therapy

Quinghao (*Artemisia annua*), also known as wormwood or Sweet Annie, had been used as a traditional medicinal plant in China for nearly 2000 years to treat malaria-like symptoms and other ailments. Artemisinin, *qinghaosu*, was identified as the active component of the medicinal plant in the early 1970s by Chinese researchers and its chemical structure characterized.[6]

Chemical derivatives of artemisinin such as artesunate and artemether were also developed as these were found to be easier to use in antimalarial treatments, although artemisinin gained first attention because its rapid onset of action and marked potency against all strains of *P. falciparum* made it increasingly valuable as a component of combination therapy.

Artemisinin and its derivatives have short therapeutic half-lives and therefore their use as monotherapies is limited. To avoid treatment failure the drugs have to be given for at least seven days. This is a very inconvenient dosage regime and runs considerable risk of patients not completing a full dose of treatment. In turn, this lack of completion of treatment leads to selection of resistant strains of *P. falciparum* and the loss of artemisinin derivatives as effective antimalarials. For this reason it was determined that artemisinin derivatives should only be administered in combination with other antimalarials with different mechanisms of action.

In collaboration with the Walter Reed Army Institute of Research, the London School of Hygiene and Tropical Medicine, and the WHO, Chinese researchers developed the combination artemether/lumefantrine (AL). Lumefantrine was a novel synthetic antimalarial (not an artemisinin derivative) and was developed in the 1970s by the Chinese Academy of Military and Medical Sciences. The ACT was the first fixed dose combination (FDC) of two unrelated antimalarial compounds.[7] The Chinese licensed the intellectual property rights for the manufacture and sale of the AL combination to Ciba-Geigy, which would later become Novartis AG. In addition to the AL FDC, other existing antimalarials, such as amodiaquine, mefloquine and sulfadoxine-pyrimethamine, have also been used in combination with artemisinin derivatives. Until recently, FDCs for these other combinations have not been formulated but the two drugs administered as loose combinations.

Artemisinin Combination Therapy as the treatment of choice

In 2000, a WHO-convened technical meeting assessed the status of antimalarial drugs and concluded that combination products were essential to sustaining the effort to roll-back malaria.[8] The AL combination had been demonstrated to be over 96% effective in clinical studies, even against resistant parasites. This, and the fact that it was an FDC, meant that it was the most appropriate drug treatment to be used - but it had a prohibitively high price. In 2001, AL was added to the WHO Essential Medicines List, and Novartis and the WHO reached an agreement in which Novartis would supply AL at cost to the public sectors of malaria endemic countries to improve access to this life-saving ACT. Both of these key decisions were influenced by the Millennium Development Goals (MDGs) which, among other objectives, emphasised improved access to the most effective antimalarial treatments.

In April 2002, the WHO recommended ACTs as first-line treatment for uncomplicated *P. falciparum* malaria in chloroquine- and SP-resistant geographical regions. The ACTs currently recommended by the WHO are AL, artesunate/amodiaquine (AS/AQ), artesunate/sulfadoxine-pyrimethamine (AS/SP), and artesunate/mefloquine (AS/MQ).

Regulating quality of artemisinin and ACTs

Given the potential risk of developing resistance to ACTs, the malaria community is taking the necessary precautions to prolong the efficacy of this drug class. These measures include: (i) use of co-formulated drugs to ensure patients consume combination treatments only; (ii) removal of monotherapies and ineffective drugs from the market; and (iii) ensuring countries and donors purchase and

finance only high quality ACTs that meet international quality standards.

Ensuring the quality of artemisinin and ACTs is one of the major challenges facing effective malaria control. To address the quality issue, major international funding agencies (eg Global Fund, President's Malaria Initiative) have established policies to purchase drugs that meet internationally accepted quality standards, such as ACTs that have been prequalified by WHO and stringent regulatory authorities, with some caveats and exceptions.

Artemisia Cultivation

ACTs are unusual in the pharmaceutical industry because they are the only high volume product - with sales of more than 100 million treatments annually - that continue to contain a natural product derived from plants. Agriculture provides many high-volume commodity food and non-food products from the cultivation of established crops that have benefited from many years of plant breeding. In contrast, *Artemisia annua*, the medicinal plant producing artemisinin for ACT manufacture, has undergone a very short period of plant breeding for improved yield and robust agronomy, despite its importance for ACT production.

Artemisia annua is native to China and is able to grow in many different climates including high altitude temperate areas in China, Vietnam and East Africa. China and Vietnam produce some 70% of the global supply of artemisinin, with East Africa producing 20%. Other countries in which *Artemisia annua* is grown include India, Ghana, Kenya, Tanzania, Uganda, Nigeria, Mozambique, Madagascar and Brazil.

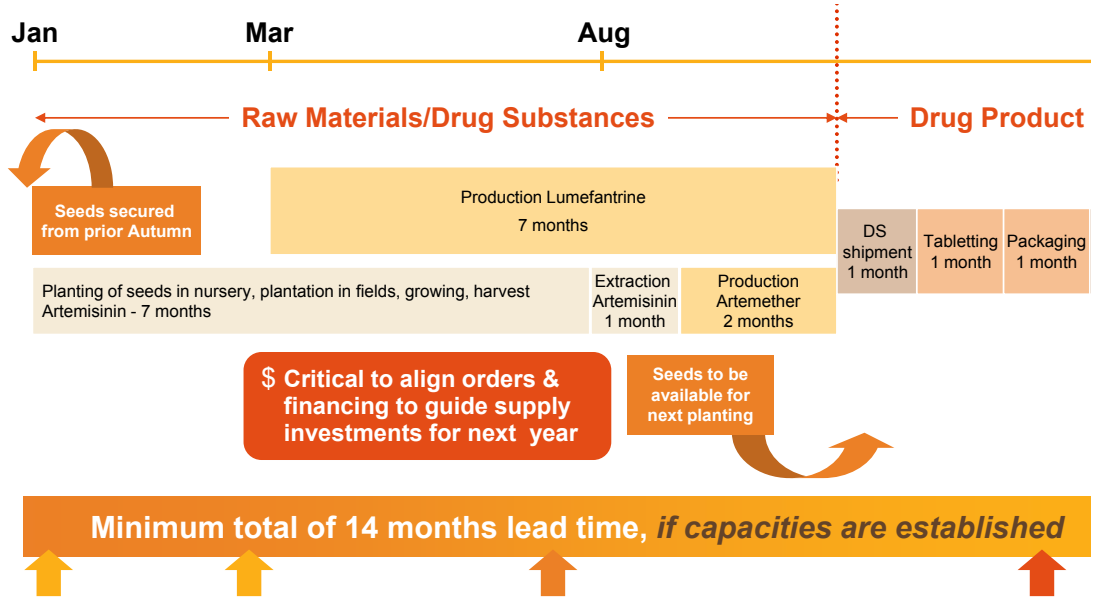
Currently, some seed selection for cultivation takes place although use of wild stands continues to occur. Artemisinin levels range from 0.01-0.3% from wild stands, 0.4% when some seed selection has taken place, to a current F1 hybrid, Artemis, developed by Mediplant in Switzerland with an artemisinin level of 1.0-1.5%. Seedlings are typically planted in nurseries and then transplanted into commercial, or more usually smallholder plots. Once transplanted, Artemisia is a relatively low-maintenance crop requiring little fertilizer or pesticides. It takes some 8 months for Artemisia to reach full growth and plants are harvested just prior to flowering and dried in fields. There is some anecdotal evidence that artemisinin content in leaves increases at the time of flowering. The dried leaves are separated from the stems, bagged separately and sent to artemisinin extraction facilities. Payment to farmers is typically based on the number of kilograms of dry leaf produced, provided the leaf contains a previously agreed threshold value of artemisinin. Currently, it is typical that a large number of smallholder farmers will be supplying a single extraction facility in the region and are contracted to grow via the extractor. There are also some examples of back integration in which the active pharmaceutical ingredient (API) manufacturer or ACT manufacturer contracts growers/extractors.

