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The debate goes on over China's ongoing production of malaria monotherapy, which is thought to promote drug resistance.

**Jane Wu**

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**Source: SciDev.Net**



Manufacturing of artemisinin-derived drugs in China

It is a godsend for half a billion malaria patients in Africa, tens of thousands of farmers in Asian countries and a range of drug companies. But the unique medical and commercial value of the **herbal extract artemisinin** have made it a contentious issue in China.

**Artemisinin, considered the most efficient treatment for malaria**, is the source of a stand-off between the World Health Organization (WHO), Chinese drug companies and the Chinese government.

In March the Wall Street Journal reported that the WHO was urging the Chinese drug company Kunming Pharmaceutical Corp. to stop producing its artemisinin monotherapy. Using artemisinin alone is thought to trigger resistance to the herb's action in malaria parasites.

**According to the journal, Kunming says that the WHO lacks evidence for the mechanism of resistance and is simply trying to remove Chinese companies from the artemisinin market.**

Last week (26 April) the WHO and Kunming officials met in Geneva for face-to-face negotiations. By the second day, news came that a 'positive' result had been reached.

According to Andrea Bosman, medical officer with the WHO's global malaria programme, Kunming has agreed to stop producing or selling oral artemisinin-based monotherapies by the end of this year.

"By October, they will stop producing or selling capsule or tablet monotherapies," Bosman told SciDev.Net.

Kunming has yet to make an official comment. But if a compromise has been reached it could be the first step to resolving a long-standing dispute.

Chinese origins

***The Chinese have used artemisinin, derived from the herb Qinghao, for thousands of years.***

In the 1970s hundreds of Chinese scientists researched ways of isolating the compound in order to protect Chinese soldiers from malaria during the Vietnam war. They successfully developed the drug, but due to a lack of patent law at the time, failed to establish a patent for it.

Then in 1990, in an effort to combat spreading resistance to the drug, the WHO recommended that artemisinin be used only in combination with other anti-malarials.

Chinese scientists have subsequently developed an artemisinin-based combination therapy (ACT) called Coartem. This remains the only fixed-dose combination therapy for malaria approved by the WHO.

Qinghao

Credit: Scott Bauer/US Agricultural Research Service

***Swiss drug firm Novartis acquired the rights to market the therapy outside China in 1994. Chinese companies continue to supply the raw material for the drug to Novartis, and China continues to hold a domestic patent for the therapy.***

But Chinese companies still produce artemisinin monotherapies alongside ACTs to meet the huge demand for cheap monotherapies in the developing world.

An official with the Ministry of Commerce, who asked to remain anonymous, said China currently controls about a third of the global market in artemisinin monotherapies. The rest is shared by African and Asian countries using Chinese production methods.

Kunming sold about US\$5 million worth of its monotherapy in 2004, according to Yu Zelin, general director of international trade at Kunming.

The Chinese authorities back the sale of monotherapies, saying that the WHO must allow them to exist alongside ACTs for a longer period of time.

"Monotherapy is still in great demand," says Yang, a government official in the malaria programme, who asked to be referred to only by his surname. And that demand is not only fuelled by the desire for financial gain: for many, worries about resistance are unfounded.

Antimalarials and resistance

"Generally speaking, combination therapy is more effective than single therapy. But any drug which has been frequently used will contribute to resistance," Zhu Dayuan, the Shanghai-based scientist who invented Coartem, told SciDev.Net.

***Zhu says there is "no scientific proof that combination therapies will have less possibility of incurring resistance" than monotherapies.***

But a number of published studies report on how malaria monotherapies can result in resistance.

In 2005, The Lancet published research from an international team that found emerging resistance to artemisinin in West Africa.

Lead researcher Ronan Jambou, of the Pasteur Institute, Senegal, says that lowered sensitivity to artemisinin in the malaria parasite was related to mutations in a gene called *serca*, which is known to be sensitive to this class of compound.

