The Global Fund's Malaria Medicine Subsidy: A nice idea with nasty implications

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Executive Summary

Phase 1 of the Affordable Medicines Facility for malaria (AMFm) is a $225million initiative that was launched in 2010 in an effort to increase access to safe and effective artemisinin-based combination therapies (ACTs) by dramatically lowering their price with a global subsidy. The AMFm also seeks to drive out oral artemisinin monotherapies as their continued use threatens the entire class of drugs due to drug resistance.

In July 2011, Africa Fighting Malaria undertook a survey in West Africa to determine the price and availability of AMFm drugs. While we find that ACT prices have dropped and there are some positive results arising from the AMFm, we do not consider these to be sufficient to mitigate unintended, but not unforeseen, and worrying consequences that have arisen as a result of this global subsidy.

For the year 2011, approved AMFm orders for just four countries, Ghana, Kenya, Nigeria and Tanzania (including Zanzibar), account for around 45 percent of the total global ACT production capacity. (Please note this is a correction to the September 2011 version, which stated the four countries account for 80 percent of global capacity.) This high demand for ACTs in just four countries threatens the availability of ACTs in all other malarial countries. The prospects of ACT stockouts for non-AMFm participants are real and imminent and the rapid increase in demand may result in a shortage of artemisinin.

Our survey and an examination of AMFm demand and supply records reveal some serious anomalies. For instance:

- Though malaria is mainly a childhood disease, 46 percent of AMFm treatment orders are for adult doses, down from around 70 percent (based on data available in August 2011) after the Global Fund began rationing adult doses.
- Three ACT manufacturers are also acting as first-line buyers in Nigeria, Ghana and Uganda with potential conflicts of interest.
- Zanzibar, a country that has almost zero malaria transmission, has ordered over 240,000 AMFm ACT treatments.
- Our survey in West Africa revealed AMFm products being sold in non-AMFm countries. The threat of leakage of AMFm drugs to non-AMFm countries is real and requires urgent action.

Though our survey was limited in scope, it revealed that oral artemisinin monotherapies remain on sale and are often sold at prices below the subsidized AMFm ACTs. No rapid diagnostic tests were offered or sold to our survey administrators nor were any prescriptions or other evidence of definitive diagnosis of malaria demanded.

In this report and on the Africa Fighting Malaria website we publicize leaked documents that confirm the scale and seriousness of the problem. In our opinion the response from the Global Fund Secretariat to the global supply problems, as evidenced in one of the leaked documents, is inadequate. The Global Fund Secretariat appears preoccupied with continuing the funding for AMFm Phase 1 and with measures to avoid 'reputational' harm.

The private sector can and should play an important role in public health, but it remains to be seen whether or not the benefits that have arisen from the AMFm could have been achieved through alternative mechanisms and potentially at lower cost. In other words, the evidence to date suggests that the opportunity costs of the subsidy have probably been considerable.

Introduction and Background

Malaria continues to be a major global public health problem, leading to approximately 780,000 deaths in 2009[1]. Current treatment guidelines for uncomplicated malaria call for the use of artemisinin-based combination therapies (ACTs)[2]. The use of ACTs has increased in the face of drug resistance to former first-line treatments of chloroquine (CQ) and sulphadoxine pyrimethamine (SP). Adoption of ACTs however was gradual and slow, even with evidence of high levels of treatment failure to the previous first-line treatments. ACTs were gradually introduced to some malaria programs during the early 2000s, but the World Health Organization (WHO) did not officially change treatment protocols recommending ACTs until January 2006.

One reason for the slow adoption of ACTs and reluctance of some donors to endorse the change in treatment policies was the high price of ACTs[3]. Artemisinin is derived from a plant extract and the process of growing the plant (*Artemisia annua*) and extracting the active ingredient is slow and significantly more costly than the process of manufacturing CQ or SP. WHO and leading malaria scientists recommend the combination of various artemisinin derivatives with a different drug that has a different active ingredient and half-life.

Changes in WHO treatment guidelines along with increased funding for ACTs from donor agencies, such as USAID and the Global Fund to Fight AIDS, TB and Malaria (GF), resulted in around 80 countries changing their treatment protocols to ACTs. Between 2005 and 2010 the number of ACTs produced increased from 11.2 million to 130.6 million, an increase of over 1000 percent.

Other than rapid and successful treatment of malaria, the main advantage of artemisinin combination therapy is in its effective control of drug resistance. Selective pressure on the parasite has led to the emergence of *Pl. falciparum* drug resistance in almost every malarial region. The use of oral artemisinin monotherapy treatments will inevitably lead to drug resistance and indeed evidence is emerging of drug resistance in Southeast Asia[4].

The majority of ACTs produced and distributed are Artemether-Lumefantrine (AL), either produced as Coartem® by Novartis or as a generic version of this medicine. Novartis and WHO agreed to a Memorandum of Understanding in 2001 whereby Novartis would supply Coartem® at cost price to the public sector. Due to economies of scale, improved efficiency, stabilization in the artemisinin market and other factors, the price of Coartem® has fallen from between $0.9 and $2.40 in 2001 to $0.36 and $1.30 in 2011, depending on the dosage[5]. This represents a reduction of between 45% and 60%.

Despite the reduction in ACT prices, the medicines remain significantly more expensive than the alternative treatments. Furthermore, the treatments available at cost are exclusively delivered to the public sector, while the private sector remains an important source of malaria treatments in many malarial countries. While ACTs are available in private pharmacies and shops, surveys have revealed that the median price of WHO approved ACTs in the private sector in Nigeria is over $7, a price that is out of reach for all but the elite[6].

