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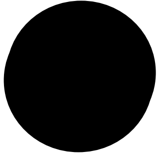

Lethal Counterfeits

Paula Park

The border between Thailand and Cambodia is a petri dish for drug-resistant strains of malaria. Scientists believe that in this region, more than 50 years ago, parasites that cause the disease mutated to fight a common anti-malarial drug, chloroquine, and multiplied. People carried these new parasite strains across the world, spreading the drug resistance. Today, these same borderland parasites show new signs of resistance. This time, it's to a combination of drugs, including one called artesunate, that had, until recently, made inroads against the spread of the disease. In 2004, the Cambodian government found that nearly one in five cases of artesunate sold by retailers in four provinces bordering Thailand lacked sufficient amounts of the active ingredient. Six years later, Cambodian health officials cracked down on the distribution of these counterfeits. By April 2010, officials had closed two-thirds of the country's 1,081 illegal retail shops, the main sellers of fakes.

"Closing down the illegal outlets is certainly going to have an effect on the availability of substandard drugs in the market," says Patrick Lukulay, manager of drug quality for the United States Pharmacopeia Convention (USP), which provided technical assistance to the Cambodian government. "More importantly, because there will be fewer substandard medicines…the efficacy of the good drugs" will be improved. The hope is that these measures did not come too late.

Scientists still do not fully understand the mechanisms of drug resistance, but they do believe that drugs with inadequate levels of active ingredients encourage mutations. The same goes for medicines that were improperly made or expired. As Chris Drakeley, the director of the Malaria Centre at the London School of Hygiene and Tropical Medicine, puts it, "Suboptimal concentrations of the drug just don't kill everything."

The malaria parasite replicates so quickly that the genes left unscathed by a low dose of medicine change and multiply rapidly, creating what is essentially a new strain. But the medicine was designed for the original mutation. Drakeley says that scientists have not yet seen evidence that full-fledged resistance has developed along the Thai-Cambodian border. Still, the parasite does seem to be developing a tolerance to the drugs.

A Global Curse

An estimated 243 million people worldwide contracted malaria in 2008, according to the World Health Organization's (WHO) most recent global count. Nearly 1 million died. Eighty-five percent of the victims were chil-

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dren. The spread of drug resistance is one of a handful of reasons why malaria has been so difficult to contain. Cambodia's experience with fake antimalarials contains all the elements of a tragedy that's repeated across the globe. A disease that kills the poor and the weak grows until a drug is created to stop it, but the proliferation of substandard or falsified counterfeit drugs breeds a resurgence of the disease.

The range of counterfeits is vast. Authorities have seized shipments ranging from pain relievers and heart medicines to cancer drugs. Fake lifestyle drugs such as sexual stimulants and obesity treatments are commonly sold over the Internet, where governments can't stop the trade. (Though there is a system to accredit web-based drug distributors in the United States.) Wealthier nations and the wealthiest people in poor nations purchase branded drugs that are controlled and monitored by skilled regulators. But the poor in developing countries often buy cheap tablets or capsules from unregulated shops like those shut down in Cambodia. In markets, the bootleg trade still proliferates. Cambodian researchers found street sellers offering sets of four or five drugs, including artesunate, in plastic bags. "In the market, people can choose the drug that is cheapest," says Duong Socheat, director of the National Center for Parasitology Entomology and Malaria Control in Phnom Penh.

According to the WHO, it's difficult to quantify the production and sale of counterfeits because they go undetected in countries that lack adequate enforcement. The six-year gap between the Cambodian government's drug market survey to the eventual shop closures is a common scenario played out in countries struggling to build effective public regulatory agencies. The Pharmaceutical Security Institute, an organization of pharmaceutical company security officers, documented 2,371 counterfeit seizures in 2009, nearly twice the 1,500 documented in 2006. Some 48 percent of the cases involved more than 1,000 doses of a single drug. The increased detection reflects, in part, an international program aimed at helping developing countries stanch the counterfeit trade. Led by the WHO, the International Pharmaceutical Manufacturers Association and Interpol, the International Medical Products Anti-Counterfeiting Taskforce (or IMPACT), provide financial and technical support to help developing countries create laws and regulations that can be used in court to prosecute counterfeiters. The task force also trains inspectors and police, and coordinates cross-border crackdowns on manufacturers and distributors.