The same study found no resistance in parasites in Cambodia, which was only using artemisinin in combination with other therapies at the time of the study. This led Jambou and colleagues to believe that the parasite is less likely to develop resistance to combined therapies than to a drug used in isolation.

There is a huge demand for monotherapies in the developing world

Credit: WHO / TDR / Crump

However, Yan Xiaohua, vice president of Shanghai Fosun Pharmaceutical, told SciDev.Net that a few cases of resistance cannot produce a general rule.

"We support the WHO's resolution on combined therapies," Yan said. "But monotherapies also have advantages that the WHO should not ignore."

***Monotherapies are less toxic*** than ACTs, making them vital for vulnerable groups such as pregnant women or babies, said Yan. He added that the WHO still purchases thousands of doses of artemisinin-based monotherapies for such groups.

Last year, the WHO told 18 pharmaceutical companies around the world to stop marketing artemisinin monotherapies, again citing the need to combat resistance to the compound.

While the Chinese Ministry of Health agrees with the WHO that combination therapy is necessary for optimal treatment of malaria, it points out that it is the misuse of drugs — not proper use under prescription — that often leads to the development of resistance.

Chinese companies, including Kunming, are unhappy with the WHO's decision. Some dispute the WHO's emphasis on artemisinin resistance. Others argue that artemisinin-based drugs are the inventions of Chinese scientists and that the WHO is denying them a share in the market.

And there are further suggestions that the WHO's decision favours Novartis, which some claim has made a huge profit out of the Coartem ACT.

Coartem: profitable or not?

Novartis insists that it sells Coartem at cost price and has made no profits out of it.

"They [Chinese monotherapy producers] may think Novartis has made a lot of money out of Coartem, but our company does not think so," says Liu Tianwei of the China International Trust and Investment Corporation (CITIC) Group, who represent Novartis in their Coartem licensing deals .

Liu says Novartis produced 33 million doses of Coartem in 2005, nine million of which were sold to the WHO. In 2006 it sold 62 million doses to the WHO, with a sales value of about US\$170 million. This year's sales should equal that.

To date, Novartis has invested about US\$100 million to expand sales of Coartem, according to Liu.

In 2001 the company reached an agreement with the WHO to sell Coartem at a price of US\$2.4 per dose.

"If Novartis wanted to make big profits it should have sold Coartem in private markets, where the price per dose can be US\$10," he said.

He added that over the years, the deal has brought profits of approximately 50 million yuan (US\$6.5 million) to Chinese companies that supply raw materials to Novartis — including Kunming.

***But the Chinese Ministry of Health has other views.***

***"Novartis has made huge profits. It sells the drug at a higher price than its cost price," says Yang.***

***He added that the Swiss company has made about US\$100 million from Coartem this year.***

From mono to combination

The Ministry of Health has also cast doubt on the WHO's standards for drug approval, as it has been several years since it approved any combination therapy apart from Coartem.

"China is so far simply a supplier of raw materials, though we have actually developed several new and effective combination therapies," says Yang, adding that the WHO guidelines for malaria treatment need to be updated to allow for new therapies.

Kunming, for example, has developed its own ACT called Acro, which, according to the Wall Street Journal, WHO officials recognise as a promising drug.

At the showdown meeting with Kunming last week, the WHO encouraged the company to submit related materials about Acro so that the organisation could begin to review the new medicine.

"The company has agreed to make every information about the new medicine available to the WHO," Bosman told SciDev.Net.

He added that Kunming also asked advice about the methods used in the WHO's review of ACTs. Acro still needs further research before it can be approved.

However, Ma Weipeng, a senior member of Kunming's research and development division, told SciDev.Net that WHO approval is not necessary for the company to sell Acro abroad.

"We can register a qualification certificate individually in local drug administrations to boost our sales," said Ma.

Strangely, the success of Acro may end up aiding the WHO's quest to stop monotherapy production.

