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Safe Medicines Project – Phase II: The Zambian Case Study

Summary

A range of antimalarial drugs were procured from private pharmacies, shops and kiosks within the urban and peri-urban areas of Lusaka, Zambia. Semi-quantitative thin-layer chromatography (TLC) and disintegration tests were conducted to measure active pharmaceutical ingredient content against internationally acceptable standards. All samples passed TLC and disintegration tests. The small sample size and limited scope of the collections preclude the authors from making any conclusions about malaria treatment standards in Zambia; however, the wide range of drugs collected, including those proscribed by the World Health Organization (WHO), indicate that there are problems with drug regulation and oversight in Zambia. Fifty-three percent of treatments collected were either oral artemisinin monotherapies or drugs that should no longer be used to treat malaria due to increased drug resistance. The artemisinin monotherapy treatments collected in this study were manufactured approximately 21 months on average after the WHO's appeal to halt their production and withdraw these clinically inappropriate drugs from the market.

Introduction

Malaria was a severe health concern in almost all countries until the mid-20th century. In the 1940s, the successful application of insecticides as part of indoor residual spraying (IRS) programs, coupled with effective antimalarial drugs such as chloroquine, brought cases and deaths down sharply and gave countries and the World Health Organization the impetus to attempt to eradicate the disease. In 1955, the Eighth World Health Assembly resolved to begin a worldwide malaria eradication campaign, and despite the fact that the campaign was eventually abandoned and considered a failure, it registered resounding successes in wiping out malaria from large regions across the globe and saving many millions of lives.

In spite of the progress made in the 20th century, malaria remains a major public health concern throughout the world. It affects over 100 countries and approximately 40 percent of the world's population. Of the 2.5 billion people at risk for malaria, between 300 and 500 million become severely ill and over 1 million

people die every year.¹ In Africa, the worst affected continent, one in every five childhood deaths is caused by the disease. The WHO estimates that an African child has on average between 1.6 and 5.4 episodes of malaria fever each year and every thirty seconds an African child dies of malaria.²

The cornerstones of a successful malaria control program are the effective use of insecticides for disease vector control (including the use of insecticide treated bednets (ITNs) and/or IRS) and effective antimalarial treatment. Increased resistance to existing insecticides, scaled back vector control programs, and increased resistance to antimalarial treatment, hampered control programs across the globe. As a result the disease surged throughout many malaria endemic countries, particularly in Africa, throughout the early 1990's. No single effect can explain the trend, but rising parasite resistance to historically effective drugs, such as chloroquine (CQ) and sulphadoxine-pyrimethamine (SP), was a substantial driver.

During the 1970s, researchers employed by the government of China discovered a new and effective malaria treatment based on an ancient Chinese herbal remedy – *Artemisia annua*. It was not until the 1990s, in the face of failing CQ and SP that researchers and public health officials began to use the artemisinin-derivative treatments in South-East Asia. In order to slow the development of malaria drug resistance, researchers combined the artemisinin-based drugs with other drugs that have different modes of action.

The Swiss pharmaceutical manufacturer Novartis Pharmaceuticals AG developed a fixed dose combination therapy, combining lumefantrine with artemether, a derivative of artemisinin. This new fixed dose combination (FDC) drug, known as Coartem[®], is a highly effective treatment for uncomplicated *plasmodium falciparum* malaria – the most deadly form of the disease and the most common in Africa. However, Coartem was priced up to 20 times more expensive than CQ, which sold for as little as \$0.10. 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 the plant and is a costly process to extract the active ingredient. 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.³ The agreement was a breakthrough for malarial countries that could afford the reduced price – but most could not. In recent years more manufacturers have begun to produce ACTs, either as FDCs, which are preferable as they reduce compliance problems, or as blister packs of two medicines packaged together.

In January 2006, the WHO issued new antimalarial treatment guidelines for the first time in 20 years officially recommending artemisinin based combination therapies (ACTs). It also publicly called for an end to the production of artemisinin

¹ World Health Organization (2007) 10 Facts on Malaria. Available at: <http://www.who.int/features/factfiles/malaria/en/index.html>

² ibid

³ Deloitte & Touche. World Health Organization. Report for the review of collaborating partner product pricing. Available at: http://www.who.int/malaria/cmc_upload/0/000/016/747/who_coartem_review_summary_report.pdf

monotherapies⁴ and helped pass the World Health Assembly Resolution WHA60.18 in May 2007, calling on all member states to support this effort.⁵ However, there is little evidence to suggest these diplomatic efforts are having an impact today.

