

## Resistance to antibiotics

# The spread of superbugs

What can be done about the rising risk of antibiotic resistance?

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ON DECEMBER 11th 1945, at the end of his Nobel lecture, Alexander Fleming sounded a warning. Fleming's chance observation of the antibiotic effects of a mould called *Penicillium* on one of his bacterial cultures had inspired his co-laureates, Howard Florey and Ernst Chain, two researchers based in Oxford, to extract the mould's active principal and turn it into the miracle cure now known as penicillin. But Fleming could already see the future of antibiotic misuse. "There is the danger", he said, "that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Penicillin and the other antibiotics that its discovery prompted stand alongside vaccination as the greatest inventions of medical science. Yet Fleming's warning has always haunted them. Antibiotic resistance has now become a costly and dangerous problem. Some people fear there may be worse to come: that a strain of resistant bacterium might start an epidemic for which no treatment was available. Yet despite Fleming's warning and despite a fair understanding of the causes of resistance and how they could be dealt with, dealing with them has proved elusive. Convenience, laziness, perverse financial incentives and sheer bad luck have conspired to nullify almost every attempt to stop the emergence of resistance.

There are good reasons to hope that the extreme threat of a resistant epidemic will never come to pass—not least that 65 years of routine antibiotic use have failed to prompt one. Even so, the lesser problems of resistance continue to gnaw away at medicine, hurting people and diverting resources from more productive uses, often in the countries that can least afford it.

## **Irresistible**

Convenience and laziness top the list of causes of antibiotic resistance. That is because those who misuse these drugs mostly do not pay the cost. Antibiotics work against bacteria, not viruses, yet patients who press their doctors to prescribe them for viral infections such as colds or influenza are seldom harmed by their self-indulgence. Nor are the doctors who write useless prescriptions in order to rid their surgeries of such hypochondriacs. The hypochondriacs can, though, act as breeding grounds for resistant bacteria that may infect others. Even when the drug has been correctly prescribed, those who fail to finish the course are similarly guilty of promoting resistance. In some parts of the world, even prescription is unnecessary. Many antibiotics are bought over the counter, with neither diagnosis nor proper recommendations for use, multiplying still further the number of human reaction vessels from which resistance can emerge.

Nor is the problem confined to people. Analysing official figures, Louise Slaughter, an American congresswoman who is also a microbiologist, calculates that four-fifths of the antibiotics used in America are given to livestock, often to get perfectly healthy animals to grow faster. That is convenient, because it produces cheaper meat, but it creates yet more opportunities for bugs to evolve resistance.

All this matters because antibiotic resistance has both medical and financial costs. It causes longer and more serious illnesses, lengthening people's stays in hospital and complicating their treatment. Sometimes people die unnecessarily. In one study, which sampled almost 1,400 patients at Cook County hospital in Chicago, researchers found resistant strains of bacteria infecting 188 people, 12 of whom died because they could not be treated adequately. At the moment, resistant bacteria threaten mostly children, the old, cancer patients and the chronically ill (especially those infected with HIV). However, there could be worse to come. Nearly 450,000 new cases of multidrug-resistant tuberculosis are recorded each year; one-third of these people die from the disease. More than a quarter of new cases of TB identified recently in parts of Russia were of this troublesome kind.

The price in money, too, is high. On the basis of the Cook County study the Alliance for the Prudent Use of Antibiotics, a non-profit group, calculates that resistance to antibiotics costs America alone between \$17 billion and \$26 billion a year—perhaps 1% of the country's vast spending on health care.

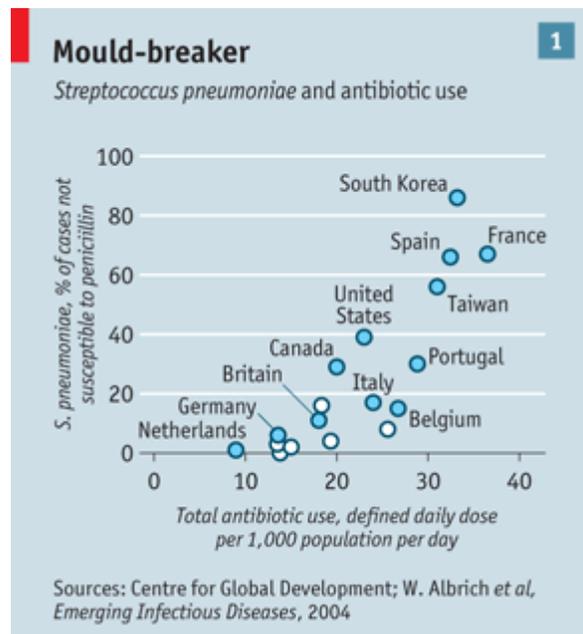
America is rich, and can afford this. Poor countries are not as lucky. And a perverse calculus puts them at a particular disadvantage. The poorer the country, the larger the share of its health-care budget typically absorbed by the cost of drugs. As a report last year by the Centre for Global Development, an American think-tank, pointed out, resistance often increases the drug bill, because patients are forced to turn from cheap, widely used drugs (whose very ubiquity

