Malaria Treatment in Africa

Africa Fighting Malaria Policy Paper
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Abbreviations

Advanced Bio-Extracts	ABE
Affordable Medicines Facility – malaria	AMFm
Africa Fighting Malaria	AFM
Antiretrovirals	ARVs
Approved Drug Distribution Outlet	ADDO
Artemisinin-based Combination Therapy	ACT
German Agency for Technical Cooperation	GTZ
Good Manufacturing Practices	GMP
Medicines for Malaria Venture	MMV
National Drug Regulatory Authority	NDRA
Non-governmental Organization	NGO
President's Malaria Initiative	PMI
Roll Back Malaria Partnership	RBM
Sulfadoxine-pyrimethamine	SP
Tanzanian Food and Drug Administration	TFDA
Thin-layer Chromatography	TLC
United Nations	UN
United States Agency for International Development	USAID
World Health Organisation	WHO

I. Executive Summary

Drug resistance due to parasite mutation was a key driver of malaria's resurgence in sub-Saharan Africa in the 1990s. Southeast Asian countries demonstrated the efficacy of a new but expensive treatment and, together with a Swiss pharmaceutical company, developed the first fixed-dose artemisinin-based combination therapy (ACT) for malaria. Few countries claimed they could afford to adopt this drug as a first line treatment. Advocates, malaria scientists and United States Congress ultimately exposed the folly of continuing to fund outdated drugs like chloroquine and sulfadoxine-pyrimethamine (SP), and donor agencies moved to meet the huge need for ACTs.

The results have been a mixture of success and systemic failure. The United States Government, World Bank and the Global Fund to Fight AIDS, TB and Malaria have substantially increased malaria control funding and through the World Health Organisation (WHO) and Roll Back Malaria Partnership (RBM) provided technical assistance to help countries change treatment guidelines to ACTs and devise strategies to finance them. As of September 2007, ACTs are listed as first-line treatments for uncomplicated malaria in every national treatment policy in sub-Saharan Africa where they are needed. The Global Fund is helping to deliver 264 million ACTs, backed by an unprecedented $471 million allocation for malaria control (42% of total allocations) in its most recent round of grants (Round 7). Largely as a result of these efforts, some African countries are reporting localized declines in malaria cases and deaths.

Yet the rising demand for artemisinin has increased incentives for producers to market artemisinin as a monotherapy. The WHO has explicitly recommended against this practice, as widespread exposure could accelerate parasite resistance to artemisinin. No new class of antimalarial treatment is expected to enter the market for at least a decade, so all foreseeable malaria treatment strategies depend on the integrity of this drug. Recent evidence from Southeast Asia suggests that artemisinin may be losing effectiveness against malaria. If this is attributable to parasite resistance, Africa may not be far behind.

Unfortunately, public health systems on the African continent remain weak and underdeveloped. Most people still seek treatment from the private sector, where substandard and artemisinin monotherapy drugs abound. Africa Fighting Malaria (AFM) has confirmed this in a recent study of private sector antimalarial drug quality in six African countries – Ghana, Kenya, Nigeria, Rwanda, Tanzania and Uganda. Antimalarial monotherapy tablets, including artemisinin, were widely available in urban and peri-urban pharmacies, with 35 percent of all treatments failing basic content testing.

This comes as no surprise. Only 20 percent of the WHO's 191 member states currently have well-developed drug regulation. Post-market surveillance of the private sector in low-income countries is practically non-existent, and national drug registries are infrequently updated or publicized. Africa has only six WHO-registered national pharmacovigilance systems to detect substandard drugs. Though the agency has made efforts to scale these up and develop new sites, resistance monitoring networks remain severely limited.

In the absence of strong national regulatory and pharmacovigilance systems, consistent leadership among donor agencies providing ACTs is critical – and sorely lacking. The Global Fund has adopted a stand-alone policy of procuring drugs not tested by competent agencies. This is intended to increase competition and spur price reductions, but it may result in the distribution of unsafe drugs. Such practice is forbidden in developed countries. The Executive Director of RBM has voiced concerns about the quality of these drugs, but the Global Fund is reticent to leave nascent copy drug companies in the lurch.

An outgrowth of the trend toward generics and copy drugs is "local production" of pharmaceuticals. Some donors aggressively advocate this concept even as they acknowledge safety risks and substantial opportunity costs. Tremendous investment of limited resources will be required to turn African factories into viable, internationally-accredited production facilities. Further, localized producers have an inclination and incentive to protect their output by lobbying for tariffs and other protective measures, which threaten to increase costs and impede access to quality drugs. Ideological support for local production destructively conflates industrial and public health policy, and provides copy drug companies little incentive to improve quality.

The latter point is most concerning as donor agencies roll out new treatment solutions like the Affordable Medicines Facility – malaria (AMFm). If approved, this initiative will adopt the commendable goal of subsidizing ACTs for private and public sector distribution. Unfortunately it plans to compromise on drug quality standards in line with the Global Fund. Without a commensurate strengthening of national regulation, postmarket surveillance and pharmacovigilance to pace the inevitable development of artemisinin resistance, such policies could result in setbacks for malaria control and public health.

Substandard drugs continue to circulate in Africa, causing an estimated 200,000 avoidable deaths from malaria alone each year. Structural reforms are elusive. Malaria endemic countries remain hugely dependent on donors, who too often reward policy failures with new aid initiatives. Eight years ago, African governments pledged to remove taxes and tariffs on malaria control technologies, and devote at least 15 percent of their national budgets to improving health care. Most are failing to live up to these commitments. Unless Africa takes its own health care more seriously, the present gains against malaria should not be expected to last.

II. Key Recommendations

- African governments must strengthen national pharmaceutical regulation. They should enact policy reforms to strengthen health care systems, namely increasing health care spending in line with Abuja promises, removing taxes and tariffs on imported drugs, and ending protectionist subsidies for local pharmaceutical industries. They should supplement these efforts with decentralized drug quality control testing using portable labs, for instance.

- Stronger global leadership on drug quality standards is urgently needed. Bioequivalence approval by a stringent regulatory agency should be a uniform standard for all publicly funded antimalarial drugs. Donor agencies should subsidize fast-tracked bioequivalence testing for ACTs by one of the stringent regulatory agency members of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

- The WHO should continue to hold the list of approved pharmaceutical products for use in developing countries. However, it should sustain sufficient funding to conduct bioequivalence testing on included products or assess bioequivalence studies undertaken by high quality laboratories independent of the company submitting the product. If neither is possible, it should abandon the prequalification program in favor of stringent regulatory approval. Approving drugs based solely on Good Manufacturing Practice standards, without full bioequivalence evaluations, is unacceptable. The Global Fund should revise its quality assurance policy in line with this standard and stop publishing an independent procurement list.