Oral artemisinin monotherapies are cheaper and easier to manufacture than FDC ACTs. The rising demand for artemisinin has increased incentives for companies to market artemisinin monotherapies. But the probability of resistance building up to a mono-therapeutic drug is greatly increased. Indeed, Noedl et al (2008) have indicated that artemisinin is losing its potency against malaria in Western Cambodia.⁶ Pascal Ringwald, a medical officer at the WHO in charge of monitoring antimalarial drug resistance, notes, "Instead of killing most of the parasite within 24 to 36 hours as before, Artemisinin derivatives now need up to 120 hours to clear some of the parasites from the bloodstream".⁷ It should be noted that artemisinin remains an effective antimalarial treatment, particularly when used in combination with a longer acting drug, but precautions must be taken to ensure its efficacy in the long run. Indeed, 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.

Donors were initially slow to help countries transition to ACTs, unable or unwilling to subsidize the extra costs to buy and properly administer the drugs.⁸ Most donor agencies and the Global Fund to Fight AIDS, TB and Malaria now fund the widespread use of ACTs for malaria treatment. Almost all malarial countries in Africa have registered ACTs as their first-line treatment for uncomplicated malaria.⁹ Despite this fact, there is still a staggering prevalence of outdated and proscribed drugs in Africa such as CQ and artemisinin monotherapies. In August 2007, the WHO counted over 80 Chinese artemisinin producers, 67 countries manufacturing oral artemisinin monotherapies and at least 94 oral artemisinin-based products currently on the market, mostly in the private sector of endemic countries.¹⁰

⁴ World Health Organization (2006) WHO calls for an immediate halt to provision of single-drug artemisinin malaria pills. Available at:

<http://www.who.int/mediacentre/news/releases/2006/pr02/en/index.html>

⁵ World Health Organization (2007) WHO informal consultation with manufacturers of artemisinin-based pharmaceutical products in use for the treatment of malaria. Available at: <http://www.who.int/malaria/docs/diagnosisandtreatment/MtgManufacturersArtemisininDerivatives.pdf>

⁶ Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM (2008) Evidence of artemisinin-resistant malaria in western Cambodia. *The New England Journal of Medicine* 359(24):2619-20.

⁷ IRIN (2009) Cambodia: Malaria gaining tolerance to some treatments. Available at:

<http://www.irinnews.org/Report.aspx?ReportId=82327>

⁸ Attaran A, et al. (2004) WHO, the Global Fund and medical malpractice in malaria treatment. *The Lancet* 363(9404):237-240.

⁹ World Health Organization (2008) Global Anti-malarial Drug Policy database - AFRO. Available at: http://www.who.int/malaria/amdp/amdp_afro.htm

¹⁰ World Health Organization (2007) WHO informal consultation with manufacturers of artemisinin-based pharmaceutical products in use for the treatment of malaria. Available at: <http://www.who.int/malaria/docs/diagnosisandtreatment/MtgManufacturersArtemisininDerivatives.pdf>

Due to the fact that public health systems on the African continent remain weak and underdeveloped, most people will seek treatment from the private sector where a wide range of drugs abound, both of good and bad quality.

Previous Results

Previous research conducted by Africa Fighting Malaria (AFM) analyzed antimalarial drug quality in six African countries: Ghana, Kenya, Nigeria, Rwanda, Tanzania and Uganda. Using the Global Pharma Health Fund Minilab,¹¹ TLC and dissolution tests were performed on over 200 samples of antimalarial treatments to see if they met international standards. The study was published in May 2008 in the peer-reviewed journal PLoS ONE and is entitled *Antimalarial Drug Quality in the Most Severely Malarious Parts of Africa – A Six Country Study*.¹²

Artemisinin monotherapies were widely available in sampled urban and peri-urban pharmacies and 35 percent of all treatments failed basic content testing.¹³ Since only 20 percent of the WHO's 191 member states currently have well-developed drug regulatory systems, this came as no surprise.¹⁴ 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.

