

@ Fake anti-malarial drugs are on the increase in southeast Asia and Africa. Now, researchers are urging stricter regulations, better law enforcement and a subsidy to provide inexpensive medications to effectively treat the disease.

PHOTO BY GARY MEEK



ABOVE: Georgia Tech Assistant Professor Facundo Fernandez, a bioanalytical chemist, and his collaborators found that some counterfeit artesunate anti-malarial drugs contain up to 10 milligrams of the active ingredient — compared to the 50 milligrams that genuine artesunate tablets contain.

Fake Pharmaceuticals

Increase in counterfeit anti-malarial drugs prompts call for crackdown and better detection.

BY JANE M. SANDERS

Aworsening epidemic of sophisticated anti-malarial drug counterfeiting in southeast Asia and Africa is increasing the likelihood of drug-resistant parasites, yielding false-positive results on screening tests and risking the lives of hundreds of thousands of malaria patients, mostly children, researchers say.

The situation has prompted an international group of researchers to urge national and international authorities to combat the problem with stringent regulations, law enforcement and the provision of inexpensive medicines to undercut the counterfeiters. Based on their own research and other scientists' studies, they outline the problem and make recommendations for addressing it in a paper published June 13, 2006 in the Public Library of Science journal *PLoS Medicine*. These researchers' work was funded by the Wellcome Trust of Great Britain and the Bill & Melinda Gates Foundation.

"The manufacture and distribution of counterfeit drugs, including anti-malarials, is a massive international problem, and few agencies are investigating it," says Facundo Fernandez, an assistant professor of chemistry and biochemistry at Georgia Tech and an author on the paper. His close collaborators include scientists Paul Newton from the University of Oxford in the United Kingdom and Michael Green from the Atlanta-based Centers for Disease Control and Prevention.

Malaria is a widespread international problem, primarily in poor and developing countries in the tropics — though some cases have been reported in Florida in the United States. The disease — transmitted by mosquitoes infected with the parasite *Plasmodium falciparum* — infects 300 to 500 million people a year. Each year, about 1.5 million of those — mostly children — die even though genuine anti-

malarial drugs are quite effective. One of the most efficacious drugs is artesunate derived from the *Artemisia annua* plant native to China.

The percentage of over-the-counter counterfeit artesunate tablets containing no artesunate apparently increased from 38 to 53 percent in southeast Asia between 1999 and 2004, according to a studies led by Newton and Professor Nicholas White at Oxford. In some countries, the majority of the available artesunate is fake, according to the Oxford studies, which are cited in the *PLoS Medicine* report.

Meanwhile, identifying counterfeit tablets has become increasingly difficult as counterfeiters have implemented sophisticated manufacturing and packaging strategies — such as including low, but ineffective, levels of the proper active ingredients and applying counterfeit holograms to packaging — to deceive investigators and consumers. In fact, Fernandez, a bioanalytical chemist, and his collaborators found that some counterfeit artesunate anti-malarial drugs contain up to 10 milligrams of the active ingredient — compared to the 50 milligrams that genuine artesunate tablets contain.

PHOTO BY P. VIROT, COURTESY OF WORLD HEALTH ORGANIZATION



ABOVE: Malaria sickened this young boy in Ethiopia. Children are at greater risk of dying from the mosquito-borne disease.

“We make no apology for the use of the term 'manslaughter' to describe this criminal lethal trade,” the authors write. “Indeed, some might call it murder. Somewhere people are directing a highly technical and sophisticated criminal trade... in the full knowledge that their ineffective 'product' may kill people who would otherwise survive malaria infection.”

Serious implications exist for the relatively new practice of incorporating ineffective levels of active ingredients in artesunate tablets, the authors note. Exposure of malaria parasites to low concentrations of artesunate in patients taking counterfeit products will greatly increase the risk for the selection and spread of malaria parasites that are resistant to artemisinin derivatives. That could lead to a loss of effectiveness for these essential medicines and an avoidable failure of malaria control, they write. In addition, the presence of small quantities of artesunate in tablets may mean that the Fast Red dye test, widely used for screening the quality of artesunate tablets, yields false-positive results, depending on how much artesunate is present in the fakes.

Also, many fake artesunate tablets contain other drugs, possibly because the counterfeiters are trying to further deceive patients and doctors by possibly producing an initial, limited benefit, Fernandez says. “For example, some of the counterfeit tablets we analyzed contained acetaminophen that would reduce a fever, or the antibiotic erythromycin, or even early-generation anti-malarials that are no longer effective.”

The researchers' analyses determined there are now at least 12 different types of fake artesunate, classified by Oxford researchers based on the counterfeit holograms affixed to artesunate packaging. Evidence suggests that production is on an industrial scale, according to research by Newton and Green published in 2001 in the British med-

PHOTO BY GARY MEEK



LEFT: Georgia Tech Assistant Professor Facundo Fernandez and his students are studying new, high-throughput screening techniques to detect and quantify the contents of counterfeit anti-malarial drugs and other fake pharmaceuticals.

ical journal *The Lancet*. For example, a non-governmental organization in Burma purchased 100,000 counterfeit artesunate tablets from one large pharmacy, the researchers note.

“At this point, we believe there are probably multiple sources, but they may be using the same distribution network,” Fernandez adds.

The authors also cite serious implications of this public health problem for tourists in malaria-prone countries. Visitors often buy unregulated artemisinin derivatives in the tropics or on the Internet. It is inevitable that counterfeit artesunate will seep into this trade, the authors predict.

The greater concern, they note, is for sub-Saharan Africa. Since 2001, artemisinin derivative-based combination (continued on page 19)

BELOW: This close-up photograph shows an *Anopheles minimus* mosquito, a malaria vector of the Orient, as she was feeding on a human host.

