Fake drugs: The global industry putting your life at risk

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In late 2012, 60 people died in two cities in Pakistan after drinking cough syrup to get high. Syrups from two separate manufacturers were involved. It was found that both were using an active ingredient – dextromethorphan, a synthetic morphine-like compound – imported from the same manufacturer in India. Indian drug authorities put a halt

to production while they investigated.

Tests in Pakistan revealed that the medicines seemed to contain the correct amount of active ingredient. But further tests revealed something that was not supposed to be there. Levomethorphan, a chemical five times stronger than morphine, was the contaminant that had caused the deaths.

In September 2013, 44 children in Paraguay were admitted to hospital with breathing difficulties. It turned out the children had all been given a locally made cough medicine. Investigators went to the factory and found import records for the dextromethorphan it contained. When they checked the World Health Organization's database of substandard and falsified medical products, they found that this came from the same batch that had caused the deaths in Pakistan.

Doctors in Paraguay were able to administer an antidote and save the children. A WHO alert went out listing the batches from the Indian factory that might be contaminated. By then the ingredient had been transported to multiple countries in Europe, north Africa, the Middle East and Latin America. It had already been made into cough medicines in Colombia and Peru, but these were recalled before they could reach patients. The batch that went to the Middle East could not be traced.

In this case, a blatantly poor-quality medicine was detected because its effects were conspicuous. A more discreet kind of substandard medicine – say, an antibiotic without enough active ingredient – probably stands a strong chance of reaching patients across the world without getting discovered.

This is a story of how the manufacture and distribution of medicines today is such a complex, globalised affair that it is often hard to track where fake or substandard medicines come from and where they go.

This is a story of how these medicines could make you ill or even kill you, even if you don't take them.

The term "poor-quality medicines" is something of a catch-all. It includes "substandards", medicines that have had inadequate quality control or that have degraded from improper storage or the passage of time. And it includes falsified medicines – fakes – that claim to be what they are not. These may not be made by the manufacturer whose name is on the package, and they may not contain the stated ingredients in the stated quantities.

Poor-quality medicines might not work. Like those peddled by Peter Gillespie, who was jailed for introducing 72,000 packets of falsified medicines into the UK's distribution system from 2006 to 2007. 25,000 packets reached pharmacies and were given to patients. These knock-off tablets were used to treat heart disease, pancreatic cancer and mental illnesses, and had none or only part of the active ingredient they were supposed to contain. This meant that those people's illnesses were left to take their course.

Poor-quality medicines can kill you if you take them. As happened with Thomas Rybinski, a 56-year-old autoworker from Tennessee, USA, who got an injection for his back pain in 2012. He fell ill and died because the medicine had contaminants that caused fungal meningitis. The batch of medicine, originating in a New England pharmacy with close to no quality control, ended up causing severe infections in nearly 800 people across the USA, killing 64 of them.

Poor-quality medicines can kill you even if you don't take them. Antimicrobial drugs (including antibiotics and antivirals) that have too little active ingredient are generally accepted to help disease-causing bugs evolve so that they develop resistance to treatment even with good-quality antimicrobials. And then these bugs spread.

Ramanan Laxminarayan is the director of the Center for Disease Dynamics, Economics and Policy in Washington, DC. He says that with some drugs, like statins or arthritis drugs, the effects of poor quality are confined to those taking them. But with antimicrobials, inappropriate use reduces their effectiveness for everyone else. "If there's misuse in South Asia then everyone is affected. It's a problem that comes up when people act in ways that don't take into account the effects of what they are doing on everyone else," he says.

"It's really no different from climate change," says Laxminarayan. "Either in terms of potential global impact, or in the fact that everyone needs to be working together to solve the problem."

The factors that speed up the development of antimicrobial resistance – high rates of infections, the overuse and misuse of antimicrobials, poor sanitation, poor-quality medicines – are more common in low- and middle-income countries, which means that so is resistance. But microbes know no boundaries, and they travel easily across the world, in foodstuffs being exported and in the bodies of humans. And often, resistant microbes can transfer genetic material to each other to become even more dangerous to humans.

The result: infections that were simple to cure, gonorrhoea for example, are back with a vengeance. Conditions like tuberculosis and HIV are getting harder to treat. In the future, routine surgery or cancer treatment could become risky. There is a real danger of returning to a time where any one of us, anywhere in the world, could pick up such an infection and find that medicine is powerless to save us from dying.