Substandard drugs continue to hamper malaria control efforts throughout much of the world. The WHO estimates that the failure of national drug regulatory authorities to maintain quality standards results in 200,000 unnecessary deaths from malaria alone each year.¹⁵ If resistance to these compounds spreads faster than researchers are able to discover new ones, gains achieved by malaria control efforts could be short-lived.

Zambian Case Study

Malaria is endemic throughout Zambia and continues to be a major public health problem. In 2005, malaria accounted for approximately 36 percent of hospitalizations and outpatient department visits, exacting a considerable toll on families and health systems.¹⁶ The burden of malaria is not only a human tragedy it is an economic one as well. Due to the debilitating effects of malaria it becomes

¹¹ Global Pharma Health Fund. The GPHF-Minilab – Protection against counterfeit medicines. Available at: <http://www.gphf.org/web/en/minilab/index.htm>

¹² Bate R, Coticelli P, Tren R, Attaran A (2008) Antimalarial Drug Quality in the Most Severely Malarious Parts of Africa – A Six Country Study. PLoS ONE 3(5):e2132. Available at: <http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0002132>

¹³ ibid

¹⁴ World Health Organization. General information on counterfeit medicines. Available at: <http://www.who.int/medicines/services/counterfeit/overview/en/index1.html>

¹⁵ World Health Organization (2003) Substandard and counterfeit medicines. Available at: <http://www.who.int/mediacentre/factsheets/2003/fs275/en/>

¹⁶ Zambia Ministry of Health. National Malaria Control Programme. Zambia Achieves Impact on Malaria: Using Results to Inform Actions. Available at: <http://www.nmcc.org.zm/files/FINALZambiafactsheetDec.08.pdf>

impossible to remain productive, not only for the person suffering from the disease but also for household members who are required to care for the sick. This has devastating effects on the economy through lost productivity due to absenteeism.

In order to assess the progress of the national malaria control program, the Zambian ministry of health (MoH) has conducted a series of Malaria Indicator Surveys (MIS) and Demographic Health Surveys (DHS). The most recent national MIS (2008) represents the second nationally-representative assessment of key malaria interventions in combination with measures of malaria-related burden, using malaria parasite and anemia prevalence testing among children under age five. The data from the 2001-2002 DHS, 2007 DHS, and the 2006 national MIS present an increasing trend in coverage rates of all malaria interventions over the past five years.

The deadliest strain of the malaria parasite, *plasmodium falciparum*, accounts for over 90 percent of all infections and the most efficient malaria carrying mosquito, *anopheles gambiae*, is the major vector. Zambia's entire population (12,160,516) lives in areas at risk of malaria.¹⁷ Malaria transmission in Zambia is seasonal and coincides with the start of the rainy season that typically begins in November-December and lasts through April-May. This is followed by a cool dry season in June-July and a hot dry season in August-October. The reported number of malaria episodes per year is 4,940,000 (2006) and the number of reported deaths is 6,484 for all ages and 3,342 in children under age five (2006).¹⁸

However, it should be noted that according to the latest MIS completed in 2008, malaria parasite prevalence in the target population (i.e. children under age five) has been reduced by 54 percent, and severe anemia has been reduced by a remarkable 69 percent. The MIS also reports that malaria infection and illness in children under age five has decreased substantially since 2002, and the mortality rate has dropped by 29 percent.¹⁹ These impressive gains cannot be attributed to one intervention specifically but rather a combination of effective vector control strategies and the availability of high-quality effective antimalarial drugs.

The two main vector control strategies in Zambia involve the dissemination of ITNs as well as the targeted use of insecticides for IRS operations in certain districts. Vector control has been scaled up impressively in Zambia. According to the MIS, "72% of Zambian households have at least one mosquito net, and 62% of households have at least one insecticide-treated net, representing an increase from 50% and 38%, respectively, in 2006". More specifically the MIS noted, "Forty-eight percent of all Zambian children under age five years slept under a mosquito net the night before the survey, while among households with at least one net, 61% of children under age five years slept under a mosquito net". Zambia also conducted an IRS program within targeted districts and the MIS noted that, "more than 40% of households reported spraying in the previous 12 months, with an increasing trend in the rural, more malarious areas of these districts since 2006". Eighty-five percent of this spraying was conducted by the government IRS program.