- Donor agency funding for malaria control should be conditional on countries de-listing oral artemisinin monotherapies from national registries. The World Trade Organisation should enact rules prohibiting the international trade in artemisinin monotherapies and reducing the tariffs on WHO-approved drugs to zero. Donor agencies should establish an agreement with manufacturers of high quality ACTs guaranteeing the purchase of a predetermined quantity of drugs. Given the lead time required to produce ACTs, it is essential to improve forecasting; however, any forecasts of projected demand should be accompanied by realistic financial guarantees from donor agencies and the WHO in order to share the risk.

- Unlike with other diseases, there are no intellectual property barriers to accessing ACTs. Both of the lead innovator companies, Novartis and Sanofi-Aventis, sell their ACTs on a no-profit no-loss basis. While increased competition in the supply of ACTs from generic companies is welcome, this does not guarantee good drug quality. Advocacy groups should therefore increase pressure on African governments, the WHO, Global Fund and other donor agencies to keep substandard drugs out of the hands of the poor at all costs.

III. Introduction: Advocates Drive Reform

Malaria kills over a million people each year, mostly young children in sub-Saharan Africa. Transmitted by *Anopheles* mosquitoes which thrive in tropical climates, the disease surged throughout this region in the 1990s. No single effect can explain the trend, but rising parasite resistance to historically effective drugs, chloroquine and SP, was a substantial driver.[1,2] Public health and regulatory systems in most African countries have long been poorly financed and managed; cheap and potentially substandard drugs were readily available from unregulated sources, where most Africans go for treatment.[3] Many people were exposed to sub-therapeutic or incomplete doses of these drugs. Malaria parasites, like many other pathogens, inevitably develop resistance to drugs, but the effect can be accelerated with inappropriate use.

Several key steps were taken to refocus efforts on controlling malaria during this period. In 1998, RBM was launched with the goal of halving malaria by 2010.[4] In 2000, the African Summit on Roll Back Malaria was held in Abuja, Nigeria, committing African governments to scaling up malaria control interventions and, one year later, increasing health budgets in order to achieve this goal.[5] Novartis AG, a Swiss pharmaceutical company, led the private sector in supporting antimalarial treatment initiatives. Building on combination treatment strategies developed by malaria scientists in the 1990s to combat resistance,[6] Novartis combined lumefantrine, an antimalarial agent not historically used as a monotherapy, with artemether,[7] a derivative of artemisinin from the sweet wormwood-plant *Artemisia annua*, to make Coartem. This and other WHO-approved ACTs quickly eliminate malaria parasites from the bloodstream and reduce gametocyte carriage, thereby interrupting malaria transmission. They are well tolerated and have no confirmed parasite resistance.

In 2001, Novartis signed a Memorandum of Understanding with the WHO to make Coartem available to malaria-endemic countries on a no-profit no-loss basis.[8] The agreement was a breakthrough for malarial countries that could afford the reduced price – but most could not. Coartem was still up to 20 times more expensive than chloroquine, which sold for as little as $0.10.[9] The reason for the higher price was largely due to the more expensive process to produce the drug, which involves a long lead time (14 months) to grow plants and a costly process to extract the active ingredient. Donors were slow to help countries transition to ACTs, unable or unwilling to subsidize the extra costs to buy and properly administer the drugs.[10] Though the WHO recommended countries adopt ACTs, it applied little effective pressure on either donors or endemic countries to change their policies.

Countries that could afford to make the switch on their own did so. In 2000, South Africa became the first to adopt ACTs in its national treatment policy.[11] Other countries recognized the threat posed by rising parasite resistance and adopted ACTs without assured donor purchases. Zambia changed its first line treatment from chloroquine to artemether-lumefantrine in 2002,[12] and Zanzibar changed its first line treatment from chloroquine to artesunate-amodiaquine in late 2003.[13] Most other countries continued to fund outdated antimalarial monotherapies.

When the Global Fund to Fight AIDS, Tuberculosis and Malaria[14] was launched by the United Nations (UN) in 2003, it was expected to exercise leadership in solving the problem of inadequate financing and weak donor agency commitment to ACTs. It was criticized, however,

for supporting the prevailing practice of financing chloroquine.[15] The agency argued that its function was to finance country-driven proposals based on available evidence, not prescribe policy.[16] Pressure from United States Congressmen[17] and malaria advocacy groups[18,19,20] prompted the Global Fund to overhaul treatment policy, and motivated major donor agencies to move toward meeting the demand for ACTs.[21]

The United States Government and World Bank subsequently launched the President's Malaria Initiative (PMI)[22] and Malaria Booster Program[23] respectively, which by 2007 contributed to a 60-fold increase in global malaria control funding over 1999 levels.[24] Together with the WHO, these agencies began fast-tracking technical assistance to help countries change treatment guidelines to ACTs and devise strategies to finance them. As of September 2007, ACTs are listed as first-line treatments for uncomplicated malaria in every national treatment policy in sub-Saharan Africa except Swaziland and Cape Verde; chloroquine remains effective in these countries and is still used as a first-line treatment.[25] The Global Fund's grants accounted for 85 percent of all ACTs procured in 2006,[26] and according to its website, it is currently helping to deliver 264 million ACTs.[27]

After stalling for much of the last decade, the RBM Partnership is generating constructive and coordinated momentum for malaria control. The disease now benefits from more public funding than ever before. In the most recent Global Fund financing round (Round 7), an unprecedented $471 million for malaria control in 27 countries was approved over the next two years.[28,29] Malaria grants comprised 42 percent of funding for all three diseases, thanks in large part to a focused effort by RBM to provide technical assistance in developing proposals. Some African countries are reporting localized declines in malaria cases and deaths.[30] The WHO has further reported over 50 percent reductions in malaria cases and deaths among children under age five in several districts of Rwanda and Ethiopia, which it attributed to mass distribution of long-lasting insecticidal nets and ACTs.[31]

Yet substandard drugs continue to hamper malaria control efforts throughout much of Africa. The WHO estimates that the failure of national drug regulatory authorities (NDRAs) to maintain quality standards results in 200,000 avoidable deaths from malaria alone each year.[32] Ongoing exposure to therapeutically effective artemisinin monotherapy tablets (and especially substandard versions) is equally deadly in the longer term in accelerating resistance. No alternative major class of antimalarial agent is expected to enter the market for another decade,[33] making it crucial to preserve the integrity of artemisinin for current and future ACTs.