## The future of artemisinin

While Kunming is negotiating with the WHO, other Chinese artemisinin manufacturers are quietly developing new ACTs and artemisinin-based treatments for diseases other than malaria.

Shanghai Fosun Pharmaceutical is joining forces with scientists in the Chinese Academy of Sciences to develop a new anticancer drug based on artemisinin. "We will begin clinical tests shortly, and we believe it will be a very promising drug on the market," said Li Ying, a researcher with Shanghai Institute of Materia Medica under the Chinese Academy of Sciences.

Whatever the outcome of the WHO's negotiations, artemisinin will, it seems, be staying in the pharmaceutical arena for a long time to come, and in ever-changing guises.

## UNITED STATES FINANCIAL INVOLVEMENT

### GLOBAL FUND

*dramatically increase resources to fight three of the world's most devastating diseases*



Since its creation in 2002, the [Global Fund](#) has become the dominant financier of programs to fight AIDS, TB and malaria, with US\$ 10.4 billion in firm pledges and approved funding of US\$ 7.6 billion for 450 programs in 136 countries. So far, programs supported by the Global Fund have averted 1.8 million deaths through providing AIDS treatment for 1.1 million people, TB treatment for 2.8 million people, and through the distribution of 30 million insecticide-treated bed nets for the prevention of malaria worldwide.

PRESIDENT BUSH - highly treatable and preventable

*"The toll of malaria is even more tragic because the disease itself is highly treatable and preventable. Yet this is also our opportunity, because we know that large-scale action can defeat this disease in whole regions. And the world must take that action." June 30, 2005*



President Bush announced the [President's Malaria Initiative](#) (PMI) in June 2005. A five-year, \$1.2 billion program, PMI challenges the private sector to join the U.S. government in combating malaria in 15 of the hardest-hit African countries. PMI's goal is to cut malaria's mortality rate by 50 percent in these target countries, freeing the citizens of these African nations from the grip of this debilitating disease.

In his [State of the Union address](#) on January 23, 2007, Bush said to Congress "I ask you to provide \$1.2 billion over five years so we can combat malaria in 15 African countries." This is part of his overall request to spend \$15 billion through the President's Emergency Plan for AIDS Relief and the Millennium Challenge Fund. Although concerns remain about some strings attached to getting those funds, the administration is moving in the right direction. Since 2001, developmental and humanitarian aid to Africa has grown from \$1.4 billion to \$4 billion annually.

### Target Countries and Funding

Angola, Tanzania, and Uganda – 1st round countries

Malawi, Mozambique, Rwanda, and Senegal – 2nd round countries

Benin, Ethiopia\*, Ghana, Kenya, Liberia, Mali, Madagascar, and Zambia – 3rd round countries

2006: \$30 million for 1st round countries

2007: \$135 million for 1st and 2nd round countries

2008: Projected \$300 million for all countries

2009: Projected \$300 million for all countries

2010: Projected \$500 million for all countries

## WORLD BANK - boosting its support



The World Bank is substantially boosting its support to combat malaria, a dangerous disease which kills more than 3,000 people a day in Sub-Saharan Africa, with a new approach to support malaria control entitled "Rolling Back Malaria: [The Global Strategy and Booster Program](#)", which will make funding available to countries to enhance existing programs to combat the disease.



NATIONAL INSTITUTE OF HEALTH - 41 percent of the world is at risk

Africa Malaria Day, April 25, 2006, commemorates Africa's struggle to fight malaria and marks the six-year anniversary of the first [African Summit on Malaria](#). On that occasion, leaders from 44 malaria-affected African nations and founding agencies of the global Roll Back Malaria Partnership gathered in Abuja, Nigeria, to deliberate on the struggle to fight malaria. The summit culminated in the historic signing of the Abuja Declaration, which committed governments to an intensive effort to halve the burden of malaria in Africa by 2010 and mark April 25 as Africa Malaria Day. Worldwide, an estimated 300 to 500 million clinical cases of malaria occur each year, resulting in an estimated one million deaths annually in Africa alone. This age-old scourge is endemic to more than 90 countries, putting at least 41 percent of the world's population at risk for malaria infection.