¹⁷ Roll Back Malaria. Zambia: Progress and Challenges towards Scaling Up For Impact. Available at: http://www.rollbackmalaria.org/countryaction/zambia.html#expand_node

¹⁸ ibid

¹⁹ Government of the Republic of Zambia Ministry of Health. Zambia National Malaria Indicator Survey 2008. Available at: <http://www.nmcc.org.zm/files/ZambiaMIS2008Final.pdf>

The national malaria control center in Zambia has a policy of expanding the use of rapid diagnostic tests for malaria diagnosis in conjunction with the use of Coartem. The treatment component of Zambia's malaria control program focuses on prompt provision of effective drugs. According to the current malaria control strategy, Zambia hopes to treat 80 percent of patients within 24 hours of symptom onset.²⁰ In the face of increasing resistance to CQ and SP, the Zambian MoH designated artemether-lumefantrine (AL) as the first-line therapy for all Zambians over 5 kg in 2003 and SP for uncomplicated malaria in children under 5 kg.²¹

According to the MIS conducted in 2008, approximately 28 percent (903/3,218) of children under the age of five years reported having a fever in the two weeks prior to the survey interview. Of the 28 percent who reported having a fever, approximately 11 percent reported having a finger (or heel) prick test, and roughly 43 percent reported taking an antimalarial drug.²² The MIS also shows that only 64 percent of children under the age of five years sought treatment from a health facility/provider within the two weeks prior to the survey interview. The MIS reveals that SP is the most common antimalarial drug given for fever. More specifically, the survey shows that approximately 21 percent of children with fever in the last two weeks were treated with SP, 13 percent with AL, and approximately 3 percent with quinine (for the treatment of severe malaria and in accordance with the national treatment guidelines).²³

It should be noted that a study conducted by Chanda et al (2007) demonstrated that AL is a successful treatment at less cost than SP, implying that AL is more cost-effective. Indeed, the study demonstrates that the health gains (treatment success) from every dollar spent are significantly greater if AL is used rather than SP. The incremental cost-effectiveness ratio is estimated to be US\$4.10. The study concludes, "The decision to adopt AL [as Zambia's first line treatment] is clearly justifiable on both economic and public health grounds"²⁴

The Chanda study also revealed that children under the age of five years in rural areas were more likely to suffer from fever but less likely to take an antimalarial drug for the febrile episode. Children living in rural areas were also less likely to take an antimalarial drug within 24 hours, compared to children living in urban areas. This indicates that access to drugs in rural areas is more of a concern. This is not surprising since the majority of health centers tend to be congregated around urban centers.

²⁰ Zambia Ministry of Health. A 6-year strategic plan. A Road Map for Impact on Malaria in Zambia. 2006–2011

²¹ Quinine is designated as the lead drug to treat complicated malaria.

²² Approximately 29 percent of these children reported taking the drug within 24 hours of the onset of symptoms.

²³ Among children treated within 24 hours of symptom onset, approximately 15 percent were given SP and 8 percent AL.

²⁴ Chanda P, Masiye F, Chitah B, Sipilanyambe N, Hawela M, Banda P, Okorosobo T (2007) A cost-effectiveness analysis of artemether lumefantrine for treatment of uncomplicated malaria in Zambia. *Malaria Journal* 6:21. Available at: <http://www.malariajournal.com/content/6/1/21>

According to the 2008 MIS, the majority of drugs (70.1 percent) were obtained from a government health facility.²⁵ However, for the purposes of this study, AFM was chiefly interested in the quality of drugs available in the private sector. In order to ascertain the prevalence of fake and substandard drugs, AFM conducted a sampling survey of 11 randomly-selected private pharmacies, shops and kiosks in the city of Lusaka and its surrounding areas. Although this small survey is by no means definitive it provides encouraging information about the scarcity of fake and substandard drugs in Zambia.

AFM staff along with a Zambian national entered pharmacies and shops and asked the assistant or pharmacist for a range of different antimalarial drugs. Two samples of all available malaria treatments were procured. In October 2008, AFM tested samples from 36 malaria treatments collected. All of the samples passed TLC and disintegration testing and were not found to be substandard or fake. Of concern was the high number of oral artemisinin monotherapy tablets found on sale as well as the prevalence of SP.

