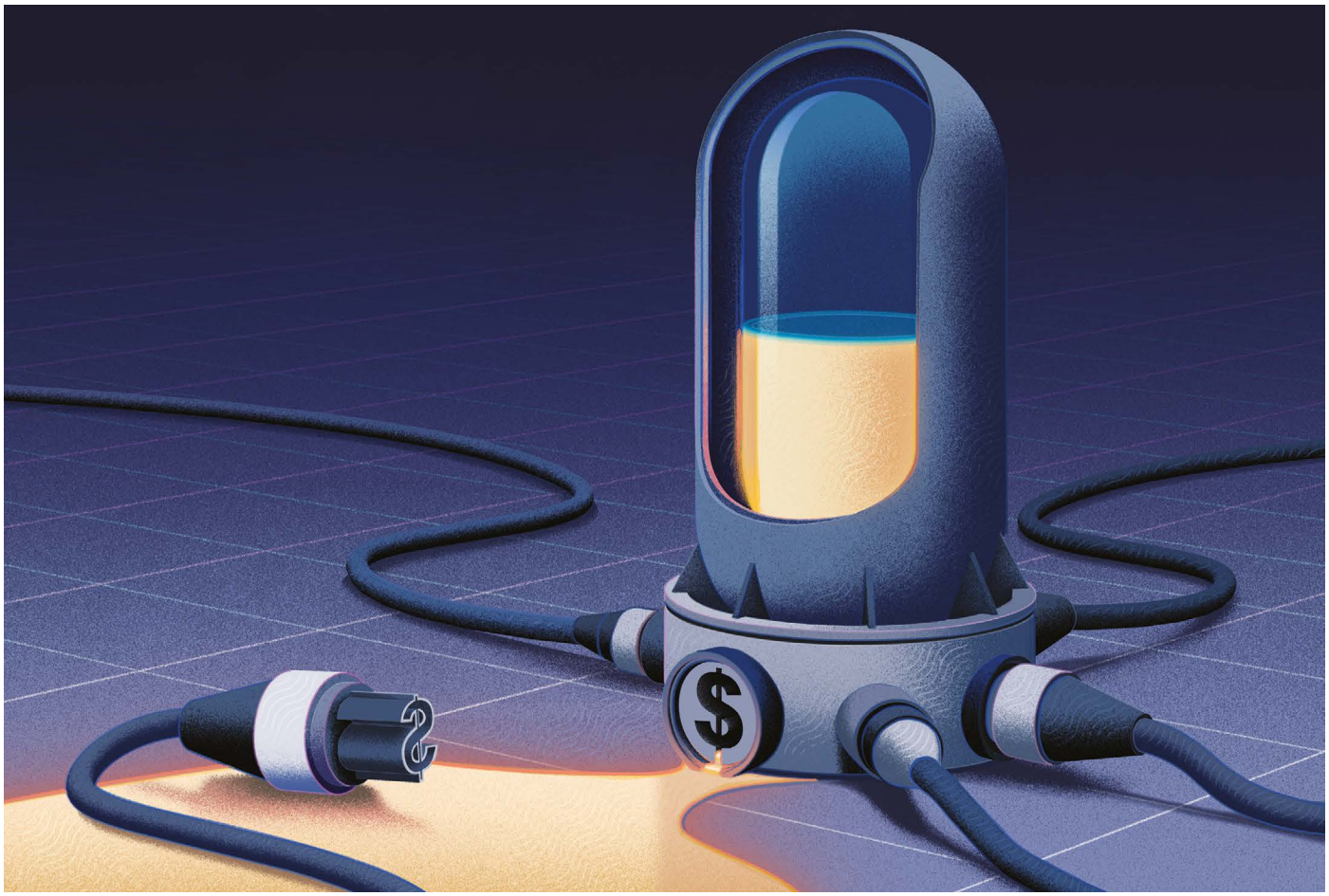


SAM CHIVERS

No money for new drugs

Despite an overwhelming global need for pharmaceutical companies to develop more antibiotics, there's little financial incentive to encourage them to act. **By Benjamin Plackett**

When scientists, public-health bodies and governments around the world warn that antimicrobial resistance is the next great health crisis, they have good reason. Since the 1960s, bacteria and other microorganisms have become increasingly resistant to antimicrobial drugs, leading to more and more people dying.

Drug-resistant diseases kill around 700,000 people each year, but a United Nations interagency group on antimicrobial resistance estimates that this could swell to 10 million a year by 2050 if no action is taken. This is more than the number of people who currently die from cancer worldwide every year.