In January 2006, the WHO issued new antimalarial treatment guidelines for the first time in 20 years officially recommending ACTs. It also publicly called for an end to the production of artemisinin monotherapies[34] and helped pass the World Health Assembly Resolution WHA60.18 in May 2007, calling on all member states to support this effort.[35] There is little evidence to suggest these diplomatic efforts are having an impact. As of August 2007, the agency counted over 80 Chinese artemisinin producers, 67 countries manufacturing oral artemisinin monotherapies and at least 94 oral artemisinin-based products currently in the market, mostly in the private sector of endemic countries.[36] Anecdotal evidence suggests artemisinin is losing effectiveness against malaria in Southeast Asia.[37] Africa may not be far behind.[38]

IV. Private Sector Regulation

The inadequacies of public health systems in many African countries means most people at risk of malaria obtain drugs from the private sector – pharmacies, shops, street vendors, general traders and kiosks.[39] These outlets are mostly outside the scope of national regulation, which is limited in many African countries by resource constraints. Ideally, NDRAs will work with the WHO and stringent regulatory agencies, notably the United States Food and Drug Administration, to develop policies on acceptable pharmaceutical treatment formulations that can be used in public facilities and sold in the private sector.[40] Companies producing approved formulations apply to NDRAs for product testing and submit their factory to inspection. If basic quality and good manufacturing practices criteria are satisfied, the branded formulations are assigned a number and added to a central database of approved pharmaceuticals.[41]

However, products sold in sub-Saharan Africa face little or no scrutiny after initial testing, approval and registration by NDRAs. A 2004 WHO survey found that 90 percent of African NDRAs were unable to perform various regulatory functions.[42] The agency has run the Secretariat for the International Conference of Drug Regulatory Authorities over the past 23 years to harmonize regulation and improve the safety, efficacy and quality of drugs.[43] Only 20 percent of the WHO's 191 member states currently have well-developed drug regulation; 50 percent operate at varying levels of drug regulation, driven by regulatory capacity; and 30 percent have weak drug regulation or none at all.[44] Post-market surveillance of the private sector in low-income countries is practically non-existent, and national drug registries are infrequently updated or publicized.[45,46]

The WHO correctly claims not to be a supranational regulatory authority. In effect, however, the NDRAs align their standards with those of the WHO, which then assumes de facto power as a collective regulatory authority. For malaria, tuberculosis and HIV/AIDS, the WHO is the standard-bearer for drugs that are purchased by donors with public money. The agency launched a pharmaceutical pre-qualification program in 2001 to provide unified standards for quality, safety and efficacy of publicly funded drugs and facilitate the distribution of HIV/AIDS, TB and malaria in poor countries with weak NDRAs.[47,48]

The WHO has two criteria for prequalification: manufacturing site visits and dossier evaluations with product safety and efficacy data.[49] While it is supposed to do both, the WHO has stated that it sometimes substitutes dossier evaluations for site visits.[50] Further, the WHO does not conduct clinical or post-market testing of these products, nor does it make any data public or accept legal responsibility for the use of approved drugs. The agency collects and analyzes voluntarily submitted pharmacovigilance data to the Uppsala Monitoring Centre in Sweden,[51] but ultimately lacks any enforcement authority.

The WHO's IMPACT program was launched in February 2006 to work with regulatory agencies, Interpol and national governments in exposing and prosecuting drug counterfeiters.[52] Though commendable, attempting to stamp out counterfeits does not deal with the potentially more important problem of widespread use of substandard drugs – which can be legal yet contain therapeutically inadequate active ingredient and may actually be more harmful to long-term resistance management. Africa only has six WHO-registered national pharmacovigilance

systems to detect substandard drugs.[53] Though the agency has convened workshops to expand on these efforts, resistance monitoring networks remained sharply limited.[54]

In 2007, AFM conducted a drug testing study in the geographic band of hyper- and holo-endemic *P. falciparum* malaria.[55] A range of antimalarial drugs were procured from private pharmacies in urban and peri-urban areas in the largest cities of six African countries: Ghana, Kenya, Nigeria, Rwanda, Tanzania and Uganda. Using the Global Pharma Health Fund's Minilab,[56] semi-quantitative thin-layer chromatography (TLC) and dissolution rates were evaluated against internationally acceptable standards.

Overall, 35 percent (73/210) of tested samples were substandard and failed either TLC or dissolution tests. 33 percent (64/195) of all treatment packs tested were artemisinin monotherapies, and 42 percent (27/64) of these failed either TLC or dissolution tests. 78 percent (50/64) of the artemisinin monotherapy tablets tested were manufactured after the WHO's January 2006 appeal to halt monotherapy production.

The impact of weak regulation is further reflected by the testing results grouped by country of manufacture. 48, 32 and 24 percent of tested samples manufactured in Africa, Asia and Europe failed, respectively. Only four tested samples were manufactured in the United States and none failed. Of the 29 tested samples manufactured in Asia that failed, 16 were manufactured in China (33 percent of all Chinese samples tested failed), 12 were manufactured in India (31 percent of all Indian samples tested failed) and one was manufactured in Pakistan.

AFM's study confirmed that antimalarial monotherapies, including artemisinin, remain widely available in urban and peri-urban pharmacies, with between a quarter and over half failing basic content testing in all six countries studied. These findings are supported by numerous other studies as well as WHO reports.[57,58,59,60,61,62] The consistent performance of Coartem across countries and locales – no samples (0/15) failed – suggested that failures among other drugs were more likely due to poor manufacturing or inadequate means of transportation rather than final storage conditions.[63]

Updated antimalarial drug registries were requested from each of the countries under study to cross-reference results. AFM was only able to obtain registries containing acceptable formulations and registered brands from Tanzania (December 2007) and Uganda (September 2007).[64] Several countries explained that they were in the process of removing artemisinin monotherapies from national drug registries pursuant to the WHO's appeal in January 2006. Tanzania was the only country from which the authors received definitive documentation that most, but not all of these drugs were removed at the time of publication. Between February 2005 and December 2007, 14 oral artemisinin monotherapies were de-listed from Tanzania's national drug registry and 11 ACTs were added.[65]

The persistence of substandard drugs and artemisinin monotherapies in the private sector risks patient safety and accelerates resistance. This is not only true for artemisinin, but other antimalarials this drug is paired with in ACTs. WHO-recommended formulations include artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, and artesunate-SP.[66]

Only lumefantrine is not widely used as a monotherapy treatment for malaria; high clinical failure rates have been reported for amodiaquine and SP across Africa.[67,68]

Minilabs and equivalent technologies provide a relatively inexpensive, versatile and robust means of identifying substandard drugs in a developing country context based at a fraction of the resources required for modern laboratory testing. Approximately 270 Minilabs are already being used in 65 countries to help public and private authorities identify counterfeit and substandard drugs.[69] Some African NDRAs, such as the Tanzanian Food and Drug Authority, use Minilab technology to test drugs at ports of entry and centrally.[70] However, these quality control measures are limited and, among regional malaria endemic countries, are still rare.

Summary of Key Points and Recommendations

- Regulation of pharmaceutical production and private vendors in many African countries remains poor.
- While almost all African countries have officially changed treatment policies to ACTs, most have been slow to remove artemisinin monotherapies from their national drug registries as the WHO recommended in January 2006.
- AFM's drug testing study found 21 different brands of artemisinin monotherapy in randomly selected private pharmacies in six African countries. Most were imported from India, China and Belgium. 35 percent of all antimalarials tested failed TLC or dissolution tests.
- In order to guard against the inevitable development of drug resistant strains of *P. falciparum*, African governments must prioritize effective regulation. This entails phasing artemisinin monotherapies out of private industry, educating consumers on appropriate malaria treatment, increasing random sampling and quality testing of drugs sold in the private sector, and strengthening pharmacovigilance to monitor treatment failure and parasite resistance.
- Donor agency funding for malaria control should be conditional on countries de-listing oral artemisinin monotherapies from national registries. The World Trade Organisation should enact rules prohibiting international trade in artemisinin monotherapies and reducing tariffs on WHO-approved drugs to zero.
- A decentralized, independent network for antimalarial quality testing using portable labs is needed in sub-Saharan Africa. At about $4000 per kit, this technology is simple and accurate enough to inform regulatory agencies about the quality of market products they oversee on an ongoing basis.

