Losing the war on bugs

Fake, or substandard medicine—some peddled by criminal gangs—is a big but hidden cause of antibiotic resistance

ELIZABETH PISANI

In the infectious disease wards of Ho Chi Minh City's main hospital for tropical illnesses, patients are arranged behind plate-glass windows like mannequins in a department store. Those that are conscious stare blankly through the glass that separates them and their frightening pathogens—cryptococcal meningitis, perhaps, or septicaemia—from the efficient hum of nurses and orderlies on the ward. A runner comes in and hands a doctor a sheaf of papers, the latest batch of results from the microbiology lab.

For the glassed-in patients—the hospital's most serious cases—these reports are rarely encouraging. The pathogens that have colonised their blood, lungs, or tissues have evolved their way around every drug that could have been used to combat them. And researchers working on the frontline of resistance blame the mutant bugs, in part, on fake and second-rate medicines.

This may be happening far away, but it is the west's problem too. In these days of global tourism, travel and migration, drug-resistant bacteria are highly mobile. "Humans think a lot of themselves," said Paul Newton, professor of tropical medicine at Oxford University, who works out of a microbiology lab in Vientiane, the capital of Laos. "But in fact we're really just exoskeletons for bacteria. They take cheap flights as often as we do."

No-longer curable variants of bugs bred in Ho Chi Minh City may be coming to a hospital near you. In 2008, an especially nasty genetic mutation that made several bacteria resistant to multiple classes of antibiotic was identified in a Swedish patient returning from India (hence its name, New Delhi metallo-beta-lactamase 1, or NDM-1). It was found in Britain that same year, and by 2013, in over 70 other countries. And it is not the only such infection to come to Europe. Multi-drug resistant staphylococcus, third-generation cephalosporin-resistant E.coli and K.pneumoniae have also travelled the world. At the last count, these infections and other resistant ones were already killing 25,000 Europeans a year—without measuring newer imports, such as NDM-1.

In recent years, there has been much wailing and gnashing of teeth about the advent of superbugs that have outwitted the drugs made to treat them. The UK added the threat of antimicrobial resistance to the National Risk Register for the first time in March 2015, worrying that "without effective antibiotics, even minor surgery and routine operations could become high-risk procedures." If bacteria with mutations such as NDM-1 were rife, doctors would hesitate to recommend hip replacements or even chemotherapy: the risk of becoming infected with untreatable bacteria would be too high. In December 2014, a government-commissioned review on antimicrobial resistance warned that drug-resistant pathogens could slice 3.5 per cent off the world's output by 2050, as well as putting 10m people into early graves every year.

Many reasons are given for this looming threat. Bugs evolve faster than drugs do. Unfortunately, there is little money in developing these drugs. Antibiotics drive their own obsolescence—the more that are sold, the more bacteria resist them. Their revenue potential is limited, as they should be prescribed sparingly, are only taken for a few days, and governments limit their price. And when doctors overprescribe antibiotics or patients take them without prescription antimicrobial resistance is boosted, especially if patients stop taking the pills the moment they feel better.

Another contributing factor is environment—in Southeast Asia, humans and animals are crowded together at close quarters in a climate that favours the growth of pathogens. But in the microbiology lab in that Ho Chi Minh City hospital, they have an additional explanation for what they are finding in their lab.

There, tiny bottles of red liquid—blood mixed with a culture medium—are upended in an incubator that looks for all the world like a wine fridge in a doll's house. The contents of some bottles are bubbling gently, indicating something is living in the blood—namely, an infection. Bacteria isolated from fizzy blood will be smeared over agar in a Petri dish and dotted with white discs, each marked with a three-letter antibiotic code. This test seeks to identify whether that particular bacterium is susceptible to each of the drugs. If yes, a clear halo will form in the red agar around the drug disc. More and more, the lab techs are reporting no halos, even for relatively newfangled antibiotics.

"It's those Indian drugs," says Dr Nguyen Phu Huong, a microbiologist, shaking her head with its 1930s bob in disapproval. "They are not strong enough for the bacteria."