Typically, hexane is used for the extraction of artemisinin and the extractors will be combining use of their capital facility extraction plant for Artemisia extraction with extraction of other medicinal plant/crop species. Due to the costs associated with transport of plant biomass, the extraction facility will be a single site receiving agricultural inputs from the surrounding region. Any capital facility will thereby serve multiple growers of multiple agricultural commodities and produce a range of products for multiple industrial end users. There is some evidence that the efficiency of extraction of artemisinin can be affected by the physiological condition of the Artemisia plants prior to harvest and that contaminant profiles affecting API

production will vary. This is not surprising given that the sesquiterpene lactone artemisinin is only one metabolite in the plant, out of many tens of thousands. Artemisinin is a secondary metabolite and the pattern of these within a plant is known to be highly sensitive to changing external environmental conditions. Impurities in the artemisinin extract can not only affect API production, but also impact on other properties of ACTs.

Growers and extractors play key roles in the artemisinin supply chain, with extractors selling-on the outputs of their hexane extraction/further processing and crystallization, of Artemisia leaf to API manufacturers who then convert the artemisinin into the various active artemisinin derivatives (artesunate, dihydroartemisinin, artemether etc) that are used in the manufacturer of ACTs.

Supply chain timelines are exemplified in the figure below that describes the supply chain timeline for Novartis's AL.



Source: Wells L (June 2008). Coartem®-the story so far. Global Access to Medicines Policy, Novartis International AG.

Artemisinin prices and supply chain economics

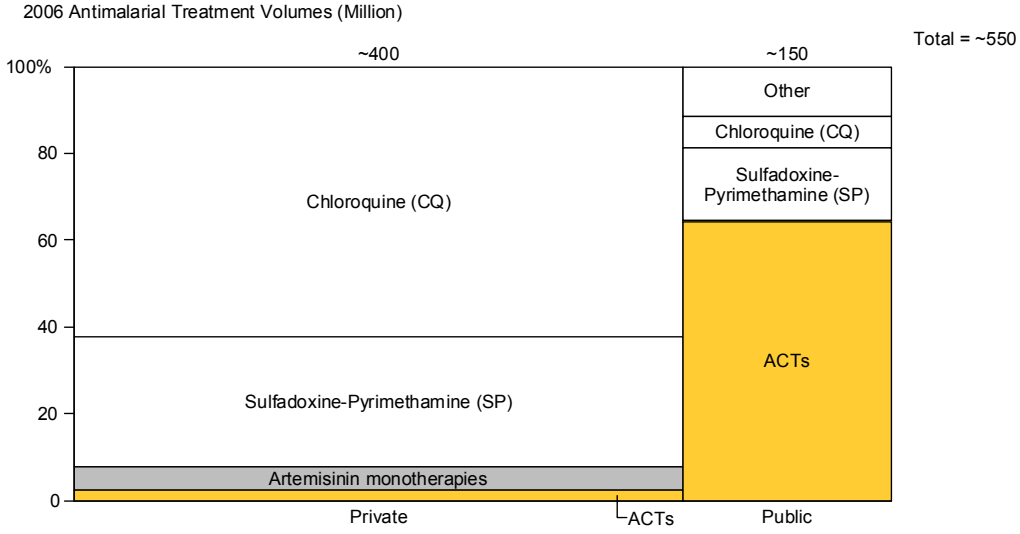
In recent years the price for artemisinin has been highly volatile and this has had a major impact on the stability of the supply chain, providing both a large incentive and also a disincentive for Artemisia growers. The market price of artemisinin is directly linked to demand forecasts and existing supplies and there are now new predictions from the RBM PSM Working Group of shortages of supply of artemisinin in the near future with the risk that the instabilities will remain.

Much of the available information on supply chain economics is anecdotal and focused on small elements within the supply chain. The information does not represent a holistic overview of the whole supply chain. Since the AE Conference there has not been time to undertake a detailed and rigorous analysis of supply chain economics, however, this is considered to be a vital component in understanding and assessing the future impact of the integration of the three AE technologies. It is therefore our view that there is an urgent need for a detailed technical paper looking at the economics along the supply chain from the seed producer through to the extractor. It is also essential that this review assesses and demonstrates the impact of changes in the price of artemisinin on the production cost of ACTs.

ACT and artemisinin market size - current and future

The market size for antimalarials was estimated at 550 million treatments in 2006, with the private sector accounting for almost 75% of the market and the public sector accounting for the rest. CQ and SP account for more than 90% of the private sector market, whereas ACTs account for more than 60% of the public sector market. In total, approximately 100 million ACT treatments were sold in 2006 and this is expected to grow significantly.

Public and private market shares in distribution channels: Private (commercial licensed; unlicensed + NGO) vs Public sector



Note: "Other" includes Mefloquine, Amodiaquine and others. ACT data based on WHO estimates and supplier interviews.
Source: Biosynthetic Artemisinin Roll-Out Strategy, BCG/Institute for OneWorld Health, WHO, Dalberg.