V. Public Funding for Drugs: Quantity vs. Quality

The Global Fund has become the premier resource for malaria endemic countries transitioning to ACTs. Its pharmaceutical quality standards, however, are a matter of ongoing concern within the malaria community.[71] At its 3rd Board Meeting in October 2002, the Global Fund specified that grant recipients would be able to purchase so-called "single and limited source pharmaceuticals"[72] that did not secure approval from either the WHO's prequalification program (Option A) or a stringent regulatory authority (Option B). Authorization of a given product by a recipient country's NDRA (Option C) would suffice.[73] This quality assurance policy applied equally to products procured for HIV/AIDS, TB and malaria control.

Management Sciences for Health Europe, a private educational organization and contractor of health services, in conjunction with the WHO prepared a background paper for a later Global Fund Board Meeting that explained the original rationale for Option C more clearly, as follows:

> Option C theoretically widens the options for procurement by countries supported by the Global Fund by increasing the number of potential suppliers. More suppliers normally lead to greater competition and lower prices.[74]

Although at the time the Global Fund Board's recommended course of action was to remove Option C,[75] the policy was revised at the 10th Board Meeting into two discrete categories: Option Ci products were submitted to the WHO's Prequalification Program or a stringent regulatory authority, and manufactured at a Good Manufacturing Practices (GMP) certified site; Option Cii products were simply manufactured at a GMP-certified site.[76]

According to this policy, Global Fund money could justifiably be used to purchase complex drugs from a production site GMP-certified to manufacture cough syrup, for example, regardless of quality, safety or *in vivo* efficacy of the specific drug. The policy further stipulated, "Once there are two or more equivalent pharmaceutical products that meet the standards in Option A or B, then Option C is not applicable," and that Option C products could be procured if Option A and B products could not be supplied in sufficient quantities within 90 days.[77]

In September 2005, the Global Fund formally created its Compliance List, a non-binding list of drugs classified according to Options A, B and C for each disease.[78] The list was intended as a reference for grant recipients though like the WHO pre-qualification program, its legal disclaimer was explicit:

> The Global Fund does not endorse or warrant the fitness or any product on the List for a particular purpose, including in regard of its safety and/or efficacy in the treatment of HIV/AIDS, tuberculosis or malaria...[and] disclaims any and all liability and responsibility for any injury, death, damage or loss of any kind whatsoever that may arise as a result of, or in connection with the procurement, distribution and use of any product included in the list.[79]

Later versions of the list describe its purpose as follows:

> An overview of pharmaceutical products subject to the Global Fund Quality Assurance Policy for Single and Limited Source pharmaceutical products that are listed in National and/or WHO standard treatment

> guidelines…[but] not designed to be a basis for countries to select products to be included in their National Treatment Guidelines or to replace any applicable and legally required procurement processes.[80]

The Global Fund Compliance List for antimalarial products is constantly changing, exacerbating an already convoluted process. Seven different versions of the Compliance List have been published over the past seven months alone (October 2007-April 2008). During this time, the Global Fund added one Option A product, nine Option Ci products (including one non-WHO recommended ACT formulation) and three Option Cii products – and removed 14 products.

Fourteen products were removed on October 10, 2007 because they were "not listed in either current national or World Health Organisation standard treatment guidelines or in essential medicine lists."[81] It is not clear why these products were included on the list in the first place, but they comprised a broad range of antimalarial formulations: generic artemether-lumefantrine suspension, artesunate-amodiaquine fixed-dose combination tablets, artesunate-mefloquine co-blister pellets and tablets, and artesunate-SP fixed-dose combination and co-blistered tablets.

On the same occasion, the Global Fund added its first non-WHO recommended ACT.[82] In this version of the list, dihydroartemisinin-piperaquine phosphate, manufactured by Holley Cotec Pharmaceuticals, was listed as Option Ci. Presumably the drug is included on a national treatment registry for one of the Global Fund's grant recipients and, by its Ci status, has submitted an application for prequalification or stringent regulatory approval.

A UN agency policy promoting non-WHO approved, non-quality assured formulations with limited public funds is counterintuitive, dangerous and cost ineffective, particularly when considering the product pipeline for new ACTs. The Medicines for Malaria Venture (MMV),[83] a public-private partnership to develop new antimalarial treatments, has had a similar formulation of dihydroartemisinin-piperaquine under development for several years. It is likely to secure approval from a stringent regulatory authority before marketing the drug through public channels. Adverse reactions or parasitic resistance arising from Holley Cotec's formulation, distributed by the Global Fund without quality assurance testing, could undermine MMV's quality assured version of the drug.

Further, quality assuring products based solely on submission to WHO's prequalification program has been problematic in the past. During the WHO's "3x5 Initiative" to provide ARVs to three million people living with HIV/AIDS by the end of 2005, the agency bowed to political pressure from senior officials and dispatched copy drugs that had been submitted to the WHO prequalification program for review, but not approved.[84] In November 2004, 18 ARVs were either removed by the companies or de-listed by the WHO, because third-party bioequivalence data did not match the manufacturer's submission.[85]

The Global Fund Secretariat is responsible for organizing random quality control testing of Option C pharmaceutical products purchased by a Principal Recipient through SGS Nederland B.V.[86] According to the Global Fund, testing covers appearance, dissolution or disintegration, and identification, assay and impurity control, among others. Testing is done on random samples from batches selected by the laboratory prior to the product being shipped to the recipient. If the product is found to be of unacceptable quality, the Principal Recipient and the manufacturer are informed and the Principal Recipient is advised to procure an alternative product. The

frequency, cost and results of quality control testing are not made public, so it is impossible to ascertain whether any Option C products procured were unsafe or ineffective, or how many have been tested.

What is clear is that the Global Fund's quality assurance policy has proved a poor incentive for Option C-producing companies to secure Option A or B status. There remains only one Option A or B product for each of three ACT formulations (artemether-lumefantrine, artesunate-amodiaquine and artesunate-mefloquine) on the Global Fund's most recent procurement list.[87] Three years after the policy was amended, countries are free to select any Option C product, since there is not "two or more" Option A or B products for any given formulation.

