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WHO calls for an end to the marketing of sub-optimal malaria treatments

By Theo Smart

Two weeks ago the World Health Organization (WHO) called on pharmaceutical companies to “immediately halt” the marketing and sale of ‘single-drug’ artemisinin medicines for malaria. The announcement is part of an effort to make certain that these drugs are used optimally — as part of a combination regimen — and to prevent malaria parasites from developing resistance to this potent class of drugs (see

www.who.int/mediacentre/news/releases/2006/pr02/en/index.html).

While the action has been welcomed by many of those involved in the malaria field, there is some disagreement over whether WHO's targeting of the manufacturers is entirely warranted, or for that matter, whether it will have its desired effect: preventing the loss of this generation of antimalarials.

Malaria background

Each year, malaria causes over 500 million acute illnesses and one to two million deaths — primarily in small children. 90% of the burden of disease is in Africa, including many regions also afflicted by HIV/AIDS. People with HIV have increased susceptibility to malaria, and coinfection can have a number of harmful consequences (see

<http://www.aidsmap.com/en/news/438CA6E4-72E0-48B4-B3FE-A0829A27B0E6.asp>,
<http://www.aidsmap.com/en/news/AAC60A71-7E7D-4C86-915C-699A2BF2E6F8.asp>,
<http://www.aidsmap.com/en/news/A9E41D88-9D3C-4385-BD15-771F4384DCB7.asp>).

Control of malaria has been hampered by the rapid development of resistance to one drug after another used to treat it.

Yet, high hopes have been pinned to the artemisinins, a powerful class of antimalaria medicine derived from *Artemisia annua*, a herb borrowed from the traditional Chinese formulary. Extracts such as artesunate and artemeter are the most rapidly effective antimalarial drugs known.

To maximise and preserve their effectiveness, artemisinins should be administered with another longer-acting antimalarial, such as lumefantrine, amodiaquine, sulfadoxine-pyrimethamine or mefloquine (although the latter drug is only recommended in areas where malaria has a low rate of transmission).

Over the last several years, these artemisinin-based combination therapies (ACTs) have been shown to be extremely effective in a variety of settings. Some studies used ACTs co-formulated into a single tablet, or packaged together in blister packs to make the co-administration of the drug easier for patients. At least one recent study demonstrated that one co-formulated ACT, artemeter/lumefantrine was packaged with instructions simple enough for mothers in rural Uganda to successfully administer in their own homes to their children with malaria (<http://www.aidsmap.com/en/news/F30B37BA-3C5F-4823-920F-E0C1EB13F3854.asp>).

On the basis of these studies and WHO's recommendations, more than 50 governments (most countries where malaria is endemic) have now adopted ACTs as the frontline treatment for malaria.

Public sector access to ACT

But, for several reasons, this has not improved access as much as one might have hoped.

The initial issue was supply. When so many countries switched over to ACTs, there was a sudden surge in demand for the drugs for use in public health facilities — from two million treatment courses in 2003 to 30 million in 2004, to 70 million for 2005. This led to a shortfall in both artemisinin and ACTs available. There simply wasn't enough of the raw ingredient available — which was ironic because the plant is so easy to grow it is considered an invasive noxious weed in parts of the world.

However, through the efforts of WHO Roll Back Malaria (RBM) department — working with the United States Agency for International Development (USAID), farmers in east Africa have recently begun to grow the plant — and there should be enough to supply an anticipated 130 million treatment courses of ACTs in 2006.

The private market

But a potentially greater problem is that many people don't access malaria treatment through the public sector. By far the largest market for antimalaria drugs is in the private sector. In Africa especially, most malaria treatment is purchased from village shops and pharmacies.

The private market is largely unregulated. However, the sale of antimalarials, in particular, occupies a regulatory grey niche because it is standard policy in many countries for the first-line antimalarials to become scheduled either for general sales or as an over-the-counter medicine — to be certain that the first-line medicine is readily available to the public.