"Indian drugs" is local shorthand for cheap, generic drugs not only from India but countries like China and Brazil. In the last decade or so, since these nations cranked up their pharmaceutical industries, their drugs have flooded market stalls across much of Asia and Africa. They are sold in tubs, blister packs, or mixed together in multicoloured cocktails and held in unlabelled plastic bags. Some are branded, others aren't. Some have sell-by dates and instruction leaflets, others don't. Even the ones stamped "BY PRESCRIPTION ONLY" can almost always be bought without a prescription. Many of these are good quality medicines which work just fine. But some are not. And the poor quality medicines are now eating into the effectiveness of medicines that once worked perfectly well.

Here's why: as they reproduce, pathogens mutate. Some of those mutations will make them more resistant to medicines.

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But the mutant pathogens usually don't reproduce as fast as the susceptible ones. If you take the correct dose of a drug and kill the susceptible pathogens quickly, the mutants never reach critical mass and die out too. But if you take only a partial, "sub-therapeutic" dose, enough susceptible bugs will survive to prolong the infection. The mutants now have less competition from susceptible strains, and more time to reproduce, build up numbers and get passed on to someone else.

Patients can expose bugs to sub-therapeutic doses by not taking the full course of a medicine. But they can also do it more unwittingly, by taking poor quality medicines. That includes medicines that have lost their potency over time—perhaps because they have been stuck in a very hot shipping container for months, then left in the sunshine of a market stall or the dank corner of a bathroom. It includes medicines that are badly formulated and don't dissolve correctly, restricting the amount of active ingredient that reaches the bloodstream. Finally, it includes medicines that never contained enough of their active ingredient, the result of sloppy manufacturing, or, more troublingly, outright fraud.

Welcome to the quagmire, where the global health community fears to tread. Here, out-and-out criminals overlap with pharmaceutical firms that cut corners while regulators turn a blind eye. Rabid non-governmental organisations (NGOs) see a Big Pharma conspiracy behind every attempt to assure quality, and western governments, facing mounting health bills, are terrified of undermining the credibility of generic medicines.

Trying valiantly to chart this quagmire is a small band of scientists who have coalesced around Paul Newton, the Oxford professor in Laos. He and his colleagues first became mired in the swamp of bad medicines a decade ago, pushed into it by the prospect of a global resurgence in malaria.

In the mid-2000s, a researcher named George Watt, working on the Thai-Cambodian border, noticed that malaria patients treated with an artemisinin-based medicine were taking twice as long as expected to clear the parasite from their bloodstreams. One possible explanation was that the disease was developing resistance to the cure. This was massively worrying because artemisinin, an antimalarial compound which Chinese scientists isolated from the sweet wormwood plant in the 1970s, was the only drug left that worked against malaria worldwide.

It was also massively plausible, because the Thai-Cambodian border is the historical epicentre of drug-resistant malaria. The first cases of resistance to the cheap and widely-used drug chloroquine were identified in this region in the 1960s (some believe because small doses of it had been introduced to the salt supply as a preventative). Resistance to sulfadoxine-pyrimethamine sprang up here, then mefloquine; no one has a good explanation why. So when Watt reported his findings to a meeting held by the World Health Organisation (WHO) in Phnom Penh in 2007, alarm ▶

bells clanged, and scientists went into overdrive trying to find out whether artemisinin was losing its power or not.

But Newton asked a different question. Was it possible that patients weren't responding to artemisinin because they weren't actually taking it? Colleagues working in Cameroon thought that what looked like chloroquine resistant malaria may have been the result of fake drugs. Long before Watts reported his findings, Newton had begun to investigate implausibly cheap tablets

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of artesunate (an artemisinin derivative) for sale in Cambodia. Though he had access to the overcrowded markets and sweltering hole-in-the-wall shops where many Asians buy their medicines, he didn't have the sophisticated equipment needed to test the pills.