## BILL GATES - one of the world's richest people gives \$766 million



Including the latest pledge, the [Gates Foundation](#) has committed US\$765.8 million to fight malaria to date...The Bill & Melinda Gates Foundation today announced that they would contribute \$500 million to the Global Fund over the next five years, and would make \$200 million of this available for the upcoming sixth funding round for which countries are currently applying. While this contribution is a welcome addition to the Global Fund's capacity to fight the biggest infectious killers of our time, it is only a small portion of the total global need – \$31.2 billion annually by 2010 for AIDS, TB and malaria.



By **Rita Rubin**, USA TODAY

## Put the kettle on: Tea is steeped in health benefits



How refreshing.

Tea, something that people around the world enjoy consuming, might actually be good for you.

"The most fascinating thing is, to my knowledge, there is no other natural product known that has such diversified effects," says Hasan Mukhtar, vice chair of dermatology at the University of Wisconsin-Madison.

Health benefits have been attributed to tea, especially green tea, nearly as long as people have been drinking it, Mukhtar and his co-authors write in the July issue of the journal *Life Sciences*. But, they note, scientific investigations of tea and the compounds found in it began less than 30 years ago, and most have been conducted in just the past five years.

Name the ailment, and research suggests tea might protect against it. Most of the studies are either population-based — for example, research shows that prostate cancer is less common in countries where people drink a lot of green tea — or in lab dishes or animals, none of which provide conclusive evidence for humans. But Mukhtar and other tea researchers point to tea's 5,000-year track record of safety and say at the very least, drinking tea can't hurt, and, most likely, it can help.

U.S. sales figures from the Tea Association suggest that, despite the dearth of human studies, many Americans already regard tea as a health drink. Last year was the 15th consecutive year that consumers bought more tea than ever, says the trade group. Retail supermarket sales neared \$2 billion in 2006, the group says.

Green tea seems to have more health cachet than black tea, perhaps because it has been the focus of more research. Although not as well-studied as green tea, black tea probably is at least as beneficial, says Mukhtar, who drinks two cups of black tea and two of green a day.

Tea polyphenols, compounds with antioxidant activity, may protect against heart disease and a variety of cancers, Mukhtar says. His own research has shown that green and black tea, when substituted for drinking water, inhibits the growth of human prostate cancer cells implanted in mice. In addition, Mukhtar has reported that topical application or ingestion of green tea polyphenols protects against skin cancer in mice.

Human clinical trials by Iman Hakim, a professor at the Arizona Cancer Center at the University of Arizona, suggest that compounds in green tea positively affect genes involved in cancer susceptibility and DNA repair, although not everyone will respond equally well.

Also, Hakim says, an ongoing clinical trial of former and current smokers with chronic obstructive pulmonary disease has found a "significant improvement" in levels of HDL, or good, cholesterol in volunteers given tea as opposed to a placebo drink.

"If tea proves to be good, it might be good to switch the kids to tea," says Hakim, who notes that tea contains less caffeine than coffee does.

John Foxe says he gives his 3-year-old six or seven cups of milky tea a day. Foxe, professor of neuroscience, biology and psychology at City College of the City University of New York, has conducted clinical trials of theanine, an amino acid in tea that, unlike polyphenols, is small enough to cross the blood/brain barrier. It is present in equal amounts in black, green and oolong teas.

"Probably quite a lot of people have heard tea has cardiovascular effects," says Foxe, whose work was financed by Unilever, maker of Lipton tea. "But that's not why people drink tea. They drink it because it makes them feel good."