Current estimates of the demand for ACTs between late 2008 and 2010 are 120-160 million courses of treatments (adult and children) per year †. In this period the currently estimated production of artemisinin is 40-50 tonnes ‡. Along with the 40 tonnes of artemisinin currently thought to be in the inventories of extractors and ACT manufacturers, this represents enough artemisinin to make 120 million adult treatment courses. As was highlighted in the previous section, there is therefore a risk that there will be a shortfall between the demand and the supply and this may adversely affect the price of artemisinin and the availability of ACTs.

Funding Artemisinin and ACTs

The majority of ACT procurement has been financed by international donors with minimal financing (purchase) by the private sector due to the relatively high price of ACTs vis-à-vis the more commonly used monotherapies - CQ and SP. The three major funders of ACTs are Global Fund, World Bank and US President's Malaria Initiative (PMI), which have jointly funded the procurement of over 200 million treatments since 2005.

In 2004, the Institute of Medicine published a report§ that proposed a new funding mechanism to finance the procurement of ACTs. The Affordable Medicines Facility for malaria (AMFm) will subsidize the cost of the ACTs by providing a co-payment to manufacturers for every treatment they sell such that the cost to the first-line buyer in-country is around US$0.10 cents per treatment, resulting in a cost to the patient that is roughly the same as the cost of CQ and SP. This mechanism of subsidy would make ACTs far more affordable for patients, and so is expected to drive out counterfeit and substandard ACTs as well as artemisinin monotherapies. The AMFm will be launched in 2009 with Phase 1 being implemented in 11 countries with a total ACT budget of approximately US$ 225M**. The AMFm is expected to fund majority of additional procurement of ACTs, and over the next few years could become the largest funder of ACTs.

Although a mechanism for subsidizing ACTs exists, there is no such co-payment or "advance market commitment" mechanism for payment to extractors and farmers. It is expected (or even hoped) that market mechanisms and contracts between ACTs manufacturers and extractors/farmers will ensure continued and uninterrupted supply of artemisinin. Based on discussions during the AE Conference, the extractors highlighted their concern that the current market environment of unpredictable demand, potential entry of new technology, sudden drop in prices and competing agricultural products has started to erode the number of farmers and extractors; and unless the global community intervenes rapidly, the next planting season could result in drastic reduction in artemisinin leading to a severe shortfall of ACTs in 2010. This concern is re-visited in the sections under "Impact" and "Recommendations".

† Based on forecasts provided by CHAI, MIT-Zaragoza, Dalberg and McKinsey

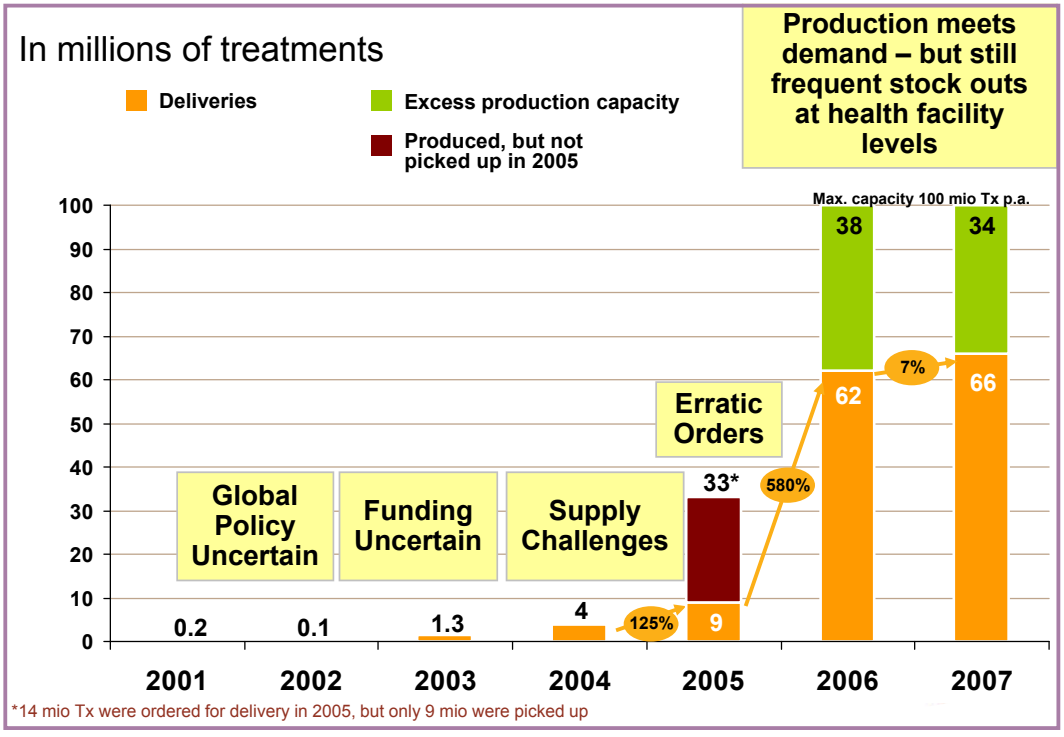
‡ Based on analysis done by CHAI, position paper provided by RBM PSM-WG, analysis and personal communication with Jaques Pilloi

§ "Saving Lives, Buying Time", Institute of Medicine. Washington, 2004

** McKinsey analysis for UNITAID

Demand versus purchase orders for ACTs

It was stated several times during the AE Conference that demand exists, funding exists, policies exist, and the political will to control and eliminate malaria exists. However the most critical elements include accurate demand forecasts and timing of procurement, which are difficult to predict, leading to waste, higher prices, delays in shipment, and stock outs. For example, based upon international demand forecasts, Novartis increased production of AL between 2004 and 2005 from 4 million to 33 million treatments. However, Novartis received orders for only 9 million. Again in 2006, Novartis increased its production capacity further to 100 million treatments (based again on projections provided by the global community) but it received orders of only 62 million and 66 million treatments during 2006 and 2007, respectively. It found that it had surplus stock of artemisinin equivalent to about 75 million treatments. Other manufacturers, including sanofi-aventis, IPCA, and Cipla have had similar experiences.