National malaria control programs (NMCPs), donor agencies and WHO face the twin problems of attempting to increase access to new, relatively expensive ACTs while trying to limit the spread of resistance to artemisinin and removing oral artemisinin monotherapies from the market. One proposal aimed at meeting this challenge was contained in a 2004 Institute of Medicine (IOM) report,

Saving Lives, Buying Time – Economics of Malaria Drugs in an Age of Resistance. The IOM study was the product of the Committee on the Economics of Antimalarial Drugs, made up of thirteen eminent scientists, public health specialists and economists, including the Nobel Laureate economist Kenneth Arrow who acted as Chair. The committee's work was initially funded by USAID and subsequently received financial support from the Bill and Melinda Gates Foundation. The essence of the committee's recommendations was to call for a global subsidy of ACTs so that they could be distributed at accessible prices through the private non-profit sectors. This report provided the foundation for what was to become the Affordable Medicines Facility – malaria (AMFm).

The AMFm is a financing mechanism hosted by the GF and designed to expand access to ACTs for treatment of malaria. The AMFm provides a subsidy for ACTs in the public and private sectors. The GF has negotiated with manufacturers a reduced price for ACTs. First-line buyers (FLBs) purchase the ACTs directly from manufacturers. The GF pays the majority of the reduced price of ACTs to manufacturers thus lowering the cost to first-line buyers. Retailers are permitted a small mark up, but the idea of the AMFm is to pass the majority of the subsidy onto consumers, who would then be able to afford the ACTs. The aim of the AMFm is to reduce the cost of ACTs to compete with CQ and SP in order to increase the availability and use of ACTs, and displace artemisinin monotherapies and poor quality antimalarial drugs from the market. The AMFm also requires participating countries to implement supporting interventions, such as public awareness campaigns and policy/ regulation measures specific to the situation in each country.

The AMFm has received financial support from the international drug purchasing facility, UNITAID, the United Kingdom and the Bill & Melinda Gates Foundation, and technical support from the Roll Back Malaria (RBM) Partnership. Funding for AMFm co-payments come from a separate GF account. Approximately US$216 million has been donated for co-payments[7]. Funds for supporting interventions come from existing GF grants. Savings from malaria grants with unspent ACT funds due to the cheaper co-paid AMFm ACTs are to be reallocated to fund supporting interventions. There is an estimated US$127 million for supporting interventions[8].

The AMFm Phase 1 pilot is currently being implemented in Cambodia, Ghana, Kenya, Madagascar, Niger, Nigeria, Tanzania (including Zanzibar) and Uganda. At the end of 2012, it will be reviewed through an independent evaluation, after which the Global Fund Board will determine whether to expand, accelerate, modify, terminate or suspend the AMFm. The first countries to embark on the AMFm pilot were Ghana, Kenya, Nigeria and Tanzania, and the majority of treatments supplied under the scheme to date have been received in these countries.

Early media reports from Kenya and Ghana revealed that the prices at which AMFm drugs were being sold at the retail level were higher than those advertised by AMFm participating country governments[9]. Price tracking surveys conducted by Health Action International (HAI) in Ghana, Kenya, Nigeria and Tanzania however found that the mean prices for AMFm ACTs in Kenya were close to the expected retail price[10]. Though the mean prices for AMFm ACTs in Ghana, Nigeria and Tanzania were higher than the expected prices, they were found to be lower than prices revealed in media reports.

Working with partners in West Africa, Africa Fighting Malaria undertook its own survey of AMFm and other malaria treatments available in private shops and pharmacies in Lagos, Nigeria and Accra, Ghana. We present the price and drug availability data below. We also undertook an analysis of diverted AMFm products in Lomé, Togo.

In addition to this primary research, we use publicly available data, interviews with relevant experts as well as some important unpublished reports, to discuss the impact of the AMFm scheme.

Initial support for AMFm

It took almost five years for the AMFm to be implemented after the publication of *Saving Lives, Buying Time* in 2004. Prior to the funding of the AMFm pilot phase, substantial efforts were undertaken to generate sufficient support from within donor agencies and among malaria scientists and other stakeholders. An example of this was the 2008 consultative meeting organized by Resources for the Future and Harvard School of Public Health. The meeting was advertised as a "Consultative Forum" and the stated purpose was to "discuss the rationale for AMFm and to explore biomedical, economic and operational challenges related to the still-controversial AMFm."[11] Two of the authors of this report attended the meeting but were disappointed by the lack of any substantial consultation or in depth discussion of the challenges. Indeed it appeared as if the purpose of the meeting was not to discuss the challenges and seek solutions to them, but to promote and cheerlead the existing plans.

Despite the fact that the US Government (USG) funded the initial IOM report, the USG has not given any financial assistance to the AMFm, as it is not convinced that there is sufficient evidence to support its roll-out. The leadership of the US President's Malaria Initiative (PMI), the lead USAID malaria program, have to date been the only program officers of any major program to voice their concerns about the AMFm[12]. In contrast, the senior management of numerous other large and influential donor agencies and governments have publicly lent their unqualified support for the AMFm.

Examples of statements in support of the AMFm include those of Michel Kazatchkine, Former Executive Director of GF, and Philippe Douste-Blazy, special Adviser on Innovative Financing for Development, who wrote in the Huffington Post that "early results indicate that AMFm is working and has brought dramatic falls in over-the-counter drug prices in Nigeria and several other African countries."[13] They concluded: "The AMFm initiative will help us to achieve even more impressive results in a campaign to eliminate malaria as a major public health challenge in the coming years. The progress we have made so far but also a major victory for a fundamental human right: the right to health care for everyone."

"… a major victory for a fundamental human right: the right to health care for everyone." - Michel Kazatchkine & Philip Douste-Blazy

In a more recent press release, Kazatchkine stated that "we are making further progress in fighting malaria in Africa by providing affordable treatment to millions of people through the Affordable Medicines Facility for malaria."[14] The press release indicated that AMFm ACTs are selling between $0.60 to $1.20 in areas of Accra, and that the Society for Family Health would sell ACTs in Nigeria at $0.20 for a child dose and $0.80 for an adult dose.