At an international symposium on tea and human health last month in Washington, Foxe reported that people who drank a solution containing about as much theanine as 10 cups of tea were able to focus better on tasks than those who drank a placebo solution.

More recently, Foxe says, he has found that as little as 100 milligrams of theanine enabled people to focus better on complicated tasks, but only when consumed with 60 milligrams of caffeine — a combination found in roughly four cups of green tea (which contains half as much caffeine as black).

"There was a profound synergistic effect," he says. "My take is, we're all self-medicating with this."

Just because drinking tea might be good for you doesn't mean adding tea extract to cereal and other foods or to dietary supplements is beneficial. "A lot of that is gimmick," Mukhtar says of products that tout tea extract as an ingredient.

A paper published in April suggests one danger of such products with high doses of green tea extracts. "There are quite a few case reports on liver damage due to taking supplements that contain tea extracts," says biochemist Chung Yang, a Rutgers University cancer researcher who co-wrote the paper in the journal *Chemical Research Toxicology*.

Liver function returned to normal when those affected stopped taking the supplements, Yang and his co-authors write. In addition, they say, studies in rodents and dogs suggest that high doses of tea catechins can damage the kidneys and intestine as well as the liver.

Tea drinkers shouldn't worry, though, Yang emphasizes: "It's very clear, there are no published reports concerning toxicity due to tea consumption."

**[http://www.usatoday.com/news/health/2007-10-07-tea-benefits\\_N.htm](http://www.usatoday.com/news/health/2007-10-07-tea-benefits_N.htm)**

## INTERNATIONAL PERSPECTIVE

**Wormwood:** This treatment for malaria was, however, lost over time. It was only rediscovered in an archeological dig in the 1970s where its medicinal use was found in a recipe inside a tomb. The formula was dated back to 168 B.C. where the Chinese chemist isolated the primary active ingredient from the leafy portion of plant called *A. annua* L. In 1972, scientists in the West called this crystalline compound "qinghaosu" or "artemisinin". Since then, studies in China and Vietnam have confirmed that artemisinin is a highly effective compound with close to 100 percent response rate for treating malaria. It has the ability to destroy the malaria parasite by releasing high doses of free radicals that attack the cell membrane of the parasite in the presence of high iron concentration. In fact, over **one million malaria patients have been cured via this method**. Their symptoms also subsided in a matter of days.

<http://www.drlam.com>

*Michael Lam, M.D., M.P.H., A.B.A.A.M.*

Malaria is a vector-borne infectious disease caused by protozoan parasites. It is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa. Each year, it causes **disease in approximately 650 million people and kills between one and three million**, most of them young children in Sub-Saharan Africa.

Malaria is commonly-associated with poverty, but is also a cause of poverty and a major hindrance to economic development.

Malaria causes about 400–900 million cases of fever and approximately one to three million deaths annually — this represents at least one death every 30 seconds.

The vast majority of cases occur in children under the age of 5 years pregnant women are also especially vulnerable. Despite efforts to reduce transmission and increase treatment, there has been little change in which areas are at risk of this disease since 1992] Indeed, if the prevalence of malaria stays on its present upwards course, the death rate could double in the next twenty years. **Precise statistics are unknown because many cases occur in rural areas where people do not have access to hospitals or the means to afford health care. Consequently, the majority of cases are undocumented.**

*From Wikipedia Eencyclopedia*

### The Current Global Picture

Malaria is a public health **problem today in more than 90 countries**, inhabited by a total of some 2,400 million people - 40% of the world's population. Worldwide prevalence of the disease is estimated to be in the order of 300-500 million clinical cases each year. More than 90% of all malaria cases are in sub-Saharan Africa.

**Mortality due to malaria is estimated to be 1.5 to 2.7 million deaths each year.** The vast majority of deaths occur among young children in Africa, especially in remote rural areas with poor access to health services. Other high-risk groups are women during pregnancy, and non-immune travelers, refugees, displaced persons and laborers entering endemic areas. Malaria epidemics related to political upheavals, economic difficulties and environmental problems also contribute in the most dramatic way to death tolls and human suffering.