There is near-consensus within the RBM community on potential problems with Option C drugs, as expressed in a letter from Dr. Awa Coll-Seck, Executive Director of RBM, to Dr. Michel Kazatchkine, Executive Director of the Global Fund.[88] As a result, the Global Fund's Board has authorized a review of its quality assurance policy for all three diseases by the Portfolio Committee.[89] Pending the outcome, this committee will recommend to the Board at the 18th Board Meeting in November 2008 a modified quality assurance policy for single and limited source pharmaceutical products.[90]

The authors infer that as a result, the earliest the policy would be changed is April 2009 at the 19th Board Meeting. In the mean time, the WHO is brokering a harmonization effort to raise the Global Fund's standards in line with the rest of the donor community.[91] Early reports indicate little substantive change to Option C; instead, standards for all donor agencies will fall in line with the Global Fund, and untested Option C products will be reviewed by an "ad hoc clinical review committee" before procurement.[92]

Summary of Key Points and Recommendations

- The Global Fund maintains a list of drugs that its grant recipients can procure. This list differs from other major donors in that it includes drugs that have neither been tested by a stringent regulatory authority or the WHO.

- The Global Fund Compliance List is constantly changing, exacerbating an already convoluted process. Seven versions have been released over the past seven months, during which time nine Option Ci products (including one non-WHO recommended ACT formulation), three Option Cii products and only one Option A product were added, whilst 14 products were de-listed.

- Option C drugs were originally included to encourage competition for drug formulations needed in developing countries and not inherently profitable to research-based pharmaceutical companies. This has subsequently reduced incentives for generic manufacturers to obtain stringent regulatory approval and potentially provide patients with substandard drugs. Though the Global Fund Board casts Option C as a temporary measure – no longer applicable when two or more Option A or B formulations are available for a given product – three years

have passed without progress towards this goal for antimalarial drugs. Both the Portfolio Committee and the Board delay in addressing this crucial issue for malaria control.

- Antimalarial drugs bought with Global Fund money and given to patients are not permissible in the European Union, United States or other developed economies. Option C drugs imply that there are Option C people. Untested Option C drugs are not acceptable in developed economies and so should not be fit for developing ones.

- Global Fund quality control testing results of Option C products should be made available to the public, along with the frequency and cost of such testing. If quality control testing is done on every shipment, the money might be better spent on purchasing high quality drugs. However, if every shipment of Option C drugs is not quality control tested, there is a chance that poor quality drugs could be distributed to patients. More data is needed to ensure an appropriate balance.

- Given the problems with regulation and oversight in many malarial countries, AFM expects the Global Fund and the wider donor community will, at a minimum, demonstrate good leadership by maintaining the highest and most consistent antimalarial drug standards possible. The harmonization process for procurement standards and the selection of *ad hoc* clinical review committee members should be public and transparent.

- Bioequivalence approval by a stringent regulatory agency should be a uniform standard for all publicly funded antimalarial drugs. Donor agencies should subsidize fast-tracked bioequivalence testing for ACTs by one of the stringent regulatory agency members of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

- The World Health Organisation should continue to hold the list of approved pharmaceutical products for use in developing countries. However, it should also either sustain sufficient funding to conduct bioequivalence testing on included products or abandon its prequalification program in favor of stringent regulatory approval. The Global Fund should revise its quality assurance policy in line with this standard and stop publishing an independent procurement list.

VI. Generic and Local Pharmaceutical Production

Regarding the impending review of the Global Fund quality assurance policy, the 8th Portfolio Committee's Report to the 16th Board cited, "concerns about the absence of key information such as: impact on countries' national programs…the exposure of the GF to liabilities due to exclusion of manufacturers…[and] market dynamics…"[93] It is unclear what liabilities the Global Fund would face, considering it is indemnified against any repercussions whatsoever,[94] but the background paper on Option C discussed above provides some insight into these concerns:

> With several countries having started local production of ARV and many of those manufacturers still having not been cleared through the prequalification process of WHO, removing Option C would create a barrier to market entry and curb the effects of competition that their presence would have created. Of course this barrier would also avoid the procurement of potentially substandard products.[95]

Although this document referred to the Global Fund's quality assurance policy before the April 2005 revisions, the practical implications are the same. Option C financing has made generic and copy drug companies dependant on Global Fund financing and the relaxed quality standards that allow them to compete for large public contracts – despite inherent safety concerns. In attempting to balance safety and cost, the Global Fund has evidently favored the latter.

In addition to potentially producing substandard products, "local production", which is synonymous with generic manufacturing, also tends be to be fraught with cost inefficiencies. Advanced Bio-Extracts (ABE) is a $25 million venture to grow *Artemisia annua* and extract artemisinin in Kenya.[96] ABE was praised at its launch in 2004 as combining "patient capital, talent and innovation" to promote development in Africa.[97] It boasted an impressive list of backers – Acumen Fund, Novartis, International Finance Corporation, Action Medeor, German Agency for Technical Cooperation (GTZ), Cordaid, United States Agency for International Development (USAID), TechnoServe and the Centre pour le Développement de l'Entreprise – and secured purchase pledges from the WHO and Global Fund.[98]

The artemisinin produced by ABE appears to be of good quality, but the company has failed to deliver it in sufficient quantity. ABE was initially supposed to supply at least 50 million tons of artemisinin annually; by 2006, that number had been revised down to 25 million tons. As of March 2007, only 10.3 million tons had actually been delivered.[99] A lack of technological know-how among inexperienced farmers, compounded by poor management decisions, appeared to be to blame for the failure to deliver on agreed contracts.[100]

Even with stronger management, local production increases costs at three distinct stages: the start-up costs of establishing the industry, the costs of subsidizing production, and the higher priced finished product. In its analysis of a hypothetical local production plant in Nigeria, the National Academies of Science found that it would cost 15 percent more to grow, extract, purify, and derive local artemisinin derivatives than to import them directly.[101]

Governments tend to protect nascent domestic industries from foreign competition by imposing high tariffs on sales and value-added taxes on imported pharmaceuticals, as well as offering tax

incentives to local companies. In Tanzania, where one local company supplies 50 percent of government orders for all drugs,[102] government tenders for pharmaceuticals offer a 15 percent contract cost reduction to domestic pharmaceutical manufacturers and levy a 10 percent tariff on imported drugs (excluding antimalarials and ARVs).[103]

Such actions, however, constrict the supply of imported drugs, which are often of superior quality, without necessarily increasing local supply appreciably. Drug tariffs and taxes are regressive, harming sick and poor consumers while raising relatively little in state revenues. Consumers may see prices significantly increase above manufacturers' prices, due to wholesaler markups along the supply chain (including those from the government, especially tariffs and taxes) with no appreciable impact on government health care spending.[104]

Donors claim that the higher costs of local production are partially offset by the creation of local jobs,[105] but this is not quite certain, particularly regarding stable, long-term employment. Jobs may have simply moved from another sector of the economy. For example, many farmers in Kenya, Uganda and Tanzania now growing *Artemisia annua* would have grown staple crops before. While they will probably have the potential to generate higher revenues by growing *Artemisia annua*, they might find themselves with no buyer if the company they supply is inefficient and out-competed. The difference between skilled and unskilled labor is also relevant. Shelys Pharmaceutical employs 800 people in Tanzania, the majority of which are skilled workers from India and the United Kingdom.[106]

De facto preference for local production ignores the fact that local manufacturers, like any company, act out of self-interest and not necessarily in the interest of public health, safety and development. When Kenya's national government decided to change treatment policy from SP to artemether-lumefantrine instead of artesunate-amodiaquine, which was produced locally, domestic pharmaceutical companies vigorously protested. They lobbied for public reviews of the proposed policy change, pressured the government to comply and significantly delayed the scheduled Global Fund grant for ACTs.[107] The preference for homegrown development solutions or "local production" may incentivize local companies to increase pressure on country-coordinating mechanisms to favor treatment focused strategies (e.g. ahead of prevention) in applying for Global Fund grants and local products over international products at the expense of quality.