Box 1 - Pre-Phase 1 praise for the AMFm[15]

"The age when the world had effective drugs against infectious diseases but let millions die each year because they couldn't afford them is over," says Foreign Minister Jonas Gahr Støre of Norway

"This partnership is an important part of the global effort to control malaria worldwide," says Dr Michel Kazatchkine, Executive Director of the Global Fund

"The Affordable Medicines Facility for malaria is a breakthrough in global health," says Robert B. Zoellick, President of the World Bank Group

"What we are doing is using market dynamics to save more lives," says Dr Philippe Douste-Blazy, Chairman of the board of UNITAID

"The Affordable Medicines Facility for Malaria could save up to 300,000 lives every year – mostly children's – by making the best treatments available at affordable prices," says Ivan Lewis, UK International Development Minister

"The Affordable Medicines Facility for malaria is a triumph of international cooperation," said Prof Awa-Marie Coll-Seck, Executive Director of the RBM Partnership

"The Affordable Medicines Facility for malaria is an exciting effort to improve access to life-saving malaria drugs, and to replace old drugs that are no longer as effective as they once were," said Dr Tachi Yamada, President of the Bill & Melinda Gates Foundation Global Health Program

AMFm and non-AMFm ACT prices

Africa Fighting Malaria partners undertook a survey of private retail pharmacies in Accra, Ghana and Lagos, Nigeria, both of which are participating in the AMFm, as well as Lomé, Togo, a country not participating in the AMFm. Samples of oral artesunate monotherapy, artemether-lumefantrine fixed-dose combination, artesunate-amodiaquine fixed-dose combination, and artesunate-amodiaquine co-formulation were collected from 22 pharmacies in Lagos and 15 pharmacies in Accra. Drug samples were obtained by local nationals from private pharmacies in non-slum areas. Local nationals posed as customers and purchased antimalarial drugs from AMFm participating pharmacies in Accra and Lagos. All drugs in all pharmacies were available without a prescription and were purchased without a rapid diagnostic test (RDT) result.

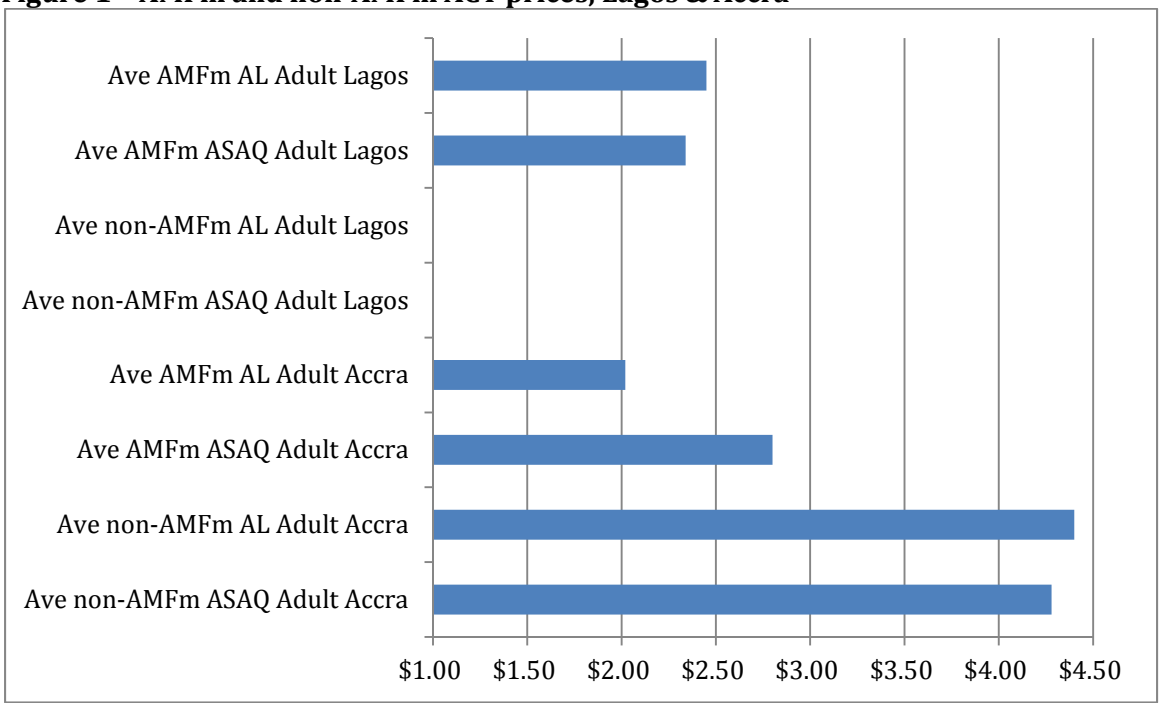
140 artemisinin-based antimalarial drugs were collected; 65 from pharmacies in Accra and 75 from pharmacies in Lagos. 46 of the 140 antimalarial drug samples collected lacked an AMFm logo on the packaging (referred to as non-AMFm drugs) and 94 samples contained an AMFm logo (referred to as AMFm drugs).

Lomé was surveyed for the presence of AMFm drugs in unofficial and official markets, to see if AMFm drugs had been diverted from either Ghana or Nigeria (or possibly other participating AMFm countries). Antimalarial drugs were found in official and unofficial markets in Lomé. Ten samples of seven batches of five artemisinin antimalarial drugs containing the AMFm logo were procured.

The expected, but not mandated, AMFm prices for an adult course of ACTs in Nigeria and Ghana are 120N[16] and 1.5 GHS[17] respectively. The Africa Fighting Malaria survey data showed that all but one of the AMFm ACTs collected in Lagos and Accra were sold above these advertised prices. In one case the recommended price, which was printed on the packaging, had been deliberately rubbed out and replaced with a higher price.

The mean price for an adult course of AMFm AL treatment was $2.31 (range $0.99-$4.61). On average, the treatment courses were marked up by a multiple of 2.82. The mean price of AMFm adult artesunate-amodiaquine (ASAQ) (both fixed-dose and co-blister) was $2.48 (range $1.28-$3.29). This price represents a mark-up multiple of 2.99.