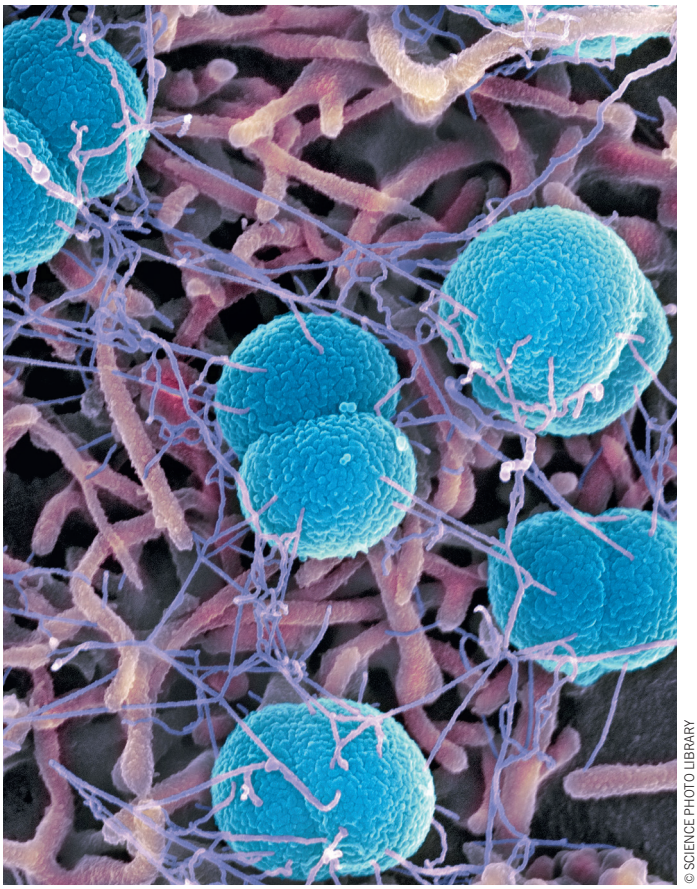
Newton's lab is based in an elegant, crumbling hospital on the banks of the Mekong. His office totters with papers that seem to have been accumulating since the lab was built in 1920—here a pile of medical journals grown crispy with age, there a Japanese monograph about scrub typhus from the 1950s. A man of shy good humour, he could have walked out of the pages of a Graham Greene novel. His timekeeping is erratic and he shuffles around the lab in mismatched knock-off Crocs, grunting encouragingly at the staff and trying to appear undemanding.

For all his diffidence, Newton can be magnetic. With a tiny budget and a lot of charm, he pulled together a multinational team of chemists, police officers, drug regulators and forensic analysts who had the equipment and skills to check what kind of pills the people sweating with malaria fevers were taking.

What they found were a lot of fakes.

Collecting samples from across Southeast Asia, his team started by looking at packaging, comparing a genuine example of a drug with the ones they had bought. In one case, packs marked "12 Tabs" were fake—the real version (12 Tabs.) ended in a full stop. They found misspelled brand names, and expiry dates that preceded manufacturing dates. Using microscopes, they spotted packs printed by silkscreen rather than the offset printing used by pharmaceutical companies. They found holograms which worked when tilted top-to-bottom instead of right-to-left.

Next, Facundo Fernandez, a professor of biotechnology at Georgia Institute of Technology in the United States, analysed the content of pills by zapping them with electrons and looking at the computer-generated patterns that emerged, a technique known as mass spectrometry. Different molecules show up as different peaks on the output graphs, so it is fairly easy to see what the active ingredients of a substance are. Yet one of the earlier samples Fernandez looked at had a shape that no one in the lab could identify at first: it wasn't the artemisinin derivative they expected, and it didn't look like quinine, Tylenol or anything else that they were used to finding in falsified drugs either. "After about two weeks, a PhD student came back and said: I think it's Viagra." Fernandez laughed ruefully. "We'd never looked at life-style drugs before. That was years ago, before we were sensitised to this kind of thing." Now, virtually nothing surprises the team.



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"Humans are just exoskeletons for bacteria": Neisseria meningitidis bacteria (blue), the cause of meningococcal meningitis

The drugs also contained pollen—which proved vital to tracing their source. Palynology, the study of pollen, is a pretty abstruse speciality but Dallas Mildenhall, a New Zealand-based scientist now in his 70s, has used it to solve crimes from art theft to murder. His analysis identified the trees involved. Walnut, wing nut and hickory trees sweep down from northern China to the Myanmar border. Wormwood, elms, wattles and firs are common further south, but creep up into China in areas north of Vietnam and Myanmar. When Mildenhall found pollen from both of these groups, he determined that they were most likely made in the zone of overlap, in southern China.