Last year, in a five-month operation coordinated by Interpol, officials in eight Southeast Asian countries seized 20 million doses of illegal medicines, arrested 33 people and closed 100 retail outlets. Similar operations by domestic or international teams have closed shops for counterfeits in Syria, Egypt, Tanzania and Palestine. In April, Interpol launched another Southeast Asian cross-border operation—its third in two years. Despite such successes, authorities say they've done little more than harass the counterfeiters. "I can't say that we are stopping the trade," says Aline Plançon, head of medical products counterfeiting and pharmaceutical crime for Interpol. "So far, we are only disrupting it."

Defying Detection

Counterfeiters are organized criminals. To create, package and distribute drug look-alikes they depend on sophisticated techniques and effective networks. Trade mimics the supply chain for legitimate drugs, incorporating manufacturers, wholesalers, shippers and retail operations. Known organized criminal or extremist groups may be linked to some parts of the chain, but the counterfeit network extends beyond any one gang. "It's a new kind of international criminal business," Plançon says.

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Not all criminals work out of Paddington station.

The products sold on the street—at the very end of the chain—are quite sophisticated. In some countries, for example, counterfeit antimalarials use active ingredients such as pain relievers. These medicines reduce fevers and ease symptoms, tricking the user into believing the product is working. But pain relievers don't stop the deadly parasite from multiplying, making people sicker and more susceptible to complications that could kill them. Authorities have seized mountains of packaging that replicates the kind used by legitimate pharmaceutical companies. Even trademark imprints similar to those used on legal drugs adorn tablets and capsules sold by criminal sellers. The groups range in size from small domestic operators to vast cross-border crime networks, making the trade all the more difficult to track. Some manufacturers in rural China operate factories right out in the open, Plançon says. Others are harder to root out. Occasionally, counterfeit drugs slip into legitimate drug-selling networks, in Europe or North America, but the problem is most intense in developing countries, where enforcement is difficult.

An ongoing drug counterfeiting trial in Nablus, in the Palestinian Territories, reveals the workings of a drug counterfeiting network involving at least 15 people, including 14 charged with "circulating and dispensing harmful drugs and medicines that are not used in the market," according to the indictment. One of the criminals is charged with printing more than 1,000 fraudulent drug labels. In the center of Nablus, the Thulathiya Company employs 500 people and operates a retail pharmacy in the center of town. Nablus prosecutor Baha Al-Ahmad says that in 2008, investigators raiding the pharmacy seized fake heart medicines and pain killers. Investigators also found drug-making equipment in the offices of Thulathiya manager and partner Bakr Abu-Hijleh, though he had a per-

mit only to sell pharmaceuticals, not to make them, according to the indictment. Abu-Hijleh and his 13 partners and associates are also charged with money laundering. Prosecutors say the partners distributed the proceeds from the fake pharmaceuticals by buying a cancer and blood-disease center in one Nablus hospital, and a 20 percent share of a second hospital. The defendants then sold the fake drugs to patients in the hospitals, according to the indictment, which states: "These dangerous, spoiled, falsified, stolen and smuggled drugs were used and consumed by Palestinian citizens causing the death of many persons."

Abu-Hijleh claims that the counterfeits were made and distributed by companies outside the country, and points out that the Syrian government has recently seized false drugs and closed an illicit drug-making factory. Abu-Hijleh also attributed his problems with the law to a competing drug company, saying that the owner may have improperly influenced the police and prosecutors to unfairly persecute Thulathiya.