Malaria happens at home, often far from the nearest clinic. So it is important to treat the infection as soon as possible (within the first 24 hours of symptoms) in order to prevent severe or complicated malaria. A child can die in the time that it takes to access treatment through a clinic. So most antimalarial medicines are bought without any contact with a healthcare worker, and often not even a pharmacist.

In such situations, coformulations and co-packaging could be extremely important. Sale of coformulations would prevent artemisinin from being taken alone — but there is only one coformulation (artemeter/lumefantrine) currently being made. Two more should become marketed by the end of the year. However, coformulations are primarily being supplied the public health sector.

Co-packaging could make proper adherence more likely and some co-packaged products are available to the private market. Furthermore, the packaging provides an opportunity to educate the patient about the correct way to use the drug (WHO has recently published guidelines on how to package these products in a user-friendly way to optimise their use

http://www.who.int/malaria/docs/Specifications_prepackaging_antimalarials_sm.pdf).

But the availability of single drug artemisinins at the village shop could easily lead to confusion and misuse — especially when these are cheaper than the co-packaged products.

Although the size of the private market for artemisinin-based treatment is still limited by the drug's high cost (see below), currently there are over 40 companies trying to supply it. Some are

respectable firms, while some are small and rather questionable operations. In a recent survey conducted by the WHO Department of Essential Drugs and Medicines Policy, "significant problems were found with substandard antimalarial products circulating through the medicine-distribution chains in the African region," which appeared "to be the result of non-compliance on the part of manufacturers with Good Manufacturing Process (GMP) guidelines."

WHO's stance

So, while the announcement from WHO may seem unusually aggressive, this is an issue the organisation has been trying to deal with for sometime. WHO has organised meetings to assist manufacturers trying to supply artemisinin drugs in a responsible way for the malaria market and previously raised the issue as recently as September (http://www.who.int/malaria/docs/Specifications_prepackaging_antimalarials_sm.pdf, <http://www.who.int/mediacentre/news/releases/2005/pr40/en/index.html>).

But the demand to end the marketing of what it considers to be sub-optimal treatment sets a precedent for WHO, which has previously chastised tobacco companies and makers of baby formula for business practices that run counter to public health interests — but never the pharmaceutical industry.

Although WHO has no legal authority to stop the sale of a drug, its recommendations carry considerable weight with national regulatory agencies and other multilateral organisations. According to reports in the media, WHO will try to disrupt the sale of other medicines, including pre-qualified antiretroviral medicines from manufacturers who continue marketing the products three months from now.

However, some of the targeted pharmaceutical companies have complained they are being unfairly demonised for idiosyncrasies of the malaria market. For example, whenever companies co-package a new combination, it has to be licensed anew in each country. This places a greater burden on the smaller companies, and could lead to a loss of manufacturing capacity if these companies are forced out of the market.

There also have been complaints about the tolerability of some of the other malarias with which artemisinins have been co-packaged. The availability of single drug artemisinins allows doctors to come up with alternative combinations as needed.

In a press release last week, Medecins Sans Frontieres (MSF) welcomed the spirit of WHO's demands, but believes a complete ban on the availability of monotherapies may be premature, noting that there are medical situations where single drug formulations are still required — "for patients who do not tolerate the other components used in combinations, or for following up oral therapy with artemisinin derivative injections in severe cases."

Others are not convinced that the artemisinins are as likely to be associated with resistance as some other drugs. WHO presents a good case for the danger in a recent report on malaria susceptibility and response rates to currently available drugs (see http://www.who.int/malaria/rbm/Attachment/20041108/SusceptibilityPlasmodium_report.pdf), but the data are not yet conclusive. Most troublesome seems to be a high rate of failure on artemeter-lumefantrine in Cambodia, but it has not yet been definitively linked with resistance.

Nevertheless, the consequences of losing this class of drug are too horrible to contemplate — there are no other miracle antimalarials waiting in the wings.