Figure 1 – AMFm and non-AMFm ACT prices, Lagos & Accra



Note – ASAQ data is related to fixed-dose combination and co-blisters combined. No non-AMFm adult AL or ASAQ was procured in Lagos.

The US PMI has conducted surveys of availability of antimalarials in the market in ten cities in Nigeria, and while the PMI price data are neither generalizable nor representative, it is interesting to note that the mean prices are similar to the prices collected in our recent survey. The mean price of AMFm-marked Coartem was $3.05 and ranged between a minimum of $1.67 and a maximum of $6.33[18].

The HAI AMFm price-tracking survey found mean prices for adult AMFm AL in formal markets to be $1.31 (range: $0.79 - $8.59) in Ghana and $1.55 (range: $0.66 - $9.84) in Nigeria. The HAI survey tracked prices in six regions of the country and from 30 formal and 30 informal sites and is therefore a more comprehensive price survey and follows a rigorous and accepted methodology. While the HAI data reflects positively on the ability of the AMFm to lower the cost of ACTs compared to privately sold branded ACT alternatives, the data show that the AMFm has been unable to lower costs to the level of SP or CQ. The wide range in prices from the HAI survey as well as our own survey and the PMI surveys however show that price reductions are not automatic nor are they universally applied.

In our survey, no non-AMFm AL or ASAQ was collected in Lagos; however, 13 non-AMFm AL and 4 non-AMFm ASAQ were purchased in Accra. In Accra, the price of the non-AMFm treatment courses was on average $4.40 for adult AL and $4.28 for adult ASAQ (both fixed-dose and co-blister).

It appears from our limited survey that the price of ACTs under the AMFm project has fallen significantly. Prior to the AMFm it was not uncommon to procure ACTs at prices higher than $7 in the private sector. It appears that the AMFm has exerted downward pressure on the non-AMFm medicines, reducing their prices as well. However, the prices are still significantly higher than the advertised and promoted reference prices. While there can be no disputing the fact that consumption of ACTs will have increased as a result of the subsidy, it is not clear that the prices are low enough to be of any benefit to the very poorest of the poor in Nigeria and Ghana, as according to the AMFm Ad Hoc Committee, "A central goal of the AMFm is to increase access to ACTs by all groups through improving the availability of affordable ACTs through all sectors."[19] As our survey only collected medicines in the urban centers of Lagos and Accra, we are unable to comment on the price of AMFm ACTs in rural areas. A comprehensive survey conducted by the Pharmacy Council of Ghana however found that in some areas AMFm drugs were being sold at 200 percent above the recommended price. In addition, the survey found that CQ remained the second most used treatment for malaria, despite high treatment failure rates[20].

One of the most important objectives of the AMFm is to 'crowd out' oral artemisinin monotherapies from the market. The Africa Fighting Malaria survey in Ghana and Nigeria produced mixed evidence on this topic. Two courses of oral artemisinin monotherapy were procured in Accra, one at $5.26 and one at $1.97. The fact that only two treatments were purchased may be interpreted positively; however, given the limited survey, we are unable to draw any conclusions on the cause of the reduced availability or indeed if there is truly a dearth of these treatments in Accra.

In contrast, our survey administrators were able to procure 20 treatments of oral artemisinin monotherapy in Lagos – nearly every pharmacy was selling them. Not only were these treatments apparently more widely available, but were sold at an average price of $1.87. Again, as with Accra, our sample size is small and a more in-depth survey will be required before any firm conclusions can be drawn on the availability of oral artemisinin monotherapies in these cities. However, these early indications suggest that these proscribed drugs are still available and may not automatically be 'crowded out' by the lower relative prices of ACTs.

It would be unreasonable to expect all oral artemisinin monotherapies to have been removed from the market; however, the fact that they remain available and can be purchased from AMFm participating pharmacies, and in most cases at a lower cost than AMFm ACTs, should be of concern. The continued availability of oral artemisinin monotherapies however isn't entirely surprising as the Global Fund Secretariat continues to allow FLBs to sell these drugs. The "Report of the Forum on Early Lessons from Implementation" of the AMFm held in Accra, Ghana in December 2010 states that while "the sale of monotherapies by first-line buyers is discouraged, *it is not prohibited*"[21] (emphasis in the original). The rationale for allowing FLBs to continue selling monotherapies, according to the report, is that to do so would "adversely affect the entry of first-line buyers to AMFm which would be handicapping."[22]

"the sale of monotherapies by first-line buyers is discouraged, *it is not prohibited*"

One of the key reasons for establishing the AMFm was to stop the sale of monotherapies. Yet such is the eagerness among the AMFm partners to increase the number of FLBs, they are unwilling to

compel them to stop selling drugs that will undermine the AMFm itself, to say little of undermining malaria treatment and control.

The survey administrators for Africa Fighting Malaria were able to procure ACTs without a prescription and without presenting any evidence of a positive malaria diagnosis. Furthermore, no survey administrator was either sold or advised to buy an RDT so as to ensure rational use of the ACTs.

Diverted AMFm drugs

As part of the Africa Fighting Malaria survey, the availability of AMFm drugs in Togo was also assessed. In addition to the regular samplings in Accra and Lagos, AMFm products were also sought in Lomé, the capital of Togo. This francophone country is not participating in the AMFm process, but several malaria experts and security consultants advised Africa Fighting Malaria that AMFm products had been diverted from Ghana and Nigeria into Cote d'Ivoire, Benin and Togo.

In a very cursory survey of the informal and formal markets of Lomé, our research team found five different AMFm ACTs (seven different batches), none of which should have been available in Togo. Africa Fighting Malaria determined that at least some of these drugs had originally been sent to Ghana and Nigeria (and in the latter, the Society for Family Health was the principle recipient for most of the diverted products found). The drugs procured from the informal markets were being sold at an average price of $0.83 a pack for bulk orders of 5 packs or more. The prices in pharmacies ranged from $1.32 to $2.06 for single treatments.