According to a report commissioned by the Global Fund, when a Global Fund grant awarded to Ghana for artesunate-amodiaquine was delayed due to provider training hold-ups, the government opted to substitute the ACTs ordered with a locally produced version.[108] This product incorporated a higher than recommended dose of amodiaquine, causing widespread adverse drug reactions. Patients attributed the problem to the new formulation and not the poorly manufactured local product. The resulting social resistance contributed to further delays in the transition to ACTs. The report concluded, "This experience points to the need to ensure the quality of the commercially available products in the country to avoid repercussions in the adherence of health care providers and users to the official combination."[109]

Even if good quality drugs are produced locally, access is not assured. GTZ's assessments of Ghana's local pharmaceutical distribution system put these obstacles in perspective:

> The private sector pharmaceutical distribution system in Ghana (and elsewhere in the subregion) can best be described as chaotic…There can be little doubt that this chaotic system impacts adversely on the availability, product security and the final price of pharmaceutical products and undermines the possibility of consumers to obtain medicines as and when they need…It is very difficult to further comment on the private sector pharmaceutical distribution system which can only be described as a public health disaster.[110]

In the same report, GTZ also states, "Locally produced drugs tend to be more expensive than imported equivalents from India and China," for reasons ranging from costly raw material imports to the expensive and inconsistent supply of electricity and water. That being said, "BMZ, GTZ, UNIDO and UNCTAD have affirmed their commitment to supporting the development of local pharmaceutical manufacturing in Ghana and the sub-region…"[111] Having made local pharmaceutical production a political priority, it seems that little can deter these agencies.

Tremendous investments of time and limited resources will be required to turn these facilities into viable, internationally accredited production facilities. But the fact remains that local production companies may be ill-equipped to tackle the significant risks inherent in forecasting actual demand for drugs, especially as they are limited by size, experience and shifting political priorities among donors. Even large companies with decades of demand-forecasting experience have guessed wrong, as described in a later section. In the short run, large companies can cover losses on inaccurate forecasts; small local production companies, however, are more vulnerable. Furthermore, large companies faced with consistent losses will eventually cut the cause of the losses; smaller companies may simply collapse.

The precise amount of money – and lives – African governments and their supporters in the international aid community would have saved by buying cheaper and potentially higher quality ingredients overseas rather than growing their own is impossible to calculate. Local production can and should promote development, but only when the market prescribes it. The international community must guard against propping up ineffective companies or initiatives, and be far more vigilant in preventing endemic country governments from using protectionism to do the same. The key to reducing costs and increasing efficiency is to allow ineffective projects to fail.

Summary of Key Points and Recommendations

- Through its Option C policy, the Global Fund has encouraged generic and copy drug producers that have become dependant on its financing to compete for global contracts. Malaria endemic governments, donor agencies and activists further promote the idea of "local production" of generic pharmaceuticals as a means to increase access.

- The cost of bringing production facilities that are not in compliance with WHO GMP up to international standards – both in limited public resources and the opportunity cost of not buying quality-assured antimalarial drugs already available – is prohibitive.

- Policies aimed at favoring local production can lead to protectionism, lower quality standards, longer lead times, higher prices and ultimately a greater disease toll. Local production usually benefits a small class of elite businessmen and politicians, while potentially harming millions of consumers.

- Decisions on which drugs to procure should be based on quality first, backed by scientific evidence and open to competitive, international tenders.

- The notion that goods must be produced locally in order for them to be more readily available ignores centuries of trade economics. Quality must come first. All local production ventures should be encouraged to submit dossiers to stringent regulatory authorities to ensure high-quality production. Aid agencies can best support local production by subsidizing fast-tracked bioequivalence testing for drugs, as the Food and Drug Administration did for the WHO's prequalification list of HIV/AIDS drugs in 2004.[112] If locally manufactured drugs can be verified as bioequivalent, they should become eligible for purchase by donor agencies.

VII. The Affordable Medicines Facility- malaria (AMFm)

As public sector channels have proved unable or inadequate to provide treatment to malaria sufferers, some members of the RBM community are championing an initiative originally proposed by the Institute of Medicine to work with private vendors.[113] The $1.9 billion AMFm is an innovative proposed mechanism that, if introduced, will subsidize the purchase of ACTs by private sector wholesalers as well as public facilities.[114] This will increase the availability and lower the price of ACTs in the hope of driving monotherapies and substandard drugs out of the market.[115]

The Clinton Foundation is conducting a pilot project in two districts in Tanzania to test the market response to such a subsidy. Preliminary feedback suggests that the average price paid by customers for the subsidized ACTs has been less than or equal to alternatives such as SP, according to exit interviews.[116] However, results from the pilot have not been able to demonstrate whether the introduction of subsidized ACTs is indeed displacing the sales of monotherapies,[117] one of the main objectives of the AMFm. Additionally, the pilot was not designed to determine whether an ACT subsidy would benefit the poorest of the poor,[118] another objective of the AMFm. The progress report covered five months of transactions, and more data is forthcoming.

Licensed pharmacies are surely an appropriate outlet for AMFm drugs, and one country-driven initiative stands out as evidence of this. The Tanzanian Food and Drug Administration (TFDA) has inspected and certified over 500 private pharmacies through its Approved Drug Distribution Outlet (ADDO) program,[119] which is now expanding with a Round 7 Global Fund grant.[120] The Bill & Melinda Gates Foundation has further donated $2.8 million over three years to Management Sciences for Health to create a model in East Africa which replicates and scales up private-sector drug seller initiatives based on the ADDO program.[121]

The RBM Board approved the technical design of the AMFm in November 2007 and created a task force to devise operational strategies for implementation.[122] The task force's progress report published in March 2008 confirmed that the AMFm will adopt harmonized procurement standards in line with the Global Fund's Option C.[123] Products in national treatment guidelines but not approved by the WHO or a stringent regulatory authority will be eligible for purchase provided they are deemed satisfactory by an "ad hoc clinical review committee" convened by the WHO. The make-up and scope of this committee are under discussion.