People and children with HIV may be particularly vulnerable. It is hard to say what will be the impact of HIV coinfection on the development of resistance in patients not taking an optimal ACT regimen but a number of studies have reported excessively long delays in treatment response in patients with advanced HIV. According to unpublished data cited by the WHO report on malaria susceptibility (above), the efficacy of artemether-lumefantrine is reduced in adults co-infected with HIV and with a CD4 count <300. Another report from Ethiopia found that parasite clearance time after treatment with artemisinin is also increased in seropositive patients.

The WHO report concludes "The risk that resistance to antimalarial drugs will extend with the AIDS epidemic must be considered seriously."

Chances of success?

But will a proscription against artemisinin monotherapy really work to preserve ACT as an option for malaria treatment? It will probably go a long way towards making sure that the public health sector uses these drugs optimally. But for the private sector, it is less clear. WHO's request is most likely to influence the more reputable firms now making artemisinins, leaving that the firms selling the poorest quality drugs to continue supplying the market. Without strengthening regulatory agencies in each country, it could be difficult to keep these products out.

Even if coformulations and co-packaged ACTs become more widely available in the private sector, supply chain management and oversight of their sale will need to be improved, because ACTs have a short shelflife. It's common for drugs to be sold past their sell by date in Africa. And when the sell by date is clearly marketed, it is common for unscrupulous dealers to repackage drugs.

A recent paper in *Lancet Infectious Diseases* reviews some of challenges in bringing new anti-malarials to the market, noting that there are many reasons and ways in which new malaria therapies could be misused in the developing world, and understanding the problems will take post-marketing and operational research that the public-private partnerships which have developed most of the coformulations simply have not planned for (Lang).

Patient education materials may be ineffective, for example. Even if patients understand dosing instructions perfectly, they still may not adhere to the package insert's advice.

People in malaria-endemic settings have been managing the illness in their families for generations. To many Africans, malaria does not have to be cured, it has to be survived. Getting through an episode is the first step to becoming less susceptible to the next episode. The perception is common that it is the fever that must be treated and once the symptoms resolve, whatever treatment is left can be reserved for when the next child gets ill. This is why malaria is being consistently under-treated. Ideas such as curing, and reducing the local burden of malarial parasites by finishing the treatment can be difficult concepts to try to convey in pictograms on the back of a package.

Supplemental and community based education programmes are the only way to tackle such deep rooted barriers to optimal adherence.

WHO and Roll Back Malaria have published guidelines (http://www.who.int/malaria/docs/RBM_Strategy_HMM_sm.pdf) to improve the home management of malaria by educating shopkeepers and others in the community, but these interventions must be funded and expanded beyond small pilot projects to be effective.

Finally, the cost of treatment will almost certainly have a dramatic impact on how people will adhere to the treatments in the private sector. The current cost of ACT in the private sector is 10-30 times higher than for old standard treatments, at between US \$2 to \$6 for an adult course of treatment.

"If new treatments for malaria in Africa are going to be of substantial public-health benefit, they will need to be bought or dispensed in place of the medicines that are failing. They would therefore need to be available everywhere that chloroquine and sulfadoxine-pyrimethamine are currently obtained and at a similar cost," write Lang et al.

Such high prices could either chase people onto older treatments that are no longer effective, or encourage them to try to stretch out their ACT to cover more than one malarial episode.

Malaria treatment needs to be free, otherwise, no amount of treatment education will keep people from misusing these drugs.

Online Resources

Roll Back Malaria

<http://www.rollbackmalaria.org/>

WHO Roll Back Malaria Department

<http://www.who.int/malaria/>

WHO and Rollback Malaria Publication

http://www.who.int/malaria/includes_en/whomalariapublications19982004.htm#2005

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Lang T et al. Beyond registration—measuring the public-health potential of new treatments for malaria in Africa. *Lancet Infectious Diseases* 6: 46-52, 2006.

The quality of antimalarials: a study in selected African countries. Geneva, World Health Organization, 2003.

And see links cited in the article.

about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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