We intend on returning to francophone West Africa to do a more thorough investigation. From what we have seen, traders in Lomé appear to be doing a great deal of business in AMFm diverted products. Criminals and those who enable them are making considerable money from this illicit trade.

AMFm Demand and Disruptions

A 2011 survey of all major manufacturers of ACTs undertaken by WHO indicates that the total annual global capacity to produce AL is around 180 million treatments. The total annual global capacity to produce fixed-does combination (FDC) ASAQ stands at around 100 million treatments[23]. Production figures are difficult to calculate as manufacturers are reluctant to share their exact production capacity, given the highly competitive nature of the ACT market. However the WHO survey gives the most accurate and credible figures for ACT production capacity.

In line with their commendable record of openness and transparency with regard to commodity procurement, the GF provides up-to-date data online of AMFm orders and deliveries. These data reveal that between January 11, 2011 and December 12, 2011, over 140 million treatment courses of AL and 19 million FDC ASAQ were ordered via the AMFm (data as of April 13, 2012). In addition, 8.5 million treatment courses of co-blistered AS+AQ were ordered. During this same period, 123 million (87 percent) AL treatment courses, 10.4 million (55 percent) FDC ASAQ treatment courses and 7.75 million (91 percent) co-blistered AS+AQ treatment courses were delivered.

The vast majority of the AMFm orders and deliveries are dominated by four countries, Ghana, Kenya, Nigeria and Tanzania (including Zanzibar). These four countries account for 78 percent of the AL orders and 89 percent of the FDC ASAQ orders for the time period assessed. In addition, they account for 76 percent of the AL deliveries and 83 percent of the FDC ASAQ deliveries. Most concerning however is that these four countries account for around 45 percent of

the total global combined AL and FDC ASAQ production capacity (61% of AL capacity and 17% of FDC ASAQ capacity).

The vast majority of the AMFm orders and deliveries are dominated by four countries, Ghana, Kenya, Nigeria and Tanzania.

These data could be interpreted in at least two ways. One could argue that the high volumes of ACTs ordered reflect the high demand for ACTs in the private sector and therefore the appropriateness of the AMFm as part of the policy mix required to increase access to these life-saving treatments. The fulfillment of these orders however indicates that there are some backlogs and delays among manufacturers, which should be a cause for concern. Of course, the high initial demand and the delays in supply could merely be initial teething problems for the AMFm and could, in time, be resolved by the private suppliers and FLBs.

Another interpretation of the high volumes ordered is less sanguine. The fact that four countries dominate the orders for ACTs should be alarming to non-AMFm countries and the non-AMFm distributors, such as the public sector, in AMFm countries. These concerns about the impact on global ACT markets and drug availability are expressed in a confidential and unpublished report prepared for the GF by the ACT Forecasting Consortium in July 2011 and leaked to the authors of this report. Africa Fighting Malaria believes that the urgency and importance of the ACT market disruptions are such that the report should be made public. For this reason we have posted the report on our website[24].

This report confirms the concerns raised above, namely that AMFm demand for ACTs is overwhelming the global market. Interviews with FLBs conducted by the ACT Forecasting Consortium reveal that these buyers expect demand to increase because, among other reasons, they expect public sector stock-outs. Such stock-outs could indeed increase in frequency and may well become a self-fulfilling prophecy caused by the AMFm because of stock-out fears. More worryingly, the ACT Forecasting Consortium report warns that the global stocks of artemisinin, at approximately 50 metric tonnes, are inadequate and "would be insufficient to meet the FLB AMFm demand plus the public tender demand for 2011."[25]

In an interview with a representative of the leading AL manufacturer, Novartis AG, Africa Fighting Malaria was assured that the public sector would be prioritized and that the partners, such as the major donor agencies and their contractors that have worked with Novartis for many years, would not be denied ACT treatments.

The US PMI, the largest bi-lateral malaria control and treatment program, however, expressed concerns about the availability of ACTs[26]. In an official comment on the availability of ACTs from traditional suppliers, PMI stated:

"PMI has noted a tightening of the ACT market and is very concerned about procuring sufficient artemether lumefantrine to meet the needs of malaria-endemic countries across Africa through 2011 and 2012. PMI will source quality assured artemether lumefantrine through all WHO Prequalified sources to meet the needs in focus countries. If sufficient quantities are not available to meet the need through Novartis and the generic suppliers, PMI will work with partners to prioritize countries based on urgency of need and reconsider its procurement strategy for 2012."[27]

PMI has noted a tightening of the ACT market and is very concerned about procuring sufficient artemether lumefantrine to meet the needs of malaria-endemic countries across Africa through 2011 and 2012.

The PMI routinely monitors ACT availability and has become an ACT supplier of last resort and has paid for several emergency shipments. ACTs procured for emergency shipments, it should be noted, are typically more expensive than ordinary planned shipments. According to PMI:

"PMI has tracked central level availability of ACTs in cooperation with the Ministry of Health in the following AMFm countries: Nigeria (selected states), Ghana, Kenya, Tanzania, and Uganda. All of these countries have experienced challenges with availability of ACTs through the public sector."[28]

"USAID/PMI has provided the following emergency supplies of ACTs in the AMFm pilot countries since September 2010:

Tanzania: 10,135,620 treatments
Kenya: 6,963,600 treatments
Uganda: 2,085,120 treatments

The following AMFm pilot countries have requested emergency procurements of ACTs through PMI through the end of 2011, which have not yet been confirmed: Nigeria, Uganda."[29]

It would be an unfortunate and ironic outcome of the AMFm, should it force public sector procurers of ACTs to source ACTs at higher cost through new, and potentially less reliable, sources.

Adult drugs for a childhood disease

According to the GF's AMFm data, around 46 percent of the AMFm orders are for ACT adult treatments of AL and ASAQ. The Africa Fighting Malaria survey administrators procured mostly adult treatments and the HAI report reveals that the most commonly available AMFm ACT is the adult AL treatment course.