Addressing the Market Gap for ACTs

During the AE Conference, Professor Chris Whitty stated that the current market for artemisinin and ACTs will experience significant ***'turbulence'***, which could last until 2015. This could make the supply situation for ACTs worse before it gets better. For example, although demand for ACTs is expected to be well funded, the timing and size of orders are unpredictable. Funding for ACT manufacturers is clear, but payment to extractors and growers is not assured, increasing the risk that they will leave the supply chain. While ACTs are highly effective against CQ and SP resistant strains, high use of monotherapy and widespread availability of substandard ACTs could accelerate the possibility of resistance to ACTs. To address these and other challenges, the market has responded (or could respond) through four different types of strategies:

- *better demand forecasting* through the gathering and analysis of more and better data; more collaboration between stakeholders and developing an agreed methodology;
- *multi-pronged fiscal responses* including access to larger amount of funds, more predictable flow of funds, longer period of funding and more flexible use of funds (eg for creating a buffer stock of artemisinin or ACTs);
- *policy response* to address issues related to resistance (for example, prohibiting the registration and use of artemisinin monotherapy); increasing availability of drugs through fast track registration of new ACTs; establishing ACTs as a drug of choice and making ACTs an "over the counter" drug, etc;
- *technology response* to stabilize the supply of artemisinin (by increasing yield and exploring the possibility of creating a non-agricultural-based artemisinin product); discover and develop the next generation antimalarials in case of resistance to ACTs, etc.

While other stakeholders are focusing on the demand, fiscal and policy-based responses, the AE partners are focused on the "technology response". The rest of this document reports on the proceedings of the AE Conference, including the outputs of the breakout group discussions, the AE technologies' timelines, impact on the market and recommendations.

Artemisia drying, Kenya, © CNAP.

“Treatment is a key part of the Global Malaria Action Plan (GMAP). The GMAP is very ambitious - and all these technologies in the pipeline can contribute to meeting its targets.”

Professor Awa Coll-Seck, Executive Director,
Roll Back Malaria Partnership

image: © CNAP.

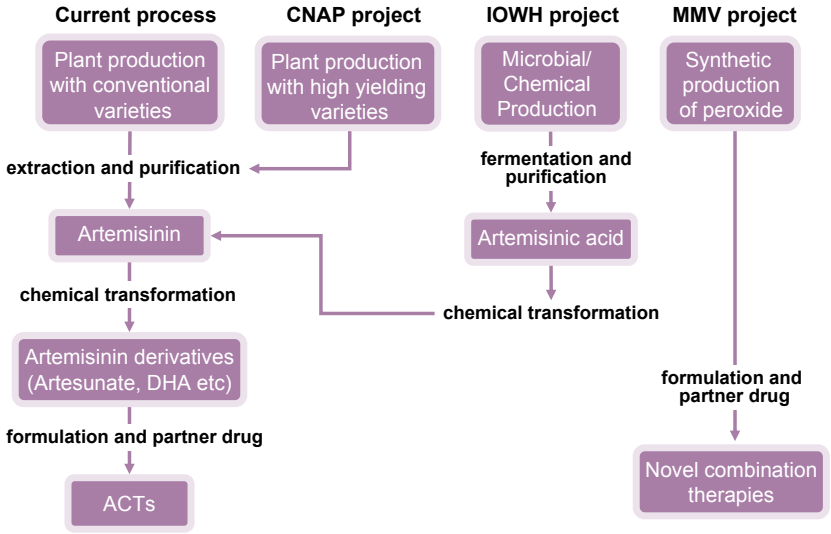
The contributions of the AE technologies to malaria treatment

The malaria community identified high costs as the most significant barrier to improved ACT uptake and market stability. The projects in the Artemisinin Enterprise share the ultimate goal of making high quality ACTs less expensive and more accessible to the people who need them.

With increased investment into ACTs there is the funding available to substantially increase the number of treatments and this will inevitably impact on the amount of artemisinin required. This necessitates a stable supply of artemisinin in the market and a stable cost of that supply. The market price of artemisinin has fluctuated widely between USD 1,200 and 120 per kilogram from 2005 to 2008. This has created massive instability throughout the supply chain with negative implications for both the growers and extractors of Artemisia at one end of the supply chain and ACT manufacturers at the other end.[9] If the growers receive lower economic returns from artemisinin and also have opportunities of producing alternative agricultural commodities, such as food crops, of greater market value, the area of Artemisia under cultivation will fall. This trend has already taken place and impacts on future supply potential.

The effective implementation of the new AE technologies will significantly increase the capacity to produce high quality artemisinin and effective antimalarial treatments. The technologies will diversify the production routes since the availability of improved higher-yielding *Artemisia annua* varieties will be complemented by artemisinin synthesized by microbial fermentation and by the manufacture of fully synthetic artemisinin-like compounds.

The ACT supply chain; role of the new technologies



Benefits of the AE technologies will arise from a variety of direct and indirect factors. For example, as described in section 3, use of higher-yielding plant varieties would have multiple benefits, including reduced agricultural production and extraction costs through to improved environmental footprint of the process. The production of artemisinin by fermentation bypasses plant production and has the potential significantly to reduce lead time enabling the market to respond much more rapidly to changing demands. New antimalarials should also be a useful tool to help mitigate the risk from parasite resistance to artemisinin. Currently acceleration in the possibility of resistance to ACTs is occurring through the high use of monotherapies and the widespread availability of substandard ACTs. With increased availability and cheapness of ACTs made possible through the use of these new technologies, an added benefit will be the decreased use of monotherapies and substandard product.

Project delivery timelines

The timing of the introduction of the AE technologies matches well with substantial increases in financing for ACT procurement such as those under the President's Malaria Initiative, World Bank and new financing arrangements such as the AMFm.

The CNAP project leading to new high-yielding varieties of *Artemisia annua* described project delivery in three different phases:

- Phase I: doubling the existing concentration of artemisinin to approximately 2% per unit dry weight for commercial introduction by October 2011;
- Phase II: increase the artemisinin yield to roughly 3.5% by 2013;
- Phase III: increase the artemisinin yield to roughly 5% by 2015.

Based on the fact that a number of high-yielding parental lines have already been identified, the CNAP team are confident that Phase I delivery of registered hybrid seed will be achieved by the end of 2011. Achieving Phase II and Phase III goals have lower confidence limits at this stage of development.

The iOWH project uses yeast-based microbial fermentation to produce artemisinic acid, which functions as a raw material for further chemical synthesis to artemisinin. Scaling-up of production over the coming time was considered to be iterative, moving from 1,000L to ultimately 100,000L fermentation tanks. This scale-up builds on the involvement of sanofi-aventis in collaboration with the University of California, Berkeley and Amyris Biotechnologies. Current timelines anticipate semisynthetic artemisinin produced in 100,000L tanks ready for sanofi-aventis AS/AQ and other commercially manufactured ACTs between 2011 and 2012.