At a south Indian restaurant in Delhi, I meet Suresh Sati. He is a large middle-aged man, often larger-than-life in his enthusiasm, who has spent a considerable part of his working life as a private investigator exposing manufacturers of falsified medicines.

His clients were pharmaceutical companies whose products were being faked. Sati would do the legwork to track down fake medicine operations and provide information to the police to conduct raids. He has since become something of a go-to person for researchers, journalists and documentary film makers interested in a close look at the falsified medicine business. "If anyone in India can tell you all about fake medicines, it is me," Sati says, quite matter-of-factly.

Within 15 minutes of sitting down, he has produced so many samples of fake medicines that our tumblers of coffee risk being crowded off the table. He collected them over years of investigations, from raids or from informants in fake medicine distribution networks.

India is one of the largest exporters of generic medicines in the world. Forty per cent of over-the-counter and prescription generics sold in the USA come from India. In the UK, a quarter of all generics come from India, and generics account for 80 per cent of National Health Service prescriptions.

Yet India's pharmaceutical sector is indifferently regulated, and Indian pharmaceutical companies have been pulled up by foreign trading partners for exporting substandard or contaminated medicines. In 2013, the pharma giant Ranbaxy was fined US$500 million for falsifying data and not meeting safety standards; in 2014, Germany suspended 80 Indian products over drug safety concerns.

Further complicating the picture is the fact that different countries have different standards. The same violations that the USA fined Ranbaxy for were brought to the attention of UK authorities, who did not deem them serious enough to punish. In 2014, the chief drug controller of India said to a newspaper: "If I have to follow US standards in inspecting facilities supplying to the Indian market, we will have to shut almost all of those."

Just how common is poor-quality medicine in India? Since these medicines tend to fly under the radar, there is limited official data. A recent WHO study estimated that around 10 per cent of medicines in low- and middle-income countries are of poor quality. In 2017, a nationwide drug survey conducted on behalf of the Indian government found 3.16 per cent of sampled medicines to be substandard and 0.0245 per cent to be fake.

These official numbers, Sati says, don't quite capture reality. At least, not when it comes to fakes. For one thing, he has reservations about the studies' sampling methods. He also says that averages are misleading because some kinds of medicines – painkillers, antibiotics, drugs for heart disease and cancer – are falsified more than others. According to him, the more commonly prescribed they are, the more often they are falsified.

Sati points at one of the boxes in front of him, a ten-strip cardboard container of Zifi 200 – a trade name for the antibiotic cefixime, used for throat infections, urinary tract infections and gonorrhoea. "Now the monsoons are beginning, and people are going to start falling ill. This sells the most. Every doctor is going to prescribe Zifi 200," he says. That makes it a popular target for the fakers.

Extrapolating from what his sources report, he estimates that 40 per cent of the Zifi 200 on the market is fake. The number is hard to verify, and it may not apply to the whole country because Sati's sources operate in Delhi and neighbouring states, but certainly the drug has been mentioned in news reports about seizures of fake medicines.

I ask if I can take a photograph of the packaging. He hands me two of the Zifi 200 strips and tells me to keep them. "There'll be more coming my way," he says. The strips even include verification codes to be sent by SMS to check if the medicine is real. I make a note to buy a strip

from a pharmacy to compare with the fakes.

Sati describes how he once got a distributor-cum-manufacturer to induct him into the racket so he could understand its workings. He pretended to want fakes made of a common brand of painkiller.

From Delhi, they drove to a small manufacturing unit in Sonepat which already had moulds for the tablets, and paid cash in advance for a batch of 100,000. Then they went to a printer in Karnal, who had the design files required to print the strips. They tasked another man with collecting the tablets and delivering them in strips.

In Delhi, Sati had cardboard packaging printed, and stamps made to emboss batch numbers and expiry dates. In a few days his batch of fake medicine was ready. Sati burnt the lot and had the manufacturer raided; he was told he would be shot if he was ever seen in the manufacturer's town.

An important step while getting fakes made, Sati says, is a question that the manufacturer asks: "Which do you want? Full-salt, half-salt or chalk-mitti?" That is, fakes with the stated amount of active ingredient, with only some of the active ingredient, or just chalk dust. Each has a different price.