In late 2011, the GF began rationing adult doses. Prior to that, around 70 percent of all AMFm orders were for adult treatment courses (based on data available in August 2011), not child treatment courses. While it is admirable that the GF addressed this anomaly, the fact that it had to intervene in this way points to a flaw in the AMFm model and indicates the potential irrationality in treatment outcomes.

In the Phase 1 AMFm countries, the burden of malaria falls primarily on children and therefore one would have expected most of the AMFm orders to be child ACT treatments. According to the WHO's Global Malaria Program (GMP), the high proportion of approved orders for adult treatment courses "makes no sense in terms of public health."[30]

At $0.15, the maximum price for FLBs for adult treatment courses of AL is higher than for child doses, which is set at $0.01 or $0.005[31]. Theoretically, this price differential might encourage higher orders of pediatric doses. In reality, however, the exceedingly low price for adult treatment courses and the considerable potential profit in selling these treatments means that the price differential is inadequate.

In the absence of any robust epidemiologic reason for the orders of adult treatments, it is likely that FLBs are ordering adult treatment courses because they contain higher levels of artemisinin and are higher value products. As such, the FLBs are acting entirely rationally and predictably in their own self-interest.

AMFm drugs for a country with almost no malaria

In addition to concerns about the volume of demand from the first four AMFm Phase 1 countries and the level of adult treatment orders, is the curiously high level of orders from Zanzibar. As has been widely reported in the scientific and popular literature, malaria transmission has declined sharply on the island of Zanzibar in recent years. According to a recent study, malaria prevention and increased access to ACTs along with improved diagnosis of malaria has reduced malaria in public hospitals by 75 percent over 5 years, and malaria deaths for all age groups has fallen by over 90 percent between 1999 and 2008[32].

According to the World Malaria Report 2010,[33] Zanzibar may be considered as having low malaria transmission. With the scale-up in funding, primarily from the GF and PMI, the Zanzibar malaria control program was able to greatly increase access to insecticide treated bednets and embarked on a widespread indoor residual spraying program. One of the most critically important elements of the successful control of malaria in Zanzibar has been the increased access to ACTs, which were made freely available in all public health facilities since September 2003. RDTs are used with every case of fever presenting in a public clinic so as to rationally diagnose and treat malaria. In 2009, malaria cases (confirmed and probable) totaled 3,830 and deaths totaled 20 for children less than 5 years of age. Zanzibar, which is a PMI focus country, recorded an estimated 2000 cases in 2010, and according to PMI, recent studies have shown that less than 2 percent of patients presenting with fever have positive malaria blood smears[34].

Despite the remarkably successful control of malaria, the Zanzibar private sector AMFm FLB ordered 241,000 ASAQ treatment courses between January and August 2011.

Despite the remarkably successful control of malaria, the Zanzibar private sector AMFm FLB ordered 241,000 ASAQ treatment courses between January and December 2011. While Zanzibar will require a stock of ACTs for confirmed malaria cases as well as a buffer stock for any potential epidemic, we can think of few legitimate reasons for such a large order. According to WHO's GMP the unreasonably high orders for Zanzibar are all the more troubling because they will be distributed in the private sector, where to date the record of ensuring accurate diagnosis of malaria has been poor[35].

Supplier and first-line buyer anomalies

Suppliers and FLBs under the AMFm scheme are selected based on various criteria. Suppliers must meet the GF's quality assurance criteria[36], and in addition, an AMFm supplier must agree:

1. to sell its ACTs under the AMFm Co-Payment scheme at a price that (i) does not differentiate between the public and private sectors, and (ii) is consistent with the reduced price for ACTs ordinarily offered by the manufacturer to the public sector;
2. not to sell or market oral artemisinin monotherapies for the treatment of patients in any country; and
3. to commit to the principles, terms and conditions of AMFm through a the[sic] signature of a master supply agreement with the GF[37].

The approved AMFm suppliers include, as of August 2011, two research-based pharmaceutical companies, Novartis and

Sanofi, three Indian generic pharmaceutical companies, Ipca, Cipla and Ajanta, one Chinese generic pharmaceutical company, Guilin, and one Ugandan generic pharmaceutical company, Quality Chemicals Industries[38].

FLBs are made up of international, regional and national drug distributors and must comply with the GF's criteria, which stipulate that the FLB must:

1. hold all licenses, waivers or other approvals necessary to export, import, sell and/or distribute co-paid ACTs, as required, within the participating country; and
2. sign a standard non-negotiable undertaking, in which the buyer agrees, among other things:
    - to abide by the goals and objectives of AMFm and, in particular, to apply a reasonable margin on the prices of AMFm co-paid ACTs;
    - to sell co-paid ACTs only within countries participating in AMFm Phase 1; and
    - to allow the GF and its agents access to staff, facilities and records to conduct reviews, as appropriate[39].

Currently, 141 FLBs have been approved by AMFm[40], including some large multilateral institutions such as the UN Development Program, Ministries of Health such as the Ghanaian Ministry of Health, as well as smaller national drug distributors and retailers. Among the FLBs however are three companies that are also listed as AMFm manufacturers, namely Ipca, Guilin and Quality Chemicals.

Among the FLBs however are three companies that are also listed as AMFm manufacturers, namely Ipca, Guilin and Quality Chemicals.

Guilin Pharmaceutical Company set up a 'branch office' in Ghana to 'explore the market there before the launch of AMFm'[41]. Since the launch of AMFm, Guilin Pharmaceutical Limited Ghana has ordered 600,000 'individual packs' of ASAQ treatments for Ghana from Guilin Pharmaceutical Company Ltd, all of which have been delivered. These orders resulted in the co-payment of $331,400.

Ipca Pharma Nigeria Limited is listed as an international office of Ipca Laboratories Limited. Since the launch of the AMFm, Ipca Pharma Nigeria has ordered 6.4 million 'hospital pack' treatments of AL from Ipca Laboratories. As of April 13, 2012, 5.15 million treatments have been delivered. The total co-payment committed for Ipca Laboratories is more than $6 million.