What Crime?

A major stumbling block in coordinating action against drug counterfeiters is the disagreement over how to define the crime—whether it is a breach of intellectual property law or a crime against persons. Generic manufacturers and branded pharmaceutical drug makers such as Pfizer and Novartis (big companies that invest billions of dollars in drug research and production) have a serious stake in this debate. On May 19, Brazil and India requested a World Trade Organization consultation with the Netherlands and the European Union over the 2008 and 2009 seizures of around 20 shipments of generic drugs, including a high blood pressure medicine called losartan potassium, which was in transit through Rotterdam and bound for Brazil from India. The compound is used in a drug called Cozaar, created by Merck, which was under patent protection in the EU, but not in Brazil or India. The consultation request coincided with the May 17-21 World Health Assembly, where the WHO hammers out global polices and plans. Both India and Brazil objected to the WHO classification of counterfeit drugs as mislabeled products, and their objections prompted an open letter to the WHO, signed by 47 non-governmental organizations, including Oxfam International. The letter questions the International Pharmaceutical Manufacturers Association's "central role" in IMPACT as well as its "transparency" and the absence of rules on disclosing real or perceived conflicts of interest. The letter also says that anti-counterfeiting regulations can be used to block imports of generic drugs—key low-cost treatments for developing countries.

International Pharmaceutical Manufacturers Association spokesman Guy Willis says "the people who are raising the concerns about interference with the generic case are overstating" the problem. Generic and branded drug company interests coincide on counterfeits because criminals also sell falsified generic drugs. The pharmaceutical manufacturers launched a media campaign targeting counterfeiting in May, opening with the observation that, "Medicine counterfeiting is first and foremost a crime against patients." Willis also points to the industry's assistance to developing countries, which he says totaled $9.2 billion from 2000 to 2007, the last year for which statistics are available.

In response to concerns voiced by Brazil and India, the WHO created a working group to decide whether to redefine counterfeits and investigate its role in preventing the spread of "substandard/spurious/falsely-labeled/falsified/counterfeit medical products." For regulators in developing countries, the terminology has serious consequences. Dr. Budiono

Santoso, Western Pacific adviser for pharmaceuticals at the WHO, says the six-year delay in Cambodia's drug crackdown stems in part from problems with terminology. Police don't investigate trade crimes, and the penalties for such crimes usually amount to no more than fines. "Many of the law enforcement agencies are not aware of counterfeits…from the perspective of endangering human life," Santoso says. Legal issues handicap law enforcement in other countries. Syrian authorities arrested 65 fake drug producers and smugglers from April to October 2009, but the laws prohibiting counterfeit drug crimes carried only financial penalties, giving the government little power to stop them. A month ago, the law was changed, says Dr. Reda Saed, Syria's health minister. Now, the crimes can carry penalties of as much as 10 years in prison and millions in fines. "We are fighting back," he adds. "There has been a big campaign from the security forces."

"Disease does not respect borders, and neither do counterfeiters."

Big Bucks

At first blush, the economics of selling false drugs seems fairly transparent: cheap ingredients, high profit margins. An investment of just $1,000 in raw materials can net from $200,000 for the least costly medicines to $450,000 for the most expensive, says Interpol's Plançon. When compared to a $1,000 investment in heroin, which yields around $20,000 in sales, there's little question why criminal organizations have jumped at the trade.