encourages the evolution of resistant strains) to dearer alternatives. That imposes a disproportionate burden on poor countries. For the cost of treating one person with extensively drug-resistant TB, for example, a hospital could treat 200 with the less lethal variety.

### Action, not panic

Broadly, there are three possible responses to this state of affairs. One is to do nothing, treating the various problems created by resistance as acceptable costs when set against drugs' much greater benefits. Here, a sense of history helps. Before penicillin—that is, before the mid-1940s—it was possible for a perfectly healthy individual to die of septicaemia from a casual, everyday cut. Many other bacterial infections, most notably TB, were similarly routine killers. The Shakespearean curse, “a plague on both your houses”, would have had real resonance then. But antibiotics and vaccines have turned it into an anachronism. Worrying about even 150,000 TB deaths a year, compared with the millions who used to die, can thus sound like a counsel of perfection. Of course, it would be better if those deaths did not happen. But restricting the availability of antibiotics, especially in poor countries where obtaining a doctor's prescription can be costly and time-consuming, would also cause people to die who might have lived.

There are basic biological reasons, too, for thinking that resistance may be self-limiting. For a bug, being resistant is costly. It has to adjust its physiology, and resistance often works by making enzymes that degrade the drug, or by producing extra copies of proteins that pump the drug out of the bacterial cell, both of which require a lot of energy. Some creatures cannot seem to manage the trick at all—at least for certain drugs. One species of *Streptococcus*, called *S. pyogenese*, has never been seen to throw up a penicillin-resistant strain, whereas another, *S. pneumoniae*, is frequently not susceptible to that drug (see chart 1). In these circumstances, the theory goes, a resistant organism is less a superbug and more a cosseted creature that can beat the competition only in the unfair arena of a hospital or a clinic. Another reason, then, for accepting the status quo.



Unfortunately, this comforting argument may not be wholly true. In the *Lancet* in 2007 Herman Goossens, a microbiologist at the University of Antwerp, laid out the results of a trial designed to investigate the idea. His team divided healthy volunteers into three groups. To one group they gave an antibiotic called azithromycin. To another they gave a second, clarithromycin. To the third they gave a placebo. They then followed the progress of the *Streptococci* in each volunteer's throat.

As expected, those who were taking the placebo showed no signs of drug-resistant strains of *Streptococcus* at any time during the study. Also as expected, the *Streptococci* in those taking the

antibiotics showed sharply elevated levels of resistance within days. What was surprising—and worrying for those who think that resistant bacteria will do better than the non-resistant wild type only while the selective pressure remains on—was that those populations of *Streptococci* which acquired resistance retained it for over a year.

The evolutionary logic behind the argument that resistant organisms are inferior is seductive. But in case it is wrong, and because resistance clearly is a problem anyway—even if a vastly smaller one than not having antibiotics at all—the second response is to try to rein in overuse.

According to an article by James Hughes of Emory University, in Atlanta, Georgia, which was published in February by the *Journal of the American Medical Association*, as much as 50% of antibiotic use is unnecessary or inappropriate. Overuse, misuse, improper dosing and the use of substandard or diluted medicines all contribute to the rise of resistance. But so too do weak health-care systems and poor or unenforced regulations. Unless a strict code of practice forbids overuse, and systems are in place to monitor their behaviour, doctors have every incentive to treat the patient in front of them—not worry about the theoretical patient a decade hence who may suffer from the consequences of overuse of antibiotics.

Reining in overuse will be difficult and will require governments, companies and health-care providers to act in concert. It might even require patients to be just a bit less selfish. Aid agencies and charities dispensing drugs freely in poor countries should ask themselves whether safeguards and the education of patients for proper use of powerful medicines are good enough, and if not what can be done to improve them. Governments, such as China's, that link financial reimbursement to the amount of drugs dispensed must abolish that perverse practice.