Most commonly, the fake pills do contain the expected drugs, though often not in the correct doses. Quite a few "antimalarials" have no active ingredient at all, but manufacturers have also filled pills with cheap anti-malarials less effective than those on the label, or drugs that reduce fever. "I think they use those deliberately to bring down fever so the patient doesn't suspect," said Fernandez. Newton was unconvinced. "My feeling is they've got a bunch of leftover powder that need using up. You use what you've got lying around, and bugger the consequences."

There seems to be a lot of white powder lying around. Fernandez has found anti-malarials containing banned carcinogens, for example. Also levamisole, which is often cut together with cocaine and has been linked to necrosis syndrome and the rotting of flesh in the earlobes and cheeks. And safrole, a precursor to ▶

Professor Paul Newton, the Oxford scientist and malaria expert, outside the microbiology laboratory at the Mahosot Hospital Wellcome Trust Research Unit in Vientiane

the party drug ecstasy. "If the untreated malaria doesn't kill you, the other ingredients in these fake pills might well," said Newton.

For Aline Plançon, head of Interpol's pharmaceutical crime division, that is one of the signs that old school drug cartels are in the game. "We have a lot of evidence now that some of the well-established criminal organisations who specialise in narcotics are getting into fake medicines." This business, she notes, offers massive profits with a low risk of ending up behind bars. "They don't pay tax, they don't pay for manufacturing standards or quality control, and often they don't even pay for an active ingredient, so it's not that hard to make a lot of money," said Plançon.

Working together, this collective of self-appointed "drug detectives" assembled the evidence. Then Ronald Noble, the secretary general of Interpol, took the scientists' dossier to the head of China's Public Security Bureau. Artemisinin was a Chinese discovery and a major contribution to the world's health. Now, Noble reported, it was being undermined by Chinese counterfeiters. And they were targeting Chinese brands, which could damage business for genuine manufacturers such as Guilin Pharma, a company which has had two of its antimalarial drugs pre-qualified by the WHO (this means they have met standards of quality, safety and efficacy). The company also had the largest production capacity for artemisinin-derived antimalarials in the world. That was in 2006; the Chinese authorities, still smarting from the SARS crisis, immediately launched a criminal investigation. They identified a network of pharmaceutical crime and jailed several people.

This response was gratifying to the scientists, demonstrating that authorities were willing to respond to pharmaceutical crime, at least when it involved cut-and-dried "bad guys." Yet this scrutiny of antimalarials revealed a grim symmetry between the way drug cops wrestle with gangs that produce fake drugs and the way drugs try to tame pathogens. In both cases, the forces of control are faced with an opponent that seems lighter on its feet, much more adaptable, and very hard to get the better of.

To help spot fake drugs, scientists working with Newton developed simple tests that changed colour if the expected active ingredients was present. One of the criminals' first responses was to put in just enough medicine to fool the tests. More recent studies of antimalarials in Southeast Asia have found no obvious fakes: no pills made only of yellow paint, or of cheap chloroquine masquerading as more expensive artemisinin. They have, however, found a surge in poor quality medicines. A recent study found that three quarters of antimalaria pills in Cambodia had sub-therapeutic levels of active ingredients—and the researchers didn't even test for dissolution. Formulating pills so that they dissolve correctly is very tricky; many of the pills that contained the right amount of drug were probably delivering them in doses too small to cure but big enough to encourage resistance.

It is an open question how many of these "poor quality" medicines are the work of criminals who deliberately manufacture shoddy products. Much of that question hovers over India, the world's third largest producer of pharmaceuticals by volume and its biggest exporter of generic medicines. In the words of whistleblower Dinesh Thakur, a former executive at the Indian generics producer Ranbaxy. "There's no doubt that [some Indian pharmaceutical firms] use one set of standards for making product for advanced western markets and one for sale in poor countries, including India." Thakur turned a spotlight on appalling production errors and outright fraud by his former employer, including medicines laced with ground glass, and drug safety test results that were made up. The US Justice Department launched an investigation that lasted nearly nine years. Eventually, in 2013, Ranbaxy admitted wrongdoing and paid a fine of $500m; it continues to sell its drugs into the American market.