Despite the clear need for more antimicrobial agents, such drugs have not been forthcoming. Fewer new antibiotics are reaching the market; the last entirely original class of antibiotic was discovered in the late 1980s. One reason is that discovering and bringing antibiotics to market is often not profitable for pharmaceutical companies.

A 2017 estimate puts the cost of developing an antibiotic at around US$1.5 billion[1]. Meanwhile, industry analysts estimate that the average revenue generated from an antibiotic's sale is roughly $46 million per year. "That's tiny and nowhere near the amount needed to justify the investment," says Kasim Kutay, chief executive of Novo Holdings, an investment firm in Hellerup, Denmark, focused on the life sciences.

As a result, many large pharmaceutical firms have dropped out of the market in favour of pursuing profitable lines of drug development, such as cancer treatments (see 'Low approval ratings'). In their place, smaller companies and funding bodies are striving to fill the gap. But fixing the economics of drug development might take a radical approach.

Pipeline problem

Deaths caused by infectious diseases have fallen by 70% since antibiotics were introduced on a large scale in the 1940s, according to the UK biomedical funding charity Wellcome. This could be in jeopardy unless the economics of the market can be re-imagined.

A 2017 review found that in one strain of bacteria, the prevalence of resistance to

levofloxacin, an antibiotic used to treat a wide variety of infections, grew from roughly 2% before 2000 to 27% between 2011 and 2015 in the Asia Pacific region[2].

"The problem is terrible and not too far away," warns Asad Khan, a microbiologist at the Aligarh Muslim University in Aligarh, northern India. "I think many governments and funding bodies haven't yet understood the scale of what we're facing."

Many economists have also been slow to act. One review found that only 55 of more than 1 million peer-reviewed economics articles in the EconLit database were related to antimicrobial resistance[3]. Papers on climate change, by comparison, totalled around 16,000. Yet economics has a significant role in the lack of antibiotics coming to market.

Any type of pharmaceutical development is an expensive process, but for antibiotics it is especially hard. One issue is that the cost–benefit ratio – how much profit will result from an investment – is much less favourable than for other drugs. "Profit is basically volume multiplied by price," says Richard Smith, a health economist at the University of Exeter, UK. For antibiotics, neither element is high enough to offset the cost of development.

Prices are low because in many countries government agencies have a role in assessing the price, not the manufacturer alone. In the United Kingdom, for instance, the National Institute for Health and Care Excellence (NICE) assesses the clinical strength and cost-effectiveness of new medicines. "The point of NICE is to try and keep drug prices low," says Smith.

Other countries have a similar set-up. For a new drug to be included in the Australian government's Pharmaceutical Benefits Scheme, which subsidizes the cost of medication, it has to be approved by a committee of health professionals and economists, who evaluate whether the drug offers value for money. Canada also regulates the price of patented medicines to keep prices low.

At the same time, physicians avoid prescribing new antibiotics to help delay the development of bacterial resistance. This means that governments and health agencies are even less likely to accept a premium for new antibiotics, says Smith. "Antibiotics used to be profitable back in the 1960s when you didn't have to consider resistance as an issue," he says.Typically, a drug is granted a 5–10 year exclusivity period, during which the manufacturer is shielded from competition from any generic versions that might be developed. But even this isn't enough to recoup the vast development costs. Once the exclusivity period expires, other drug makers can enter the market – and, without the need to account for large research expenditures, they can drop the price.

According to a policy review[4] by the UK Office of Health Economics, the relatively short treatment cycle for a course of antibiotics reduces the volume that can be sold. Antibiotics are typically prescribed for a couple of weeks, whereas therapies for chronic diseases are taken for months or even years.

In a 2003 study, researchers found that an injectable antibiotic is roughly three times less profitable than are drugs used for the treatment of cancer[5]. Drugs for musculoskeletal conditions, meanwhile, are around 11 times more lucrative.

Costly developments

One approach could be to reduce the cost of antibiotic development. As microbes have evolved more mechanisms to evade the antibiotic arsenal, the challenge of devising new drugs has increased – and with it, the cost. "We've lost the low-hanging fruit now," says Jeremy Knox, who leads Wellcome's policy and advocacy programme on drug-resistant infections.

"I think many governments and funding bodies haven't yet understood the scale of what we're facing."