Regulators need to do better in their monitoring and public-health surveillance, so that counterfeit or substandard drugs (containing less than the proper dose of active ingredients, for example) are not given to unwitting patients. More could also be done to encourage the development of rapid and portable diagnostics—a mushrooming field—so that antibiotics are popped only when they are useful.

Ultimately, though, the relationship between doctor and patient is paramount. Doctors need to be sterner, and patients need to accept that antibiotics are not always an appropriate prescription. Medical associations can put in place more rigorous training and drug-dispensing protocols—insisting, for example, that doctors check that patients have completed their courses of antibiotics.

All of this would help, but much of it goes against the grain of human nature. Ms Slaughter has another proposal. She has introduced into Congress a bill that would limit the agricultural use of antibiotics.

### **Ignorant humans, smart microbes**

There is, however, a third approach to the problem of resistance. This is to make new antibiotics, to which bacteria will not, at first, be resistant. Perhaps surprisingly, many of the best weapons in the armoury are still decades-old drugs that would have been familiar to Fleming and his

contemporaries. Here, it is the last two causes on the list that are to blame: perverse financial incentives and bad luck.

April 7th each year is marked by the World Health Organisation as World Health Day. Like all such days of action, it must have a slogan. This year the theme is resistance to antibiotics and the slogan is “No action today, no cure tomorrow”. Action—or, rather, success—has been sadly lacking in the recent past. Between 1983 and 1987, 16 new antibiotics won approval from America’s Food and Drug Administration. Since 2003 only seven have done so (see chart 2). Moreover, some of the details are even worse than that. Drugs firms have not, for instance, come up with a breakthrough TB drug in many years, although some new ones look promising.



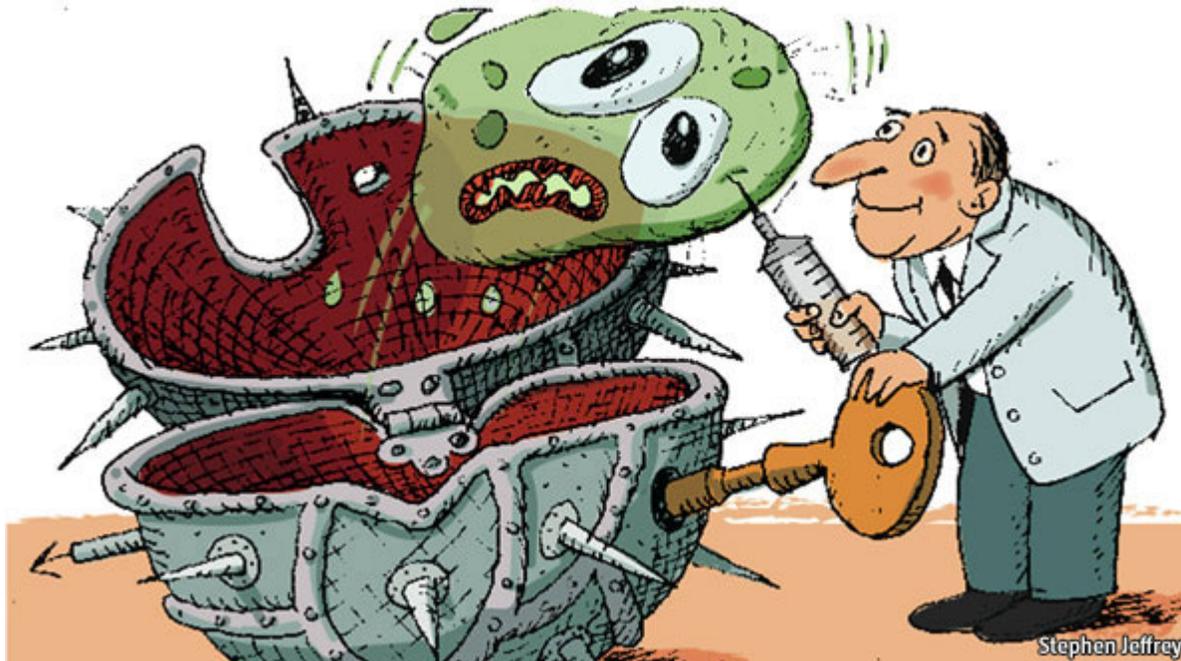
There are several reasons for this. One is that the early researchers were lucky. Just as the modern pharmaceutical industry began with the development of aspirin, a drug that has never been bettered for many applications, so penicillin and its contemporaries—easily discovered because they have strong effects—are not easy to improve on.