The deliberate production of low-quality drugs by licensed manufacturers makes policing sub-standard medicines very difficult. "We can't criminalise all sub-standard drugs, because we want manufacturers to own up quickly when there has been a genuine error," said Mick Deats, a former City of London Police officer who now runs a WHO system that alerts health authorities to reports of bad drugs. "But in some cases you see a pattern of consistently low quality. Then you're out of the accidental and back in to the criminal. The level of evidence you need to tackle that, though, it's just extraordinary."

Perhaps. But India's drug regulatory authority doesn't seem to be setting the bar very high in the first place. It says no action should be taken against a manufacturer who produces medicines that include at least 70 per cent of the stated active ingredient—a level that would do much to promote resistance for many pathogens and that would never meet European standards.

Yet for all this, India is still performing an important service. Besides feeding a giant domestic market, the country exports over $15bn worth of pharmaceuticals each year, almost all of them generics. Good generic medicines are made with the same ingredients as a big-name drug, usually after the patent on the original brand has expired. Many generics manufacturers go through a rigorous WHO-monitored pre-qualification process, and operate to the same standards as the best-known companies. But their products are a lot cheaper, because they don't need to recoup huge research, trial and marketing costs.

> "Only five countries in all sub-Saharan Africa have a lab that meets WHO standards for drug quality testing"

Drugs that would be unaffordable if bought from the pharmaceutical giants that invested millions in their development are now within reach for poor people and poor countries. This makes generic manufacturers the darlings of health activists, and the bane of innovative companies. Ironically, the entrenched antipathy between these two groups is protecting the manufacturers of bad generics; vociferous NGOs see Big Pharma behind every attempt to impose higher standards. "There seems to be a belief in some NGOs that companies that make generics are philanthropic organisations," said Newton. "But they're making drugs for exactly the same reason as Big Pharma, to make a profit. They are flawed capitalist enterprises like any other." Big Pharma, for its part, is stuffed with slick-suited marketing executives happy to broadcast the flaws of generic medicines to help undermine patients' confidence in them.

Regulators in wealthy countries don't want to focus public attention on the quality of generic medicines because their public health systems prescribe them to keep costs down. Dinesh Thakur recognises the political dilemma facing drug regulatory agencies. "Most regulators are walking a fine line between assuring good manufacturing practice and the availability of drugs. Access to affordable drugs is very politically charged right now."

"Access to medicines" is still more of a mantra than "access to good quality medicines." Thakur, who now heads Medassure Global Compliance Corporation, a company which helps drug manufacturers source high quality ingredients, said that Indian pharmaceutical companies are taking advantage of that zeitgeist to avoid being held to higher standards. Others agree. Every time the WHO tries to take on the issue of drug quality, the Indian government objects.

Kees De Joncheere, the WHO's director of essential medicines and health products, avoids pointing fingers at individual countries. "Look, no minister of health deliberately wants to have low quality products on their market, that's clear. But when we talk about good manufacturing practice, well, how safe is safe enough? There's a perception in some quarters that some countries are putting up manufacturing standards so that others can't compete."

Producer countries don't have any obligation to guarantee the quality of the drugs they send abroad: the rule is buyer beware. But many importing countries don't have the means to check what they buy—only five countries in all of sub-Saharan Africa have a laboratory that meets WHO standards for drug quality testing. One proposal, borrowed from the airline industry, is to make the countries responsible for the safety of the medicines they produce, no matter where they will be sold. Airlines that come from countries with poor safety standards are subject to blanket bans in other countries, regardless of the standards at an individual airline. This solution is fairly simple, but politicians haven't had the courage to push for it.

Ranbaxy-style scandals notwithstanding, rich countries are good at assuring the quality of the drugs they import. That has made them complacent about the fact that people in other countries are taking medicines that don't work. It doesn't help that the studies by Newton and his colleagues that first turned the spotlight on bad drugs were about antimalarials; malaria doesn't kill voters in rich countries and politicians paid little attention.

Many of the pathogens now building up resistance because of poor quality drugs in Ho Chi Minh City, Lagos and Chennai will spread worldwide. When they arrive in Europe, they will be treated with good-quality medicines that will no longer work. Everyone, everywhere, should be able to trust the medicines they take. But for rich countries, improving the quality of the medicines consumed in the developing world is also a matter of self-preservation. If we don't do more to support higher production standards in India and elsewhere, bad bugs will continue to spread the world over. P

"I'm just starting my February retox."