The MMV project leading to new totally synthetic molecules with the same active peroxide moiety as artemisinins, plans that the lead compound from the second generation of synthetic peroxides will start Phase I clinical trials in 2008/9. The current timeline is for the development of a combination product to be completed and the product ready for launch by 2015.

Table: Impact of AE technologies on the ACT supply chain

Impact	CNAP	iOWH	MMV
Decreasing overall lead-time for ACTs enabling faster response to meet sudden demand spikes	Little impact envisaged	Fermentation and chemical synthesis shortens the lead time for artemisinin production	Laboratory synthesis substantially reduces the manufacturing lead time for new antimalarials
Reducing the cost of Artemisinin (or the key antimalarial component in drug)	New Artemisia varieties will lead to higher yields of artemisinin per hectare thereby decreasing the cost of agricultural production and extraction	The cost of semisynthetic artemisinin is unclear at this stage as the project is still in development stage. But it is understood that to be commercially viable, semisynthetic has to be competitive with current high quality plant derived material. As with all industrial processes, the production of semi synthetic artemisinin is expected to undergo continuous optimization to reduce cost.	It is premature to comment on the cost advantages of endoperoxides relative to artemisinin.
Overall supply market stabilization	The new varieties will have higher yields of artemisinin and it is anticipated that the agronomic performance can also be improved to increase the robustness of the crop for cultivation at different geographical locations. Working with growers during trialling should increase confidence in Artemisia as a crop and stabilize interest in production providing the market for artemisinin stabilizes	Even with larger quantities of artemisinin coming from better yields and higher acreage, there will be a need for a reactive supply capacity to meet short-term mismatches in supply and demand. Owing to the short lead time for production, the semisynthetic artemisinin will allow rapid ramp-up if new mechanisms to finance malaria treatment lead to higher than anticipated uptake of ACTs.	Even if the containment of artemisinin resistance is not the primary cause for the use of a non-artemisinin based combination antimalarial, a higher variety of starting materials for making effective antimalarials will create healthy supply competition and create resilience in the supply chain for ACTs
Overall demand market stabilization	One of the key reasons for demand supply mismatch is lack of affordability and poor ability to predict purchasing behavior when products are unaffordable (both for external donor financed public sector purchases and out-of pocket private sector purchasing). Eliminating uncertainties in purchasing behavior will stabilize the ACT demand market.		
Quality of antimalarials	Increased volumes of affordable ACTs made possible by the three technology interventions will decrease incentives for counterfeits and by undercutting the price of monotherapies will also prevent their widespread use.		

6

image: © CNAP.

Conference recommendations to the malaria community

A key component of the 2008 AE Conference was detailed discussions by stakeholders in breakout groups. The stakeholders were invited, in these breakout groups, to assess the impact of the three new technologies on the ACT supply chain as described in the preceding section. Significantly they were invited also to provide a series of recommendations on how best to ensure smooth and effective integration of products derived from the new technologies into the supply chain so that the products contribute to the envisaged growth in demand for ACTs.

Recommendations for all AE partners:

AE technologies should be used only for the manufacture of high quality ACTs

The Conference considered it important that the outputs from the AE technologies should be used only for the manufacture of high quality ACTs. AE technologies such as high-yielding or semisynthetic artemisinin should not be available to counterfeiters and monotherapy producers.

A mechanism should be developed in collaboration with RBM Procurement and Supply Chain Management Working Group (RBM PSM) and other relevant stakeholders to ensure that outputs are not diverted to the manufacture of other products. Regulating access to artemisinin derived from high-yielding plants or fermentation processes will be a supply chain-wide responsibility. This could potentially be achieved by artemisinin batch-tracking systems to ensure that all artemisinin output is accounted for throughout the supply chain.

An effective, joined-up communication strategy should be developed by the AE partnership

It is essential that the AE provides regular updates to the wider malaria community on progress, approximate timelines for delivery and likely impact on artemisinin and ACT prices. As part of this activity it will be important to address the impact of artemisinin production through fermentation and the development of synthetic peroxides on farmer confidence, particularly given the continuing role of plant-derived artemisinin in the supply chain for the coming years.

As with the introduction of any new technology, the market anticipation of synthetic peroxides and semisynthetic artemisinin could further destabilize the market if farmers and extractors feel discouraged from growing and processing Artemisia. It is crucial that communication with stakeholders is clear, and that farmers and extractors are incentivised to continue to grow and process Artemisia at adequate capacities until the new technologies are available at commercial scale.

Establish a stakeholder forum

In order to ensure that there is a high level of awareness of the work of the AE partners, a regular forum for stakeholders should be established to maintain active discussion on key topics relating to the development and deployment of the AE technologies.

There is a large number of new “data points” in the ACT market which need to be shared with the global stakeholders including the roll-out of the

AMFm, new funding from Global Fund for Round 8 malaria grants, progress in development of new technologies by AE and other partners (several other groups are researching the possibility of increasing artemisinin yield), etc. As with other large public private partnerships, the ACT industry is comprised of several different actors. There is a need for improved communication and transparency between and within the public and private companies and institutions in order that stakeholders may make better informed decisions. While an annual conference helps to share information, it is insufficient for stakeholders to keep abreast of the changes in the market.

There should be recognition of the ongoing requirement for all three of the emerging technologies for the foreseeable future of global ACT use and malaria eradication.

Recommendations for CNAP:

Develop new communication networks

New communication networks should be developed to ensure the wider community as well as growers and extractors in major growing locations of Africa and Asia are aware of progress and regional developments in field trialling the new high-yielding varieties. Experience gained in different environmental and climatic conditions of cultivation should be widely communicated.

Develop and maintain farmer and extractor confidence

Farmer and extractor knowledge, confidence and participation are essential to the successful uptake of the outputs of the CNAP work. These key elements should be developed by the early engagement of farmers and extractors in field trialling, training and transfer of good agricultural practice through extension services - all of which are components that need to be delivered as part of an effective global roll out. It should also be clearly communicated to farmers and extractors that using farm-saved seed from hybrid high-yielding plants will lead to reduced yields.

Assess the impact of new variety development on impurity profiles

As the development of new varieties could impact on artemisinin extraction including impurity profiles, this aspect should be assessed early through interactions with extractors, derivatisers and ACT manufacturers.