The preclinical stages of antibiotic research and development (R&D) are the most risky and create the biggest financial burden. They account for close to 45% of the total costs, not least because many promising avenues of investigation don't pan out, leaving manufacturers with a large bill for very little gain. Conventionally, antibiotic development starts by searching for antibacterial compounds in nature – often those synthesized by other microorganisms. These chemicals are then put through a series of experiments to see whether they can be scaled up, whether they're safe for humans, and what the ideal concentrations would be.

There have been calls, however, for researchers to use more-sophisticated approaches in a bid to speed up these early stages. Advances in big-data analysis could be exploited to make antibiotic research more profitable. In a study this year, scientists trained an artificial-intelligence (AI) system to predict which molecules might have antibiotic properties[6]. The program trolled through online chemical libraries and flagged a compound, called halicin, that is structurally different from conventional antibiotics, yet still kills bacteria.

In January, Exscientia, an AI drug-discovery company in Oxford, UK, used similar methods to create a drug, called DSP-1181, to treat obsessive–compulsive disorder. The firm said it completed the exploratory phases of research in just one year, compared with the average of 4.5 years.

Furthermore, health-care leaders have attempted to improve management of the generic antibiotics already in use. One simple approach is drug rotation: when resistance to an antibiotic reaches a crucial level, physicians stop prescribing it and use an alternative. During this 2–4 year pause, the resistant bacteria are unable to survive. The first drug can then be used again.

However, the results from countries that have tried such an approach are disappointing. During the 1990s, the United Kingdom reduced prescriptions of sulfonamide antimicrobials by 98% to tackle resistance in *Escherichia coli*, but resistance to the drugs remained high[7]. And a trial in Sweden to reduce trimethoprim resistance had a similar result[8]. The scientists behind the Swedish study concluded that resistance remained high because the replacement drug had a very similar mechanism of attack to trimethoprim. If more forethought is given to the replacement drug – such as ensuring it is sufficiently different to the antibiotic it's replacing – then drug rotation stands a better chance of success, say the authors.

However, even if techniques such as AI allow biologists to beat the odds and discover a molecule that attacks microbes in a new way, there are still substantial hurdles to overcome before it makes it to market. "It's a difficult field," says Susu Zughaier, a microbiologist at Qatar University in Doha who is searching for antimicrobial molecules. "Not only do you have to find a new compound that kills bacteria, but it also needs to be stable, non-toxic to humans and work at a low dose so as not to leave residues in the liver and kidneys after treatment."

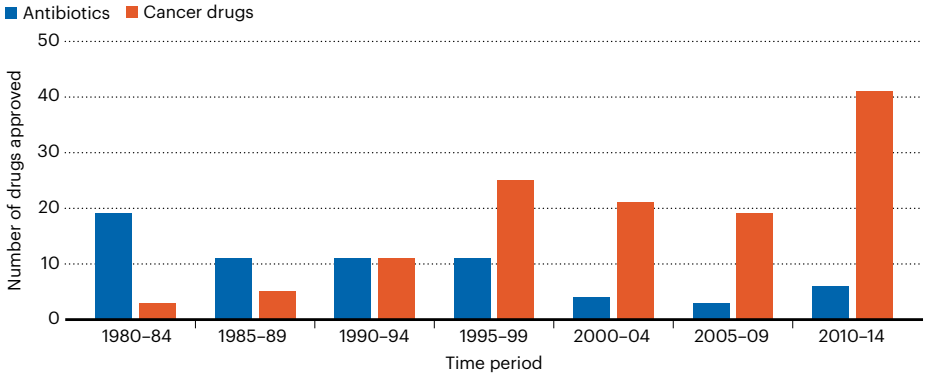
Small change

Some drug companies have already thrown in the towel on antibiotics research. Novartis in Basel, Switzerland, for example, called a halt to its search in 2018. Its chief executive said that the business would focus on other areas, such as cancer treatment. This followed similar announcements by Sanofi in Paris the same year, and by AstraZeneca in Cambridge, UK, in 2016. Only four major pharmaceutical companies still have active antibiotic research programmes.

Some smaller companies and charities, however, have anticipated the public-health problems that are likely to arise from a lack of investment in antibiotics.

LOW APPROVAL RATINGS

In the United States, the number of new antibiotics approved for use declined between 1980 and 2014, but approvals for cancer drugs rose.



SOURCES: ANTIBIOTICS: C. L. VENTOLA *PHARM. THER.* **40**, 277–283 (2015); CANCER DRUGS: J. SUN *ET AL. BMC SYST BIOL.* **11** (SUPPL. 5), 87 (2017).