According to Sati, the practice of adding a fraction of active ingredient to fakes began to be seen in India around 15 years ago, as drug controllers and consumers began to realise that there were fake medicines in the system. Manufacturers of fakes saw it as a way to protect themselves, as the medicines might have some effect and draw less attention. And if they were caught, it allowed them to claim that it was a case of production error rather than outright fakery.

Besides, the simplest tests to detect fakes are colorimetric ones, which

detect the presence of an ingredient but not its concentration. So it was less likely that fakes with some amount of active ingredient would be found out. While this might work well for the manufacturers, it is bad for the patients – who receive sub-therapeutic doses, too low to properly treat their illnesses – and terrible from the perspective of antimicrobial resistance.

"Sub-therapeutic dosing, by definition, contributes to antimicrobial resistance," says Elizabeth Pisani, an epidemiologist and a visiting senior research fellow at the Policy Institute, King's College London.

"Bugs are mutating all the time," she explains. Some of these mutations make the bugs slightly more resistant to drug treatment, but the mutants are usually at a disadvantage among non-mutants because it takes them more energy to reproduce.

Our antimicrobials work most effectively against the non-mutant versions, but a full therapeutic dose further ensures that slightly resistant versions are eliminated too. However, if you have only a fraction of the active ingredient, it's going to knock out the susceptible ones first and there might not be enough left over to knock out the slightly resistant ones. "That creates elbow room for the slightly resistant ones to reproduce because the competition has been wiped out," says Pisani. "And that's how a mutant version becomes a dominant strain."

She adds that falsified medicines with zero active ingredient can contribute to resistance too. People taking blanks will often switch to a next-line antimicrobial drug, thinking that what they've already taken was ineffective. Pathogens then get exposed to a drug that would ideally only be used on rarer, resistant infections.

What is usually measured in testing for fakes and substandards is the amount of active ingredient. But even when medicines contain the

correct amount, not all of it may actually be available for absorption by the body. Pisani says the poor formulation of medicines probably greatly increases the proportion of drugs that are delivering sub-therapeutic doses.

All things considered, Pisani suspects that poor-quality medicines are a significant contributor to antimicrobial resistance. But while laboratory studies, modelling and common sense all point to the link between poor-quality medicine and resistance, it would be hard to study directly in humans. As Pisani puts it, "The way we would normally test those things is in a large human trial, and we can't actually give people crap medicines, right?"

Yet, unintentionally, that's exactly what's happened in recent history.

In the 1950s, malaria was rampant along the Thai–Cambodian border. In an attempt to keep the disease at bay, public health authorities began to pre-emptively distribute chloroquine, the antimalarial drug of choice at the time. By 1960 they were lacing cooking salt with chloroquine in an attempt to administer it to as many people as possible.

But drug-laced salt isn't an ideal way to take medicine. So, of course, it led to large numbers of people receiving sub-therapeutic doses. Chloroquine-resistant parasites began to emerge and spread. Similar patterns were observed in other places in the world where there was mass administration of chloroquine. And by the 1970s chloroquine was essentially useless against the P. falciparum form of malaria.

It's hard to say of course if this is the full story. Paul Newton, professor of tropical medicine and director of the Lao–Oxford–Mahosot Hospital–Wellcome Research Unit at Vientiane, Laos, explains that other factors, such as poor course adherence or flawed prescription practices, may also have played a part.

But chloroquine may be making a comeback now, Newton says. "There's some evidence, from countries like Malawi, that resistance to chloroquine is declining. Maybe in the future chloroquine could be used again, in combination with other medicines."

Yet this hope is threatened by fake antimalarial drugs. Newton says that some fake antimalarials in Asia and Africa contain the wrong active ingredients. There are antimalarials that are not supposed to contain chloroquine but do. Parasites in patients that take them get exposed to drugs they shouldn't be – and start building resistance, without our knowledge. Worse, other fake antimalarials contain antibiotics, contributing to resistance in other disease-causing bacteria.

Since chloroquine was introduced in the 1940s, other antimalarials have been produced, and the parasites have responded by developing resistance to them. "Now there's severe problems with falsified artemisinin combination therapy (ACT) in western and central Africa," says Newton. "This is of enormous concern because ACTs are the standard, modern, effective therapy for falciparum malaria and they clearly save lives."