Impurities in plant-derived artemisinin increase the cost of extraction and decrease the shelf-life of the end products: it is thus crucial that impurity levels are continuously monitored. Extractors should ensure that farmers use high-yielding Artemisia plants and that they are effectively trained in good agricultural practices. Extractors in various locations should use plant varieties selectively bred for climate-specific high-artemisinin yields with ACT manufacturer-established impurity thresholds to control impurity variation between different locations.

Recommendation for iOWH:

Deliver forward looking communications

As the iOWH project develops, forward-looking communications about the project will be essential and should provide updates on target price and volume estimates in order to enable growers and other stakeholders to adjust to the changing artemisinin landscape.

Recommendation for MMV:

Maintain awareness of progress as the project develops

The new synthetic endoperoxide under development by MMV is subject to all the risks associated with drug research and development. Stakeholders should be kept aware of progress at each stage of the lengthy development process.

Recommendations for the wider malaria community:

Conduct credible demand forecasting

The Conference noted the essential need for accurate demand forecasting. A single set of demand forecasts, universally available and regularly updated, should inform the wider community and ACT manufacturers.

If the demand for artemisinin increases as forecasted over the next four years, it will be crucial both to recruit new farmers and to keep current farmers cultivating Artemisia to increase total artemisinin output. Measures will need to be taken to quantify the gap between the capacity of qualified API and ACT manufacturers, and the actual market demand for ACTs. If the price of artemisinin is stabilized, it will create a more beneficial and predictable market that will ultimately result in higher uptake of ACTs in malarious regions. Reestablishing manufacturer and farmer confidence in forecasts will be important to the scale-up of plant-derived artemisinin. Ongoing forecasts being conducted by RBM's PSM Working Group and other stakeholders, such as the Clinton Foundation, and ACT manufacturers need to be made more robust and made available on a real-time basis to the global community.

RBM and UNITAID should develop an agreed set of planning assumptions to support demand forecasting.

Analyse ways in which supply and demand for artemisinin can be effectively managed

Supply/demand mismatches have had a major negative impact on the supply chain for artemisinin in recent years.

The highly volatile market price for artemisinin has proved to be both a major incentive and disincentive for the production of plant-derived artemisinin. The market price of artemisinin is directly linked to demand forecasts and existing supplies. As a result, it is crucial that forecasting is streamlined to a single well-informed party, and existing supplies are accurately communicated to relevant actors within the AE. The technologies under development will help to stabilize the supply of artemisinin in the market. Additionally, supplemental supplies of artemisinin will enhance confidence throughout the supply chain due to the development of buffer stocks which will act to resist massive price fluctuations.

RBM PSM Working Group and relevant stakeholders should consider mechanisms and design an action plan to mitigate future supply/demand mismatches. Suggested ways forward included: buffer stocks, fair trade/price arrangements, farmer incentives, financial risk sharing, the development of grower cooperatives and off-take arrangements. An open and transparent options analysis should be carried out within a year, to assess the relative merits of these suggestions.

RDTs must be fully integrated into the therapy mix

The significant scale-up of the use of rapid diagnostic tests for malaria recommended by the Global Malaria Action Plan was noted. This scale-up should be

integrated into the therapy mix in parallel with the development of a strategy for the treatment of patients who do not have malaria.

Use of non-ACTs to be minimized in order to maximize the benefits of the AE technologies

RBM PSM, working closely with other stakeholders including the MMV Access team, should consider how regulatory and health guidance mechanisms can be used to minimize the use of counterfeit drugs, monotherapies and Artemisia teas thereby maximizing benefits of the new AE technologies.

The pharmacopeial status of artemisinin as a starting material should be confirmed

The Conference considered it important to work to achieve consensus that, from a regulatory perspective, artemisinin should be considered to be a starting material rather than an API. Artemisinin is typically converted into various APIs including artemether, artesunate, DHA, all of which are then subject to a greater degree of scrutiny and quality assurance. The physical and chemical characteristics of APIs are normally described in monographs of international pharmacopoeias. This clarification is critical for the AE, especially iOWH, which is manufacturing semisynthetic artemisinin, and for all potential users of this product.

A full regulatory and cost analysis of this area should be undertaken by at least one major regulatory body, and preferably more, within a year to avoid the risk of differential decisions in this area by different regulatory bodies. The RBM Regulatory Task Force should work together with ACT and API manufacturers to consider and clarify whether and how changing the source of artemisinin may impact existing registrations. This will involve assessing detailed information on specification, manufacturing process and related issues held in registration files.

Enhance competition in the ACT market by developing local production in malaria-endemic countries

During the Conference, the desire that malaria-endemic countries have local production of antimalarial treatments at international quality standards was highlighted. Buyers of artemisinin are currently limited to a small number of pharmaceutical companies (see Appendix for list of WHO PQ suppliers). Sales financed through the Global Fund and other donors are also presently limited to only a few suppliers. Strengthening local suppliers, especially in Africa, to reach international quality standards could potentially increase the number of ACT manufacturers and have a subsequent effect of increasing the use of high quality ACTs and limiting the use of monotherapy and poor quality ACTs. Donors and international regulatory bodies should consider pathways to promote sustainable and appropriate development of regulatory and pharmaceutical capacity in these countries that is sustainable.

Develop a better knowledge of the capacity in the extraction and derivatisation sector

The lack of detailed information on current capacity in the extraction and derivatisation sector was noted. RBM PSM Working Group should review the current capability to extract artemisinin from plant material by undertaking a quantitative economic study and assessment of current global extractor/derivatiser capacity.

Annex 1. Conference Programme

THE 2008 ARTEMISININ ENTERPRISE CONFERENCE
October 8-10 York UK

Meeting the Malaria Treatment Challenge: Effective introduction of new technologies for a sustainable supply of ACTs

Focus

The focus of the Artemisinin Enterprise (AE) Conference, which is co-sponsored by the Roll Back Malaria Partnership, will be the role of the AE and the new technologies that the three partners are developing for introduction into the Artemisinin Combination Therapy (ACT) supply chain. Delegates to the meeting will include stakeholders from the entire supply chain, from growers to producers of active pharmaceutical ingredients (APIs) and ACT manufacturers and will also include representatives from malaria-endemic countries, international technical organizations, and other relevant contributors.