While Uganda's Quality Chemicals Industries is yet to manufacture ACTs for the AMFm, it is listed an eligible manufacturer. As described elsewhere, Quality Chemicals Industries was established in 1998 as a pharmaceutical manufacturing facility[42]. In addition to some private investors, the major shareholders of Quality Chemicals Industries are Cipla and the Government of Uganda[43]. The manufacturing facility was only completed in 2008 and in 2010 the World Health Organization approved the facility for the manufacture of Cipla's AL[44]. Quality Chemicals Limited, a 'partner' company of Quality Chemicals Industries, has ordered 2.6 million individual treatment courses of AL for the private sector. Quality Chemicals Industries has ordered 12.4 million AL hospital pack treatments for the public sector. To date, 2.2 million individual treatment packs have

been delivered to Quality Chemicals Limited for distribution to the private sector. The co-payment committed to Quality Chemicals and Quality Chemicals Industries for both the public and private sector AMFm orders is $15.6 million[45].

These three cases should raise concerns among GF donors and malaria stakeholders about the potential for manufacturers and FLBs to receive both the upfront co-payment as well as profit from the mark-up of the ACTs when they are sold (and this mark-up can be considerable given the evidence presented in this report). The case of Quality Chemicals should be of particular concern given the potential for abuse as the company is procuring drugs from a shareholder company and supplying another shareholder, namely the Government of Uganda.

In addition, monotherapy artemisinin products apparently manufactured by Cipla and Guilin are still available for sale in Lagos and Accra, and in most cases at a cheaper price than the AMFm ACTs (it is of course possible these products are counterfeits –neither Guilin or Cipla responded to our correspondence).

AMFm Rationing and the Global Fund Secretariat's Response

Given the concerns about the high demand from FLBs, the ACT Forecasting Consortium proposes the use of pricing to shape demand and to establish a rationing scheme. Worried about the high proportion of adult doses ordered and delivered, the Consortium propose 'tilting' payments towards child doses that are less expensive and use less artemisinin.

Africa Fighting Malaria was leaked the draft Global Fund Secretariat's response to the Consortium's report. As with the original report, we believe that the urgency and scale of the problem requires us to make the response public and it can be downloaded from our website[46].

"the original AMFm Phase 1 Co-payment Trust Fund will be depleted by mid-August 2011."

In responding to the Consortium's report, the Global Fund Secretariat confirms that without rationing, "the original AMFm Phase 1 Co-payment Trust Fund will be depleted by mid-August 2011."[47] The Secretariat recognizes that grant agreements cover the provision of ACTs in the public sector and it states that it "will seek to honor all such public sector orders." The Secretariat goes on to suggest various ideas for rationing and constraining AMFm demand. These include:

- only approving co-payments "for countries whose cumulative orders have reached the estimated ACT demand for *the total duration of AMFm Phase 1*" (emphasis in original),
- only approving requests from manufactures with a ratio of actual to planned deliveries of at least 75 percent,
- only approving orders that will be delivered no later than six months from the date of co-payment request, or June 2012, whichever is later and requiring a certain proportion of child or infant formulations/packaging,
- limiting allowable freight costs of 5% of the co-payment value, as most ACTs have been delivered by air at an average cost of 12% of co-payment value. The reduced payment will force most suppliers to ship the ACTs by sea.

Implicit in the proposals made by the Secretariat is an acceptance that the FLBs are not responding in the way they

anticipated and may not be acting in the best interest of public health.

However, it is more likely that the FLBs are acting entirely rationally given the economic incentives and are seeking to maximize their stocks of the highest value ACTs.

The orders of adult treatment courses should be of great concern given that malaria is a problem primarily for children. Of course, the epidemiology of malaria may have changed sufficiently with increased access to insecticide treated bednets and indoor residual spraying so that now adults account for 46 percent of cases. We would expect markets to react far more rapidly to actual demand than epidemiologists can study disease rates. However, it is more likely that the FLBs are acting entirely rationally given the economic incentives and are seeking to maximize their stocks of the highest value ACTs. Stocking lower value child doses of ACTs is less economically attractive, given the fact that child doses still take up important storage and display space, but attract lower potential profits.

In addition, the low prevalence of definitive diagnosis and even of RDTs means that adult ACTs are probably being sold irrespective of whether or not the customer has malaria. Although increasing the use of RDTs was not one of the major AMFm goals, the GF's AMFm funding proposal to UNITAID states that technical assistance with implementing partners will be given to ensure training of public and private healthcare workers in effective diagnosis and treatment of malaria and appropriate storage and dispensing of ACTs[48].

The Secretariat concludes its comments on the Consortium's report by arguing for sufficient funding to allow it to meet the Phase 1 co-payments. There is little to no recognition from the Secretariat that the AMFm may actually be perverting and harming the ACT markets and in fact harming malaria treatment. In a tone that can only be called churlish, the Secretariat writes "The reality of the context in which the AMFm operates is that even stellar results from the independent evaluation, while necessary, may not be sufficient for some parties to acknowledge that AMFm Phase 1 has worked."[49] One could counter, perhaps equally churlishly, that it seems as though there is no amount of evidence that the Secretariat will accept to acknowledge that the AMFm Phase 1 is not working as planned.

Given the funds invested in the AMFm, the Secretariat has obvious incentives to show that it works. This fact is revealed in the December 2010 "Report of the Forum on Early Lessons from Implementation" referred to above. In discussing the replenishment of the AMFm, the report states that "the most important priority is to demonstrate that AMFm works; this would form the basis for replenishment efforts."[50] Regrettably the report then immediately states that "Implementation research has not been a key priority to date," and that "Implementation research budgets have been reduced."[51]

This same report explains that "early signs that AMFm is starting to work" include the fact that co-paid ACT deliveries are being made, the co-payment structure is set and transparent, and ACTs are cheaper. In addition, according to the report, evidence of success is found in the fact that national marketing campaigns have been launched and supporting interventions have started[52]. With the exception of cheaper ACTs, all these measures of success are in fact simply process indicators and cannot reasonably be considered any evidence that the global subsidy is increasing access to ACTs, improving quality of treatment and driving out artemisinin monotherapies. Even if we were to accept the reduced price of ACTs as a measure of success, this is

hardly a convincing measure. With $225 million dollars committed for Phase 1 subsidies, it is hardly surprising that prices are falling. The more important question is whether this success could have been achieved at lower cost and with alternative strategies and programs. It is not clear how the Secretariat intends to demonstrate that the AMFm has worked if the implementation research budget has been reduced.