The task force further underscored the AMFm's commitment to "local manufacturing," recommending that the AFMm, "Determine an approach to increase the number of prequalified ACT manufacturers, including manufacturers in endemic countries where possible, without any concession on the quality."[124] And finally, the task force recommended that all ACTs be distributed through both licensed pharmacies and "community level stores/vendors/providers who benefited from a light training course and accept supervision by local health professionals" with the goal of "maximizing points of access."[125]

The balance between maximizing access to ACTs, ensuring good quality drugs and fighting parasite resistance is a delicate one. A 2006 study modeled the impact of a global subsidy for ACTs and concluded that it would ultimately delay the emergence of artemisinin resistance.[126] It noted, however, that resistance to partner drugs in ACTs – e.g. amodiaquine or SP – could lead to a more rapid emergence of resistance to the combination treatment. This could become problematic if vendors and individuals resell ACTs in areas where resistance to the partner drug exists. Echoing the WHO's Guidelines for the Treatment of Malaria published that same year, the authors caution "a larger subsidy is not necessarily a good thing if it excessively encourages the use and misuse of ACTs."[127,128]

Though the task force has commendably recognized the need to strengthen pharmacovigilance for ACTs, it has not given this supporting intervention the priority it demands. It recommends:

> As a minimum requirement, countries that wish to access AMFm should identify a national focal point for pharmacovigilance. This focal point does not have to be malaria-specific, and ideally should be someone in the pharmacovigilance department of the National Drug Regulatory Authority (if there is one) [sic]…Technical and financial support to bring countries in a position to establish pregnancy exposure registries and conduct active surveillance in sentinel sites to collect adverse drug reaction /adverse effect rates, but not as a prerequisite.[129]

Pharmacovigilance systems are sparse in Africa,[130,131] and would benefit from substantial AMFm resource commitments. This is the surest way to guard against and, if necessary, manage resistance while maximizing access to ACTs.

While AMFm's goal of increasing access to ACTs is commendable, the opportunity cost of spending up to $1.9 billion on a single, untested mechanism for treatment – as opposed to proven preventative interventions, training a new generation of medical entomologists, and research to find new or more effective insecticides – may be prohibitive. More research is needed to demonstrate that the Clinton Foundation's pilot project in Tanzania would work over time and elsewhere. The AMFm pilot project in Tanzania was carefully monitored, and private actors knew that conducting business according to the study assumptions (that they would pass the savings along to consumers) would ensure more AMFm money through a full scale roll-out. The Tanzanian pilot project demonstrated that the operations of the market, even when carefully guided, are not assured. Its success may be due to the degree of scrutiny under which it was conducted.

Surveys carried out by Ministries of Health, Health Action International-Africa and the WHO found significant discrepancies in both public sector and private sector drugs among African countries; the cost of hydrochlorothiazide, a diuretic, ranged from about half the international reference price in Cameroon to 38 times the price in Nigeria.[132] Tariffs, taxes, distribution and wholesale costs as well as dispensing fees vary widely between African countries, according to Health Action International.[133] Even within a country, generic price variations between public and private sectors were significant. For example, private sector generic prices in Cameroon were 4.6 times higher in the private sector than in the public sector.[134] AFM's drug study found evidence of price variations within the private sector as well: the same antimalarial drug from the same manufacturer cost up to five times as much depending on the pharmacy.[135] Differences in

regulations as well as distribution and warehousing costs are likely to make the AMFm subsidy vary in effect and outcome in different countries.

Once subsidies have been established the eyes of the international community are spread out across numerous subsidy points, it is likely that such price discrepancies both within and between countries will emerge. A 2008 study of the generic pharmaceutical market in Canada found manufacturers' rebates to wholesalers and pharmacies not being passed along to customers by way of lower priced generic drugs.[136] If this reflects market response to such subsidies in the developed world, the potential for market distortions are much greater.

Other practical questions need answering before the AMFm goes forward. For example, what if the mere bulk of the ACT storage means general traders and shops cannot stock the sweets and Coca-Cola also sold? Furthermore, much more needs to be done to study business models of rural shops and traders, which should be the target of the AMFm as this is where the poor access medicines. As the AMFm confronts these challenges, mission creep is inevitable. Instead of getting cheap quality ACTs to poor people in rural settings, the AMFm might ultimately settle for middle and upper class communities through accredited urban pharmacies – where wholesaler margins and end prices can be more easily controlled. If this is the case, it may displace existing markets of ACTs. As currently conceived, the AMFm has departed from the original idea of an ACT subsidy as proposed by Prof. Arrow.[137]

Summary of Key Points and Recommendations

- The AMFm has the potential to increase access to drugs and is innovative in using the private sector to distribute ACTs. AFM commends the initiative in principal but has concerns. Potential harm could come from the AMFm unless it restricts the drugs procured under the program to only those of known quality, whether approved by a stringent regulatory authority or at a minimum WHO prequalification.

- Without strengthening regulatory capacity in most African countries, the AMFm will increase incentives for counterfeiters and substandard manufacturers to find ways into the supply chain. As the AMFm extends to more countries, it will become increasingly difficult to ensure that subsidies granted to wholesalers are passed on to consumers.

- The AMFm represents a tremendous opportunity cost – it involves a substantial investment of public resources in an untested mechanism for treatment. There is no public evidence that the AMFm has exhausted other potential areas of investment. In addition, it is not clear how treatment needs will change as preventative tools, such as long-lasting insecticidal nets and indoor residual spraying currently being scaled up, begin to impact case rates.

- A fraction of the proposed budget for the AMFm could support an independent, decentralized drug quality testing network using portable labs.

VIII. What Africa Still Lacks: Functioning Health Systems

When trained and well-equipped, doctors, nurses, lab technicians and health care workers provide critical data on malaria cases, which must be accurately collected, aggregated, analyzed and reported to health officials in order to assess future treatment needs. Artemisinin has a 14 month production cycle and relatively short shelf life of twenty-four months, making accurate demand forecasts critical.[138] ACTs are available in different dosages based on body weight and unlike SP, which can be administered in a single dose, they can comprise up to 24 pills taken over three days.

Donor agencies were late to realize that ACTs posed logistical challenges distinct from conventional antimalarial treatments.[139] Early demand forecasts spearheaded by the WHO and UNICEF failed to take into account supporting resources required to effectively transition public sector health facilities to ACTs.[140,141] In the absence of functioning health systems for malaria control, donor agencies based forecasts on need (enough to treat everyone at risk) and not effective demand (orders that can be fulfilled on schedule), which led to vast overestimates of what could practically be administered.

In 2004, the WHO projected that the global need for ACTs in 2005 would be over 130 million treatments,[142] yet actual demand only amounted to about 25 million treatments,[143] resulting in shortages in 2004 followed by over-supply in 2005 and 2006.[144] Major suppliers such as Novartis and Sanofi-Aventis,[145] who based at least some demand expectation on WHO and UNICEF forecasts, have either destroyed surplus ACTs or declared a substantial loss in the past few years.[146] In December 2006, when funds were supposed to be flowing to treatment, Novartis shut down its production facility in Suffern, New York, to prevent overstock that would expire on the shelves.