In 2018, for example, Novo Holdings launched a finance package known as Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR). The $165-million initiative will invest in companies in the early stages of antibiotic R&D. The initiative was designed not to make money for the investment firm, but to bolster antibiotic research by ensuring ideas got off the ground. "It was our first fund that would sacrifice returns in order to make an impact," says Kutay. "Our idea was to fund antibiotic companies in phase I and then others would take the baton to run the development through to commercialization."

By 2019, however, things were not going to plan. Many of the investors and large pharmaceutical companies that Novo Holdings had assumed would take over after its early investments had, like Novartis, decided to move away from antibiotics. Others had simply gone out of business. According to data collected by Novo Holdings, the average share price for an anti-infective drug company has tumbled by 71% since 2018, and several companies focused on antibiotics have been forced to file for bankruptcy.

A similar programme, called CARB-X, was established in 2016 with funding from government agencies in the United States, Germany and the United Kingdom, as well as several foundations and charities, including Wellcome and the Bill & Melinda Gates Foundation in Seattle, Washington. That programme has an even greater budget — $500 million — but it has run into the same problems as REPAIR. "When we set up CARB-X, there was still a reasonable amount of private investment, but in the last two years we've seen a drop off in that confidence," says Knox.

It is not clear how long such funds can prop up the early stages of antibiotic R&D without knowing whether another entity — government or charity — will help further down the line. "We've found ourselves needing to fund companies on an ongoing basis, and that's draining resources," says Kutay. "We need money for the later stages of development."

Fortunately, there are signs that the industry is beginning to respond to the economic problem of antibiotics. In July, the International Federation of Pharmaceutical Manufacturers and Associations announced the AMR Action Fund. The antimicrobial-resistance initiative involves 24 companies, including Novo Holdings and Novartis. It aims to bring between two and four new antibiotics to market by 2030, and has so far committed nearly $1 billion to support the research needed to achieve this goal.

Knox is hopeful that the fund will help start-ups graduating from initiatives such as CARB-X and REPAIR. Although grants and cash injections are useful, the fundamental market forces that make antibiotics such an unattractive proposition remain unchanged.

The Netflix model

To make antibiotics more economically viable without charitable intervention, some healthcare providers and drug firms are switching to a model whereby antibiotics are paid for through a subscription. Buyers would pay a pre-agreed amount to use as much or as little of the drug as they need. It's described as the Netflix model, says Kutay. The model would include an up-front payment to companies during the early stages of development as a further incentive to get research under way.

A UK scheme to pay for some antibiotics in this way began in June. Health secretary Matt Hancock said that the government will pay pharmaceutical companies for access to new antibiotics, rather than on a per-pill basis. Initially, the UK government will award two contracts to pharmaceutical companies under the subscription model by the end of this year. The firms will receive their first instalments during the expensive early stages of R&D. In a statement, Hancock said that this approach to payment "breaks down restrictive barriers to offer companies a vital springboard to foster innovation and develop potentially life-saving new products".

The move has been welcomed by large drug firms. Pfizer in New York City said it was "delighted" with the news. Others have been more cautious. "It's a very promising development, but it still has some way to go with the red tape and bureaucracy," says Laurence Roope, a health economist at the University of Oxford, UK.

There are signs that other countries are considering a similar approach. In 2018, the then head of the US Food and Drug Administration, Scott Gottlieb, suggested that government health-care programmes could pay for new antibiotics through licensing fees. A policy review by researchers at Duke University in Durham, North Carolina, proposed how this could be done[9]. The report recommended that government bodies work together, in a similar way to the UK model, deciding which drugs qualify for subscription payments, rather than implementing a blanket rule, to ensure that only sufficiently innovative antibiotics benefit from the revenue stream.

Knox thinks the AMR Action Fund could push other countries to adopt the Netflix model. "I don't have a crystal ball," he says, "but I think it will put pressure on governments to act because they've previously been able to deflect and say the industry is the problem. With the AMR Action Fund, that will be harder to do." Indeed, when the fund was announced, the French Secretary of State for Economy and Finance, Agnès Pannier-Runacher, acknowledged the need to address pricing, but called for it to be tackled at a European level.

The need to develop antibiotics is pressing, yet the blockage in the production pipeline persists. To tackle this, the economics of the antibiotics market needs to be re-imagined — and this might mean governments have to pay more to use less. "It's the entire economic model that's broken," says Kutay.

Benjamin Plackett is a freelance science writer in London.

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