Dr. Hélène Degui, executive director of French-based NGO Centrale Humanitaire Médico-Pharmaceutique, blames globalization in part for a surge in counterfeit drug exports to developing countries. Goods flow in from all over the world, new gadgets and clothes but also bad drugs. "People who aren't informed about fake and real drugs buy the fakes," Degui says. "How can you determine which is the right drug, which is the false drug?" says Roger Bate. A senior fellow at the American Enterprise Institute and an expert on counterfeit drugs, Bate thinks that on the surface it would make more economic sense for criminals to create fake batches of expensive drugs sold in Europe and North America. A single dose of a leukemia medicine, for example, might net around $5,000 compared with a dollar or less for a malaria pill in the developing world. But the leukemia medications are sold under controlled conditions in hospitals, making it harder for counterfeiters to get their products into the supply chain. According to Bate, the broader international market and economics of counterfeit drugs are not well understood. As an analogy, Bate describes a bar of beauty soap he discovered in a market in India, wrapped in cardboard with an image that replicated those on branded soap packages. The branded soap cost barely 25 cents. The counterfeit cost even less. The product itself is much cheaper to make because it contains little or none of the ingredients designed to soften skin. The counterfeiters "have to be making millions of those to make a profit," Bate says. "That's one of the reasons it's so scary, they are continuing to find markets for drugs that they are selling for less than a dollar."

Control and Collaboration

Disease does not respect borders, and neither do counterfeiters.

In May, a Pfizer-sponsored study found that Western Europeans spend around $14.3 billion a year on medicines sourced outside the regulated channels; many are counterfeits. Low levels of counterfeits even slip into the tightly controlled U.S. drug system through online retail outlets and direct mail. The U.S. Immigration and Custom Enforcement agency seized counterfeit or substandard drugs valued at more than $2.7 million from 2003 to October 2009. Some 87 arrests have resulted in 90 convictions. The fake medicines originate outside American borders, but Peter Pitts, president of the Center for Medicine in the Public Interest, says that eventually the counterfeiters will move into the world's biggest economy in a significant way. "These are businessmen, and they understand the economics of their business," Pitts says. Cracking down on the trade in developing countries will reduce the spread to developed states.

"Countries must control what they let into the market—and should know what's actually in the market," Sabine Kopp says. As quality assurance and anti-counterfeiting programs manager for the WHO, she oversees the global strategy to combat the trade. Health officials alone can't stop criminals from selling bad drugs, and police aren't trained to identify the chemicals in a compound or analyze a compound's health effects. Neither can be effective unless the legal system offers penalties that hold manufacturers and suppliers accountable for the severity of their crimes. Countries that work together have a better chance of scuttling the trade. Plançon advocates systematic capacity building, country-by-country. This means creating new laws, training police to enforce them and funding consistent policing of the drug markets, by both police and health officials. Interpol and the WHO lack funds to create an international system of enforcement, which is necessary to break down the trade. Plançon estimates another $10 to $20 million would be needed over the next five years.

Raising awareness among governments, law enforcement agencies and health departments is also key. The Tanzanian Food and Drug Administration publicized a 2008 crackdown that resulted in the seizures of 100 types of substandard anti-malarial and cardiac drugs, as well as the closure of four pharmacies and 18 informal drug shops. Now it continues to publish newspaper and magazine advertisements about drugs on the market and seizures of counterfeits.

To turn successes into sustained drug-control systems, governments have to be as well organized and sophisticated as the criminal drug trade. The Cambodian administration had to learn that lesson over time—six years, in fact. It needed to identify the counterfeit problem, then build a team to collaborate on the closure of the illegal outlets. According to Souly Phanouvong, regional manager for drug quality and information in Asia for United States Pharmacopeia Convention, the Cambodian government blacklisted pharmacy owners who had been warned several times to stop selling substandard drugs. They can no longer work in the industry.

The USP creates standards for food and drug ingredients in the United States, and worked with the Cambodian government to train the very pharmacists found selling substandard drugs because they knew no better. Now, they are taught to inspect suppliers' paperwork for proper registration and examine packages for flaws that indicate they were made by a counterfeiter. The pharmacists also learn to recognize the paperwork provided by the country's legally registered wholesalers and to reject unfamiliar products. It's the kind of enforcement that the WHO and Interpol would like to see replicated around the world. "If you reform the activities of one country, you will definitely touch the other countries," Plançon says. "If you cut one link, it will have implications on every other." ●