A drugs seizure in 2012 highlights just how large the problem of fake ACTs is. Customs officials in Luanda, Angola, were examining a shipment of loudspeakers when they found that they had been used to smuggle pornographic DVDs and strips of fake Coartem, an ACT manufactured by Novartis. In all, the shipment yielded 1.4 million packets of fake Coartem with no active ingredient, enough to 'treat' more than half of Angola's annual malaria cases. The fake ACT had been sent by sea from Guangzhou, China. Both the shipping company and the recipient denied knowledge of the fake medicines and no one was prosecuted.

Ensuring medicine quality is a global challenge. A pill might be

manufactured from ingredients sourced from multiple countries, shipped via several ports, packaged and repackaged in various countries and ultimately sold via an internet pharmacy. The number of points at which fakes or substandards could enter the chain is staggering, so international coordination is essential.

The WHO database that helped save the lives of children in Paraguay is a start. But a crucial tool is regulation, the responsibility for which could be shared better.

"The approach to assuring medical quality now is always to throw things at the regulator in the country of use," Pisani says. "It's easy to yell and moan and say they shouldn't be allowing for crap medicines to get out of Indian factories. But actually, we've chosen a system that works that way."

"Instead of controlling very tightly the quality of medicines made from this one Ranbaxy factory in India, that are currently being shipped to 83 countries, we're going to make the regulators of all of those countries, some of which are two people for a population of 19 million, we're going to make it their responsibility. Which I think is absolutely crazy."

It would be much more effective and efficient to require a greater share of quality control and regulation at the point of origin, she says. "And right now, there's none. Zero. Legally."

Pisani would also like to see more shared and sustained accountability. She takes the example of the aviation industry and the European Union: safety concerns involving only a few airlines from a particular country could lead the EU to blacklist all airlines from that country. It's a way to incentivise the industry and its regulators to collectively improve standards. "We could contemplate doing something similar for medicines," she says, "but obviously it's politically difficult. Right now,

it's an entirely globalised industry that we're trying to regulate locally."

In Delhi, Suresh Sati is sceptical of the Indian government's attempts to regulate poor-quality medicines at a local level. In 2009, the health minister introduced a scheme to reward whistle-blowers who alerted regulators about quality problems. "Not a single person has come forward," Sati says. He also believes the laws and their enforcement are lax and no one really pays the price for making fake drugs.

"The margin from selling fake medicines is more than from selling heroin. With heroin you're scared of the police, but here you're not." And so those who run fake medicine operations continue to do so with relative impunity. One of them even warned Sati that if he persisted with his investigations he would be dissolved in a boiler, a threat that few are in a better position to make convincingly than the kingpin of a fake medicine racket.

In 2010, Indians consumed the most antibiotics per person in the world. Medicines, including antimicrobials, are easily available over the counter despite rules that forbid this. A study published in 2018 found that a large number of antibiotics were on sale without being approved either in India or in the country of the manufacturer.

To preserve the effectiveness of antimicrobials, regulators need to prevent their overuse and misuse just as they need to prevent the use of poor-quality fakes.

The fake tablets that Sati gave me, Zifi 200, should contain cefixime as their active ingredient. Cefixime is classified as a third-generation cephalosporin, which is on the WHO's list of critically important antimicrobials, and within it is categorised as "Highest Priority". Cefixime is also on a list of drugs in India called Schedule H1, a classification introduced by the government in 2014 to regulate access to

drugs, specifically as a counter to the spread of antimicrobial resistance. A Schedule H1 drug can only be sold against a prescription, and the pharmacist is required to maintain a record of the sale, the prescribing doctor and contact information for the patient.

Some medicines, including Zifi 200, use an SMS verification service to combat fakes. Text the code and you soon get a reply to say if your medicine is genuine or not.

I sent off a text message with the code on one of the strips Sati gave me. As expected, it failed. Later, I went down to a pharmacy to see if I could buy a strip of Zifi 200. The pharmacist, with dismaying cheerfulness, handed me a strip without asking for a prescription or recording the sale. This one passed verification. There I was with two identical strips of tablets – one that was fake and should never have been made, and one that lacked a prescription and should never have been sold.

What to do if you suspect you have fake medicine

In the UK contact The Yellow Card Scheme; in the US contact The FDA ; in India contact the Central Drugs Standard Control Organization; in Australia contact The Department of Health.