A second and unpredicted problem is that modern science has failed to help. Drugmakers have poured huge sums into applying genomics and proteomics (the study of how proteins behave) to the problem. It has not worked. Despite the millions spent, argued David Payne of GlaxoSmithKline, a big British drugs company, in a paper in *Nature* a few years ago, his firm and others came up empty-handed: “It was clearly very hard to find targets, so we stopped.” Other drug-research chiefs share his frustration. Mark Fishman of Novartis, a Swiss company, says that after a similar lack of breakthroughs in genomics “we’ve gone back to the brute-force method of screening millions of candidates that kill a bug—and then evaluating them for safety in humans.”

There are signs that the pipeline at the larger firms is running dry. In February Pfizer, the world’s biggest drug company, announced deep cuts in its research budget. Among the programmes affected is the company’s antibiotics effort. Pfizer insists that it is not being axed, but merely shifted from Western laboratories to China.

Bad luck can befall anyone. The other reason for the lack of new antibiotics, though, is less forgivable—if understandable. Few in the industry will admit it in public, but investing in antibiotics is not that attractive. Existing drugs, resistance aside, work well enough. Since resistant infections are still a small proportion of the total, although serious for those who suffer them, the market for drugs that overcome them is small, too. It is restricted further by the fact that much of the resistance problem is in poor countries that cannot afford flashy, new drugs.

Moreover, successful treatment with antibiotics effects a cure. Repeat prescriptions are unnecessary. That is good for the patient, but bad for the drug company.



None of this means that antibiotic research has been abandoned completely. Like some other areas of drug research, though, it is increasingly the province of boutique biotechnology firms, rather than the huge emporia that are traditional pharmaceutical companies. For example, Theravance, based near San Francisco, has come up with an antibiotic that treats skin infections, including some caused by MRSA, an especially nasty type of *Staphylococcus* that is resistant to many antibiotics. Cubist Pharmaceuticals, of Lexington, Massachusetts, took a chance on another antibiotic that attacks MRSA. Daptomycin, the drug in question, had already been tested and rejected by one of the big boys, Eli Lilly. The company's researchers found that the drug caused muscle damage and recommended dropping it. Cubist's researchers, however, worked out how to adjust the dose to deal with this side-effect. Daptomycin is now a commercial success.

Such success is the exception rather than the rule. In the hope of changing this, the Infectious Diseases Society of America (IDSA) has put forward its "10x20" plan, which calls for the development of ten new antibiotics by 2020. The IDSA proposes financial incentives, such as tax credits, guaranteed markets and prizes, to encourage investment in research and development. It also argues that new drugs that attack especially problematic diseases should get extra patent protection.

### **A tragedy of the commons**

A big part of the trouble is that the gains from the overuse of antibiotics are private, whereas the losses are public. Problems such as these are rarely soluble without outside intervention. Ramanan Laxminarayan of Princeton University, who has been thinking for many years about how to deal with the question of resistance, suggests the answer is a mixture of incentives and

scourges. Prize funds, or guaranteed-purchase arrangements for new drugs and the rapid-diagnostics systems that would allow them to be deployed appropriately, would help overcome the financial problem of antibiotics being cures, rather than just treatments. Stricter dispensing guidelines for doctors and pharmacists might help deal with the moral hazard of overtreatment.

A bit of realism would be good, too. Derrick Crook, a consultant microbiologist at Oxford, where Florey and Chain once worked, observes, "It is hard to massively restrict the use of antimicrobials when they are doing good. It is possible that the enormous use in Asia is a good thing for a short time in a given country." That, combined with ignorance about precisely how much the unnecessary use of antibiotics contributes to increasing resistance, makes restriction highly controversial.

Tim Peto, a colleague of Dr Crook's at Oxford, though sceptical of the idea that resistance might bring about a catastrophe, also notes that much of modern surgery relies on the risk of infection remaining low. At the moment, it is close to zero. If resistant strains raise it to even 5%, let alone 10%, a lot of orthopaedic surgery, cataract replacements and other discretionary but life-enhancing procedures would simply stop. That would not be the end of the world, but it would be a step backwards. And it would be a shame if it had been caused by a failure to take proper notice of a warning, all those years ago, sounded by one of the men whose legacy would thus be squandered.