Overall, 21 different brands of malaria treatments were procured. The majority of the samples collected were in tablet form; however, two brands of suspension powder AL for pediatric use were procured as well as a brand of soft gelatin capsules containing Artesunate and Amodiaquine (ASAQ). Four different brands of SP were found, one brand of Halofantrine, one brand of Mefloquine and one brand of Amodiaquine. Several different ACTs were procured, ranging from five different brands of AL, two different brands of Artesunate + SP and one brand of ASAQ sold as a 'soft gelatin capsule.'

Worryingly, five different brands of oral artemisinin monotherapy tablets were collected. On average, these drugs were manufactured approximately 21 months after the January 2006 WHO appeal to cease production. Although monotherapies are cheaper, it is imperative that countries enforce strict legislation clamping down on the sale of monotherapy drugs. As noted previously, the only effective drugs available to combat malaria are artemisinin and artemisinin derivatives.

Furthermore, the researchers also found public sector Coartem on sale in the private sector. As noted previously, the Swiss pharmaceutical manufacturer Novartis signed a Memorandum of Understanding with the WHO to make Coartem available to public facilities in malaria-endemic countries on a no-profit, no-loss basis. Coartem distributed to the public sector is contained in a uniquely designed and easily identifiable package. The package includes pictograms on the cover in order to assist illiterate patients in taking the correct dosage at the correct time. These drugs are not available to the private sector that often pays 10 times the price of drugs purchased by the public sector. There is thus an enormous economic incentive to steal or enter into illegal contracts with public sector officials to secure these drugs. Thus when one finds public sector drugs being sold in the private sector it means that the taxpaying public are cross-subsidizing the private sector.

Of the pharmacies and shops visited, only two assistants or pharmacists asked who would be using the drugs i.e. an adult or a child. At one pharmacy, child doses of

²⁵ Approximately 88 percent of Coartem treatment was obtained through a government health facility as was 67.2 percent of SP. Respondents also reported using medications already present in the home (12.5 percent) or purchased at a shop (7.2 percent).

public sector Coartem were sold to the researchers, even though this was not specified. At a different pharmacy, generic versions of Coartem were sold to the researchers as brand name Coartem – i.e. when the researchers requested Coartem, they were handed the generic version and told that it was the same drug.²⁶

Researchers asked one pharmacist who sold oral artemisinin monotherapy tablets whether or not he was aware of the consequences for drug resistance due to the ongoing use of these drugs. The pharmacist's response was that he was aware that the Government of Zambia had called for a halt to the sale of oral artemisinin monotherapies but that he considered the drugs to still be effective, cheaper than ACTs and in demand from his customers. For these reasons he confirmed that he would continue to sell oral artemisinin monotherapies.

Policy Recommendations and Conclusion

It is imperative, if the scale-up in malaria control and treatment is to be sustained, that malarial country governments do more to monitor the sale of malaria drugs. It is understandable that pharmacies and shops continue to stock and sell SP and CQ given the historic use of these drugs, their low cost, and the fact that they may provide some relief to patients and could even cure them. However, drug resistance will only increase as these drugs continue to be used. It is far less excusable for pharmacies to sell oral artemisinin monotherapies and for drug manufacturers to continue to market them. Evidence of drug resistance to artemisinin based drugs in South-East Asia is increasing and could spread, as has happened in the past to other malarial areas. No new classes of antimalarial drug will be made available in the foreseeable future and therefore every effort should be made to protect ACTs.

Spot checks by MoH officials and regular quality tests of malaria drugs on sale should improve malaria treatment in Zambia. In addition, Zambian officials should educate pharmacists on the dangers of selling oral artemisinin monotherapy tablets and should consider fines for any pharmacist found selling these drugs.

The Zambian Government should do more to tighten controls of its medical stores. The theft of Coartem and its subsequent sale in private shops and pharmacies must be curtailed. Not only does the theft of Coartem deprive patients that seek treatment in public clinics and cost taxpayers, but it undermines the potential for-profit market for the sale of this drug. The theft of public sector Coartem and its sale in the private sector is not unique to Zambia; AFM researchers have found similar occurrences in several other African countries.

Along with improving oversight, the Zambian Government should continue its impressive malaria control activities. Prevention, as the adage goes, is always better than cure. If the Zambian Government can reduce the malaria case load, it will not only reduce the need for malaria treatment but will also lower the selective pressure on drug resistant strains of the parasite.

²⁶ TLC testing of this generic found it to be of good quality.