<http://nobelprize.org>

## Malaria

### The issue

Malaria is a common and life-threatening disease transmitted by mosquitoes, currently endemic in over 100 countries. Each year, more than 500 million people suffer from acute malaria resulting in more than 1 million deaths – approximately 90% of these in sub-Saharan Africa. Children under 5 years of age account for 82% of all malaria deaths, and every day close to 3000 children die of the disease. Malaria has lifelong effects on cognitive development, education and productivity levels. The disease causes an average loss of 1.3% of annual economic growth in countries with intense transmission. The evidence shows that malaria is not a consequence of poverty but a cause of continuing poverty.

### The opportunities / the solutions

- Malaria is both preventable and curable. Providing access to effective treatment and simple preventive measures, such as insecticide-treated nets (ITNs) and indoor residual spraying, will help to achieve the goal of controlling malaria.
- Global investments in malaria such as the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria, the World Bank Booster Program, US President's Malaria Initiative, and others increased steadily from 1998–2005.
- Countries are recognizing the importance of changing policies from ineffective single-drug therapies to effective treatment such as artemisinin-based combination therapies (ACTs).<sup>1</sup> They are also implementing programmes to protect households with long-lasting insecticidal nets<sup>2</sup> and conducting indoor residual spraying campaigns to control vector mosquitoes.

### The challenges

- Many programmes are lagging behind as countries do not have sufficient managerial and technical skills and lack capacity to absorb the funding.
- While there are specific goals for malaria control, there has been no clear strategy on how to achieve targets and measure progress/impact. Without developing consensus on a comprehensive strategy, the effort by many partners will not be effective.
- Malaria needs funding both for commodities and for technical assistance to countries. Effective technical assistance will ensure that commodities are distributed and used appropriately and that the money helps to achieve longer-term goals.

### The costs

- On average it will cost US\$ 3.4 billion a year to effectively reduce the malaria burden. Resources still fall short of what is needed – the gap worldwide is approximately US\$ 2.7 billion a year.
- The WHO's newly created Global Malaria Programme (GMP) has a funding gap for 2006–2007 of US\$ 80 million.

## **MISDIRECTED EFFORTS**

2006

### ***The simple herb is converted to a synthetic - big business to profit***

Norvatis in partnership with East Africa Botanicals (EAB) is in the process of popularising the growing of the Chinese herbal plant, *Artemisia annua* (or qinhao), from which, Artemisinin molecule is derived.

The World Health Organization (WHO) describes Artemisinin derivatives as the most effective and the last hope in the near future in the battle against malaria whose parasite has developed resistance to all known drugs.

This is good news to Kenyans and sub-Saharan African people who have expressed jitters since the WHO pre-qualified Artemisinin derivative drugs as the only potent drugs against malaria, a disease that continues to kill people in their thousands annually and leading to loss of millions of man-working hours.

In Kenya, malaria is the leading cause of mortality and morbidity, particularly among pregnant women and children under five years of age.

Statistics from the Ministry of Health suggest that between 20 - 25 percent of all deaths can be attributed to malaria, which also accounts for up to 30-50 percent of hospital admissions.

Up to 28 million Kenyans (70 percent of the population) are at risk and at any one time 1.5 million pregnant women are susceptible particularly in Western, Nyanza and Coast.

Norvatis, a Swiss pharmaceutical and principle player in ACTs, saw net profits rise to \$2.17 billion from \$1.96 billion in the first quarter of 2006, beating analysts' forecasts for \$1.8 billion. Sales rose 18 percent to \$9.82 billion.

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<http://www.ibtimes.com/articles/20070423/earns-novartis.htm>

*Information taken from*

***Kenyans to reap from 'Chinese' malaria herb***

*By HENRY NEONDO*

*Kenya Times 2006*

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