The objectives of the conference will be to:

- Inform stakeholders in the supply chain about the technology projects undertaken by the AE
- Assess the potential impacts of the new technologies – opportunities and challenges
- Explore the timelines for introduction of the new AE technologies, strategies for their effective introduction and integration into the supply chain
- Define how the AE can interface with the efforts of the Roll Back Malaria Procurement and Supply Chain Management (RBM-PSM) and Affordable Medicines Facility for malaria (AMFm) working groups, and the Medicines for Malaria Venture (MMV) Access group

Structure of the meeting

The meeting, to be held over a period of two and a half days, will include presentations, panel discussions and a breakout session. Stakeholders representing all the relevant sectors will participate in the breakout groups. The major output from the conference will come from these groups. They will:

- Provide new understanding of the impact of the new technologies; discuss potential challenges that may result from their introduction
- Propose strategies to overcome these problems and suggest actions needed to ensure effective progress

The discussions and recommendations of the AE Conference will be assimilated into a final report that will be shared with the attendees and global stakeholder community (including RBM-PSM, AMFm Task Force and MMV Access group).

For those individuals who are not able to attend in person, arrangements will be made to broadcast the conference over the internet.

There will be an opportunity to visit the facilities of the Centre for Novel Agricultural Products (CNAP) at the University of York and meet the CNAP Artemisia Research Project team.

Day 1 October 8 **Session 1:** Opening and keynote lecture		
1400-1630	Introduction to the Centre for Novel Agricultural Products (CNAP) at the University of York, tour of laboratory facilities and CNAP Artemisia Research Project (optional)	Professor Dianna Bowles, Chair of Biochemistry, CNAP, University of York
1800-2000	Reception in the Atrium of the Department of Biology with buffet dinner and drinks	Welcome by Professor Brian Cantor, Vice-Chancellor, University of York
2000-2100	Keynote lecture	Mr Alan Court, Senior Adviser to the Office of the Secretary General's Special Envoy for Malaria, United Nations

Day 2 October 9 **Session 2:** New technologies for artemisinin supply from the Artemisinin Enterprise Chair for the session: Stephen O'Brien MP Chairman of the UK All Party Parliamentary Group on Malaria		
0845-0900	Introductory remarks	Mr Alan Court, Senior Adviser to the Office of the Secretary General's Special Envoy for Malaria, United Nations
0900-0915	Overview of the Artemisinin Enterprise	Dr Tom Brewer, Senior Program Officer, Bill and Melinda Gates Foundation
0915-1000	Fast-track breeding of high-yielding varieties of *Artemisia annua*	Professor Ian Graham, Weston Chair of Biochemical Genetics, Director, CNAP, University of York
1000-1045	Semisynthetic artemisinin: a new source of artemisinin from synthetic biology	Dr Tue Nguyen, Vice President, Institute for One World Health
1045-1115	Coffee	
1115-1200	Novel synthetic therapies for the treatment of malaria	Dr Ian Bathurst, Director of Drug Discovery and Technology, Medicines for Malaria Venture

Session 3: Current context for ACTs Chair for the session: Stephen O'Brien MP Chairman of the UK All Party Parliamentary Group on Malaria		
1200-1230	Background structure and challenges of the current ACT supply chain - gaps and issues	Professor Christopher Whitty, Chair of International Health, London School of Hygiene and Tropical Medicine
1230-1330	Lunch	

<u>Session 4:</u> Context for introducing the new AE technologies into the ACT supply chain Chair for the session: Silvio Gabriel Executive Vice President, Head of Malaria Initiatives, Novartis		
1330-1335	Introductory remarks	Chair
1335-1425	Panel updates on current challenges in API sourcing strategies	Dr Björn Treptow, Novartis Dr Valerie Faillat-Proux, sanofi-aventis Dr Antonio Longo, Sigma Tau Dr Won June Chang, Shin Poong Dr D C Jain, IPCA
1425-1510	*Panel updates on regulation and prequalification of artemisinin APIs*	Dr Raul Kiivet, WHO Prequalification of Medicines Programme Professor Dora Akunyili, Director General, National Agency for Food, Drug Administration and Control, Nigeria
1510-1540	Tea	
1540-1550	Role of a donor in malaria control	Dr Dana Dalrymple, Senior Research Adviser, USAID
1550-1630	Financing – the changing landscape with AMFm AMFm – making it happen	Dr Jan Van Erps, Commodity Services Coordinator, Roll Back Malaria Partnership Mr Andrew Freeman, Corporate Initiative Officer, Global Fund
1630-1645	CHAI demand forecasting	Dr Inder Singh, Director of Drug Access, CHAI/ Clinton Foundation
1645-1700	Demand forecasting – current and future issues	Professor Prashant Yadav, Chair of Logistics Systems, MIT Zaragoza
1700-1750	Panel discussions: Manufacturers' reflection on the session 4 updates and issues raised	Dr Björn Treptow, Novartis Dr Valerie Faillat-Proux, sanofi-aventis Dr Antonio Longo, Sigma Tau Dr Won June Chang, Shin Poong Dr D C Jain, IPCA
1750-1800	Closing remarks	Chair
1900 -2200	Reception and dinner at Merchant Adventurers' Hall Dinner speech: Sustainability in agricultural supply chains in the developing world	 Dr Harry Swaine, Syngenta AG

Day 3 October 10 **Session 5: Breakout session: Introducing new AE technologies – impacts and issues** Chair for the session: Chris Hentschel President and Chief Executive Officer, Medicines for Malaria Venture		
0845-0915	Introduction to the rationale for the breakout session and guidelines for discussion	Ian Boulton, TropMed Pharma Consulting
0930-1245	Breakout session with facilitators	The session will address: • Potential impact of the new technologies and how they could change the current situation • Potential challenges in the introduction of new technologies • The strategies to be adopted to maximise the effectiveness of introducing the new technologies • Actions to be prioritised and undertaken now to overcome potential challenges arising at the time of introduction of the new technologies
1300-1400	Lunch	
1400-1545	Presentation of reports from breakout groups, followed by plenary discussion	
1545-1615	Tea	

Session 6: Future actions Chair for the session: Tom Brewer Senior Program Officer, Bill and Melinda Gates Foundation		
1615-1645	Review of reports and summing up of breakout session	Ian Boulton, TropMed Pharma Consulting
1645-1800	Panel discussion of breakout conclusions, how best to start working to introduce AE new technologies into the API/ACT supply chains and develop a set of agreed future actions	Professor Awa Coll-Seck, Executive Director, Roll Back Malaria Partnership Dr Chris Hentschel, Medicines for Malaria Venture Dr Tom Brewer, Bill and Melinda Gates Foundation Professor Jean-Paul Moatti, Global Fund Dr Jan Van Erps, Roll Back Malaria Partnership
1800-1815	*Concluding remarks*	Professor Awa Coll-Seck, Executive Director, Roll Back Malaria Partnership
1815-1830	Final comments	Professor Dianna Bowles on behalf of the Artemisinin Enterprise
1830 onwards	Closing reception and buffet dinner in the Atrium of the Department of Biology	