"This is a reputational risk to the Global Fund and donors to the Co-payment Fund." - Global Fund Secretariat

The Secretariat concludes its comments on the Consortium's report by stating that "since the HAI price tracking studies suggest that AMFm Phase 1 is headed in the right direction, a failure to assure adequate funding *during the remainder of the test of concept* is self-defeating. This is a reputational risk to the Global Fund and donors to the Co-payment Fund."[53] (Emphasis in original.) The AMFm is about much more than just price and even if the prices of subsidized ACTs are decreasing, as expected, these gains are apparently being achieved at considerable costs. The motivation for donors should be improved and expanded rational treatment of malaria and if this is shown to be harmed by the AMFm, the program should be shut down immediately and funds reprogrammed. Yet the Secretariat's statements reveal that their concerns are related to the reputation of the GF and the AMFm funders. This alone should cause a high degree of skepticism about the motivations of the Secretariat in supporting this initiative.

Primum non nocere

The authors of this paper recognize the importance and value of the private sector in the provision of healthcare, including public health services. Evidence from Cambodia and from a controlled trial in Kenya suggest that the private sector can play a very constructive and important role in increasing access to ACTs. However the results from these countries should be reviewed carefully.

In Cambodia, the ACT subsidy program was accompanied by robust efforts to increase the use of RDTs[54]. After several years of the Cambodia program, adherence to the recommended price for ACTs was 'variable' and "the popularity of AMTs [artemisinin monotherapy] amongst some providers still prevailed, despite having been banned a year before." Furthermore the Cambodia drug subsidy reveals that "these effects may tend to benefit relatively accessible populations rather than the more remote and poorer communities."

In Kenya, an ACT subsidy for pediatric ACTs significantly increased the percentage of children receiving ACTs following the onset of fever[55]. In addition, it was reported that "in most cases, subsidised AL was purchased at the recommended retail price." However as the authors of this study explain, there are a number of differences between this controlled trial and the AMFm roll-out. The Kenya trial was conducted under tight experimental conditions and focused on access to pediatric ACTs.

While we acknowledge the importance of the private sector, we also recognize that private actors will respond rationally to the incentives created by governments or donors so as to maximize their private gain. Although there is great merit in the idea of using the private sector to increase access to ACTs, the early indications from AMFm Phase 1 suggest that there are some unintended, if not unforeseen, consequences that are proving disruptive and counterproductive.

A fundamental maxim of medical ethics is "first do no harm." This applies to medical doctors, public health policy makers and

donors alike. Given the urgent problems associated with the AMFm as described in this report, malaria scientists, program implementers and the broader malaria stakeholder community should be holding AMFm implementers to even higher standards to demonstrate that the scheme will truly improve malaria treatment and save more lives than other initiatives, and does no harm. It is the opinion of the authors of this paper that the malaria advocacy community has been effective in ensuring that donor agencies increase funding for malaria control and treatment. However the advocacy community has been particularly ineffective in ensuring proper oversight of malaria spending. This is a serious shortcoming because although malaria programs need more money, they need that money to be spent well and appropriately. More money spent badly could, as we are likely to see with the AMFm over the next few months, do more harm than good.

The opportunity costs of the AMFm are considerable and it would be highly irresponsible and a betrayal of those living with malaria to ignore the problems associated with the AMFm.

Conclusion

The AMFm is still in its early stages. The price of ACTs has fallen in the private sector, and hence demand has probably increased considerably for these products. Yet our survey and the publicly available data show that it is already disrupting procurement for ACTs in the public sector and could potentially be severely undermining malaria treatment programs in several countries. Some of these problems may be overcome over time (pressure on retailers to lower price, and manufacturer's management of supply may also improve too) but there are serious anomalies with orders and suppliers that should be carefully reviewed in the short run. The fact that the largest bi-lateral donor agency is facing difficulties in procuring sufficient ACTs should be seen as a major failure and direct consequence of distortions created by the AMFm. The benefits of the AMFm seen to date do not, in our opinion, mitigate these costs.

Based on the evidence from Cambodia, there may be a valid role for a malaria subsidy to play, however major reforms will be needed for the AMFm to be considered a success. We believe that far greater emphasis should be placed on increasing access to and use of RDTs. Furthermore, FLBs must bear a far greater share of the risk for procuring ACTs if any rational ordering and supply of malaria treatments is to be achieved.

The major donor agencies and the wider malaria stakeholder community should hold the Global Fund Secretariat to the highest possible standards to demonstrate that the AMFm is successful not only in reducing prices of ACTs, but in actually improving rational use of ACTs and improving malaria treatment outcomes. Given the response by the Secretariat in leaked documents to date, we are not convinced that it will pay sufficient attention to these crucially important metrics.

The GF is laudably transparent in providing details of orders and deliveries of ACTs. This transparency should be extended to all AMFm policy decisions and documents from all AMFm funders and stakeholders.

We regret to note that the aggressive advocacy and activism in favor of the AMFm effectively shut out all but a few voices that called for a more measured, careful approach that put greater emphasis on diagnosis and rational treatment. While the AMFm remains an interesting model that could still be useful as one of several strategies to improve malaria treatment, we believe that its time has passed. With evidence of decreasing malaria

transmission, the AMFm may simply encourage irrational overuse of ACTs.

Evidence to date suggests that the AMFm was pushed forward too far, too fast and with too much money.

Note: In conducting the research for this paper, Africa Fighting Malaria contacted the Global Fund Secretariat on several occasions over a three-week period for official comment and responses. No substantive response was ever received.

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