To shed light on the perils of poor demand forecasting and to sketch out potential solutions to this critical issue, the Center for Global Development convened a Global Health Forecasting Working Group in early 2006. Key recommendations from its report, published in February 2007, suggest that demand forecasting can be enhanced by "improving the capacity to develop credible forecasts; mobilizing and sharing information in a coordinated way; and sharing risks through contractual arrangements that are relatively new to global health but have been used successfully in other fields."[147]

The authors highlight the fact that in the procurement of ACTs, suppliers bear nearly all of the supply-side risks (inventory, storage, and drug safety), as well as the demand-side risks (grant approval timing and pricing), with national governments bearing only the risk that donor supplies may not be sustainable. In a mature profit-orientated western drug market it is sensible for the companies to take the risk of demand not living up to forecasts. But when the innovator companies are selling their drugs at low profit or no profit, and forecasting is consistently inaccurate – driven by desire rather than anything more grounded – it makes sense to share the responsibility for forecasting failure. The donors as well as the forecasters should bear some of the cost, perhaps by contractually agreeing to purchase the amount forecasted for the following year. That way they have an incentive to push the forecasters for greater accuracy.

A Memorandum of Understanding provides a possible model for such an agreement. One currently exists between the WHO and Novartis,[148] but in light of consistent forecasting failures it has proved irrelevant. A new agreement should be made between donors (notably the Global Fund, WHO and World Bank) and companies that demonstrate they can supply high quality ACTs in sufficient quantities. As part of this new agreement, companies would be responsible for supplying a certain amount of good quality drugs and donors would commit to buying that amount. Both groups would then be taking some responsibility.

The AMFm task force has identified the need to improve demand forecasting for both public and private sector ACT distribution. Its success will ultimately depend on strengthening underlying health systems on which accurate forecasts crucially depend. The 2001 Abuja Summit committed African governments to spending 15 percent of national budgets on health care.[149] Seven years later, while a select few have made progress towards this goal, few even come close.[150] The effects are evident in the widespread delay in implementing Global Fund grants. A study commissioned by the Global Fund in 2007 identified "inadequate systems for monitoring and evaluation, limited human resources capacity and poor investment in overall health systems," as problems shared by Ghana, Nigeria and Guinea-Bissau, the three countries under review.[151]

Public health experts have begun to acknowledge that malaria eradication, recently revived as an eventual target by the Gates Foundation, can only occur by strengthening local health systems.[152] In 2006, the World Bank and Global Fund jointly commissioned a report to examine how both worked together in combating HIV/AIDS, known as the Shakow Report after its author.[153] Though the focus was not on malaria, the report provided insights into the roles and relationships of these major donors as they relate to health systems strengthening. It reported overlapping efforts by the two agencies, which increased transaction costs and hindered aid efficiency. It recommended strengthening the respective roles in development of the two agencies – the World Bank as a financier of health systems and the Global Fund a financier of disease control programs.

This delineation of responsibilities has its opponents. For example, what is the point of providing drugs without sufficient medical personnel to prescribe and monitor their use? Academics working in the HIV/AIDS field have argued against the Global Fund only procuring drugs and ignoring health care workers salaries,[154] and were presumably in support of the Global Fund's explicit section on "health systems strengthening" in its Round 7 proposals.[155] However, this is not the job of a multilateral agency with a specific and difficult role to play just because country governments supported by the Global Fund do not invest enough in medical training or health systems.

Health systems strengthening and ACT forecasting are now the purview of the RBM Harmonization Working Group[156] and Procurement and Supply Chain Management Working Group,[157] respectively. Though these groups are working to improve coordination among donors, they may shy away from stronger criticisms and policy recommendations that need to be made. Ultimately, improved forecasting is not simply a matter of better coordination among

donors and the private sector. It depends entirely on health systems strengthening, which in turn depends on African countries taking a stronger stance on health care policies.

Summary of Key Points and Recommendations

- The WHO and UNICEF aim for higher spending but bear no responsibility or cost for overzealous and inaccurate demand projections. Unrealistically high estimates of drugs needed can have as pernicious effects in the medium and long-term as underestimates. Precise estimates based on accurate systems of measurement are crucial to ensuring steady supply.

- A new Memorandum of Understanding should be signed by the Global Fund, WHO and World Bank, and companies that demonstrate they can supply high quality ACTs in sufficient quantities. Such an agreement should make companies responsible for supplying a certain amount of good quality drugs which donors would commit to buying. This is one way to ensure public agencies share responsibility for accurate forecasts.

- If the international community decides that health systems need more attention then the appropriate agency, the World Bank, should take responsibility. The Global Fund does not have the technical expertise to support health systems development, and simply supporting AIDS, TB or malaria support staff could bias the systems allocation in each country in a particular disease's favor, and perhaps against the allocation of resources to more important health interventions, such as immunizations.

- AFM recommends that the RBM Harmonization Working Group produce an independent report for malaria, akin to the Shakow report, analyzing, assessing and making recommendations on the complementarity of the Global Fund, World Bank and PMI's malaria control financing and implementation.

IX. Conclusion

This report discusses some of the recent successes and great challenges in malaria treatment, notably exposing some of the policy reforms needed to achieve a sustained improvement in malaria treatment outcomes in Africa. The key recommendations at the beginning of this report and at the conclusion of each section summarize these issues and suggest constructive ways forward. Malaria country governments, donors, UN agencies and advocates should take note.

Malaria country governments should improve oversight and regulations to reduce the distribution and sale of counterfeit and substandard drugs. They must also ensure the removal of artemisinin monotherapies from the market and national drug registries, and invest in educating consumers about the use of ACTs. More routine quality control testing of antimalarial drugs should be conducted using portable lab technologies, which are increasingly available. Donors should assist local regulatory agencies to improve oversight and NGOs should independently collect data on drug quality.

Donor agencies should ensure that public funds are only used to purchase malaria treatments that have been tested and authorized by a stringent regulatory authority or are WHO-approved. The Global Fund should abandon its stand alone compliance list for malaria treatment and the WHO should maintain the list.

UN agencies, such as the WHO, should increase both assistance to and pressure on member countries to remove artemisinin monotherapies from the market and improve oversight and regulation. Specifically, the WHO should assist malarial countries to establish new formularies that exclude artemisinin monotherapies.

Donor agencies should establish an agreement with manufacturers of high quality ACTs guaranteeing the purchase of a predetermined quantity of ACTs. Given the lead time required to produce ACTs, it is essential to improve forecasting; however, any forecasts of projected demand should be accompanied by realistic financial guarantees from donor agencies and the WHO in order to share the risk.

Innovative solutions to increase access to ACTs using both the private and public sectors should be explored. While the AMFm holds the promise of increasing access to these much needed medicines, there are numerous questions about its design and suitability that must be answered before committing considerable public funds to the venture. Public funds used on any particular scheme carry with them opportunity costs, and more debate is required to assess whether funds devoted to the AMFm could not be better spent elsewhere.

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