Annex 2. Conference Participants

NAME		AFFILIATION
John	Allen	Hill & Knowlton
Eddie	Anderson	Adorso Farms
Richard	Ansbro	GlaxoSmithKline
Patricia	Atkinson	Bill & Melinda Gates Foundation
Jaya	Banerji	MMV
Elspeth	Bartlet	CNAP
Ian	Bathurst	MMV
Achille	Benakis	Geneva University
Steven	Bentley	NIAB
Ellie	Bertani	Bill & Melinda Gates Foundation
Marc	Blanchard	Artemisinin & Farming International
Ian	Boulton	TropMedPharma Consulting
Dianna	Bowles	CNAP
Tom	Brewer	Bill & Melinda Gates Foundation
Birgit	Buergi	Cambridge Infectious Disease
Anthony	Butler	University of St. Andrews
Caroline	Calvert	CNAP
Jaap	Campo	IDA Solutions
Won June	Chang	Shin Poong Pharmaceutical Co. Ltd.
Elizabeth	Chizema Kawesha	National Malaria Control Programme, Zambia
David	Clayton	CNAP
Cristianne	Close	Syngenta
Renia	Coghlan	MMV
Awa	Coll-Seck	Roll Back Malaria
Alan	Court	United Nations
Malcolm	Cutler	FSC Development Services Ltd
Dana	Dalrymple	USAID
Eduardo	de Azeredo Costa	Farmanguinhos
Ankita	Deshpande	Clinton Foundation
Graciela	Diap	DNDi
Antony	Ellman	NRI
Valerie	Faillat-Proux	sanofi-aventis
Philippe	Farabolini	sanofi-aventis
Henri	Farret	sanofi-aventis
Hilbert	Ferreira	Farmanguinhos
Diane	Freeman	PSI Cambodia

Silvio	Gabriel	Novartis
Kodzo	Gbewonyo	Bioresources International
Ameet	Gheewala	AfroAlpine, Uganda
Charles	Giblain	Bionexx
Ian	Graham	CNAP
Prudence	Hamade	Medecins Sans Frontieres
Heidi	Hanson	Bill & Melinda Gates Foundation
Chris	Hentschel	MMV
James	Hickman	iOWH
Colin	Hill	Botanical Developments UK
George	Jagoe	MMV
Dharam Chand	Jain	IPCA Labs
Bruno	Jansen	Dafra Pharma International.
Tom	Kanyok	Bill & Melinda Gates Foundation
Raul	Kiivet	WHO
Gopinathan	Kizhikkilot	AVT Natural Products
Satheesh	Kumar MN	AVT Natural Products
Jeremy	Lefroy	East African Botanicals
Paul	Lalvani	RaPID
Tony	Larson	CNAP
Wendy	Lawley	CNAP
Yi	Li	CNAP
Antonio	Longo	Sigma Tau
Pedro	Melillo de Magalhaes	Campinhas University, Brazil
Gretchen	Meller	Bill & Melinda Gates Foundation
Christopher	Migoha	Tanzanian Food & Drugs Authority
Jean-Paul	Moatti	Global Fund
Nazeem	Mohamed	Kampala Pharmaceutical
Kathleen	Monroe	iOWH
Zuma	Munkombwe	Pharmaceutical Regulatory Authority
Jack	Newman	Amyris
Tue	Nguyen	iOWH
Rachel	Nugent	Center for Global Development
Stephen	O'Brien	All Party Political Group on Malaria
Kileken	ole-MoiYoi	Harvard University
Chris	Paddon	Amyris
Teresa	Penfield	CNAP
Jacques	Pilloy	OTECI/Artepal
Erwin	Protzen	Advanced Bioextracts
Ralph	Rack	JSI

Anne	Rae	CNAP
Debs	Rathbone	CNAP
Duncan	Rotherham	CNAP
Aloka	Sengupta	Strides Arcolab
Kheng	Sim	NCMP Cambodia
Xavier	Simonnet	Mediplant
Inder	Singh	Clinton Foundation
Debbie	Smith	University of York
Duong	Socheat	NMCP Cambodia
Rodger	Stringham	Clinton Foundation
Li ‘Lily’	Su	Guilin Pharmaceutical
Harry	Swaine	Syngenta
James	Tibenderana	Malaria Consortium
Björn	Treptow	Novartis
Jan	Van Erps	RBM Commodities Services, Head
Ajit	Varma	Amity University
Veronica	Walford	DFID
Wei ‘Will’	Wang	Guilin Pharmaceutical
Christopher	Whitty	ACT Consortia / LSHTP
Thilo	Winzer	CNAP
Prashant	Yadav	MIT, Zaragoza
Shunmay	Yeung	Oxford-Cambodia
Hashim	Yusufu	NAFDAC Nigeria

Annex 3. Abbreviations

Active Pharmaceutical Ingredient	API
Amodiaquine	AQ
Artemether – lumefantrine	AL
Artemisinin combination therapies	ACTs
Artemisinin Enterprise	AE
Artesunate	AS
Bill & Melinda Gates Foundation	BMGF
Centre for Novel Agricultural Products	CNAP
Chloroquine	CQ
Fixed dose combination	FDC
Genetically modified	GM
Global Fund to fight AIDS, TB, & Malaria	GFATM
Global Malaria Action Plan	GMAP
Gross Domestic Product	GDP
Insecticide Treated Nets	ITNs
Institute of One World Health	iOWH
Indoor Residual Spraying	IRS
Intermittent Presumptive Treatment – infants	IPTi
Intermittent Presumptive Treatment – pregnancy	IPTp
Long-lasting Impregnated Nets	LLINs
Medicines for Malaria Venture	MMV
Mefloquine	MQ
Millennium Development Goals	MDG
President's Malaria Initiative	PMI
Production & Supply Management	PSM
Roll Back Malaria Partnership	RBM
Semisynthetic Artemisinin Project	SSAP
Special Programme for Research & Training in Tropical Diseases	TDR
Sub-Saharan Africa	SSA
Sulfadoxime – pyrimethamine	SP
World Health Organisation	WHO

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