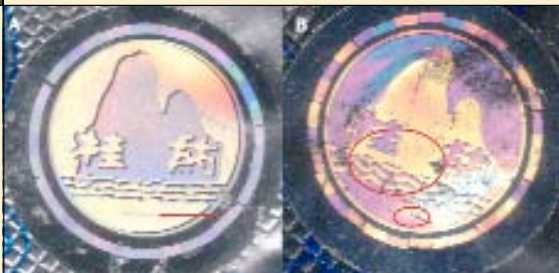


PHOTO COURTESY OF CDC



Counterfeit Contents

Novel analytical techniques are targeting fake anti-malarials.



ABOVE: Researchers have identified genuine and fake Guilin Pharma artesunate blister pack holograms found in mainland southeast Asia. The photo at top is the genuine hologram.

RIGHT: These images show two different fake artesunate blister pack holograms.

PHOTOS BY PAUL NEWTON, COURTESY OF WELLCOME TRUST

Researchers led by the Georgia Institute of Technology are developing novel analytical chemistry techniques to detect and quantify the contents of counterfeit anti-malarial drugs and other fake pharmaceuticals. The manufacture and distribution of these fake medications is a growing problem in third-world countries, where the mosquito-borne illness malaria is widespread.

A report on this research — funded by the Society of Analytical Chemists of Pittsburgh and the Wellcome Trust of Great Britain — will be published this summer in the journal *ChemMedChem*.

Georgia Tech Assistant Professor of Chemistry and Biochemistry Facundo Fernandez began studying counterfeit anti-malarials two years ago using conventional analytical chemistry techniques based on liquid chromatography and mass spectrometry. But these methods required more than two hours to analyze just one sample. So he and his graduate students developed new, high-throughput ionization techniques that now allow them to complete the same analyses in just five seconds per sample.

"This is a new generation of techniques in mass spectrometry," Fernandez says. "We don't probe our samples under vacuum like you normally do with mass spectrometry. We can hold a solid sample under atmospheric pressure and use one of our new tools to ionize its surface components. The ionized particles are subsequently analyzed by mass spectrometry. This method eliminates the time and costs associated with sample preparation."

Specifically, Fernandez and his students have worked to improve two recently developed analytical chemistry

techniques — desorption electrospray ionization (DESI) developed by Purdue University and direct analysis in real time (DART) developed by the Japanese company JEOL.

The researchers use DESI to screen anti-malarials in hopes of quantifying the amount of the active ingredient artesunate in counterfeits. In DESI, researchers use a high-speed, charged spray containing alcohol and water. Typically, this solvent mixture reacts with a solid sample, such as a tablet, picking up molecules from its surface and transferring them to a detector. But artesunate is a relatively unstable molecule that fragments easily and causes DESI to lose its sensitivity. So Fernandez and his students have now added an alkylamine compound to the alcohol-water mixture to form a stable molecular species, preventing artesunate fragmentation and thereby increasing sensitivity. They call this process "reactive DESI."

DART, on the other hand, involves an ionizing beam of marginally stable helium atoms generated by an electric discharge. The DART ionization mechanism is still not completely understood. In ongoing research, Fernandez and his students are working to interface DART with other instruments to help understand the chemistry behind the methodology. To date, they have interfaced DART with a mass spectrometer, but the latter is typically too bulky and expensive to use in a field setting. So researchers plan to interface DART with a similar instrument called an ion mobility spectrometer (IMS), which is used in airports to detect explosives. They hope the pair of techniques could be used in the field to screen solid samples of anti-malarial drugs.

"Our findings not only demonstrate the usefulness of DART for rapid screening of counterfeit drugs, but also have unprecedented implications for malaria control," Fernandez and his co-authors report in *ChemMedChem*. "We foresee that both DART and DESI will have a tremendous impact in a variety of scientific fields, ranging from drug quality control, screening and discovery to biological applications, such as metabonomics and/or proteomics."

@ Read online at: gtresearchnews.gatech.edu/newsrelease/detect-fakes.htm

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BY JANE M. SANDERS

therapy (ACT) has increasingly become the first-line malaria treatment in Africa. Authorities estimate that 130 million courses of ACT will be used in Africa in 2006.

“The high cost and shortage of ACT provide a favorable situation for the spread of fake artemisinins that could put the lives of thousands of African children at risk,” the authors write. They urge authorities to implement tighter controls on drug importation, as well as a subsidy of up to \$500 million a year to ensure that ACTs provided through the private sector are relatively inexpensive and locally affordable so there is no financial advantage in unwittingly purchasing a fake.

“It will be an avoidable tragedy if a lack of political will and action allows fake artesunate to compromise the hope that artemisinin derivative-based combination therapy offers for malaria control in Africa and Asia

and results in the emergence and spread of resistance to the artemisinin drugs, shortening the useful life of these vital medicines,” the authors add. “As global efforts to control malaria rely heavily on these drugs, these issues deserve urgent action to prevent a public health disaster in the malarious world.”

In related research, several of the authors, led by Fernandez, are studying new, high-throughput screening techniques to detect and quantify the contents of counterfeit anti-malarial drugs and other fake pharmaceuticals. This research will be published in an upcoming edition of the journal *ChemMedChem*.

@ Read online at: gtresearchnews.gatech.edu/newsrelease/fakes.htm

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LEFT: Georgia Tech Assistant Professor Facundo Fernandez, back row left, works with his students Leonard Nyadong, first row; Carrie Pierce, second row; Arti Navarre, third row left; Christina Hampton, third row right; and Mark Kwasnik, back row right. They are creating high-throughput screening techniques to detect and quantify the contents of counterfeit anti-malarial drugs.

PHOTO BY GARY NEEK

