

## Superbugs: Why Pharmaceutical Companies Are Resistant to Antibiotics

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It takes about A\$1.4 billion, 10,000 molecules and 12 to 15 years of research and development to get one new medicine approved for use in Australia, according to the pharmaceutical industry peak body, Medicines Australia. But while the world faces a future of "superbugs", pharmaceutical companies seem resistant to making an investment of that size to bring a new antibiotic to market.

Antibiotic use, and inappropriate antibiotic use, is responsible for the emergence and spread of these bugs, says [Peter Taylor](#), assistant director of Microbiology at the Prince of Wales and St George hospitals and a lecturer in Pathology at the University of New South Wales. "The other contentious point is to do with the liberal use of antibiotics in veterinary medicine and agriculture (meat production) globally that leads to unwitting transfer of antibiotic resistant strains with our food."



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The World Health Organization (WHO) has warned that a health emergency of global proportions may result without the antibiotics needed to combat multi-drug resistant bacteria that are spreading around the world. WHO recently identified antimicrobial resistance as one of the three greatest threats to human health.

Medicines Australia reports that, already, 7000 Australians die each year from drug-resistant bacteria, such as Golden Staph infections – that's about 20 Australians a day.

"Antibiotic resistance is one of the foremost issues that will affect healthcare worldwide, including Australia, in the coming decades," agrees [Thomas Gottlieb](#), president of the Australasian Society for Infectious Diseases, who has served on advisory boards for big pharmaceutical companies Novartis, Pfizer, AstraZeneca and Janssen-Cilag.

A [paper](#) published in the Medical Journal of Australia earlier this year by Gottlieb and Graeme Nimmo, president of the [Australian Society for Antimicrobials](#), reports that, for many bacterial pathogens, resistance to last-line antibiotics is now commonly found in Australian hospitals and, to an increasing extent, in the community.

Gottlieb and Nimmo list as examples the "golden staph" bacterium, methicillin-resistant *Staphylococcus aureus*, and a prevalent cause of infection, multiresistant *Escherichia coli* or E-coli, along with multiresistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci.

"The growing ineffectiveness of once-reliable drugs has seen healthcare professionals increasingly turning to alternatives that are more toxic, more expensive and less likely to be orally available, putting increased pressure on a strained hospital system," claim Gottlieb and Nimmo. "In addition, compared with susceptible bacteria, antibiotic-resistant strains are associated with increased patient morbidity and mortality and increased costs of health care."

According to an [article](#) carried by international news agency Reuters, only two new antibiotic classes have been approved in the last 40 years, despite the fact that antibiotic-resistant bacteria present a growing threat. "(It's) an issue where commercial consideration doesn't really match the public health need," concluded Thomas Lonngren, a former executive director of the European Medicines Agency in London. His US counterpart, commissioner of the Food and Drug Administration, [Margaret Hamburg](#),

echoed in late 2010: "We need new and better drugs – and we need them now ... yet the pipeline is distressingly low."

## Antibiotics Versus Profits

In 2010, there were more than 2950 medicines under development. This figure included more than 800 cancer drugs and 250 cardiovascular medicines, but only 83 antibiotics, reports [Medicines Australia](#).

Part of the problem is that the business case for developing an antibiotic – especially one for the percentage of people currently resistant to them – is extremely poor, according to Taylor, who tests patient samples and reports on antibiotic resistance. One of the first cases of a patient infected with an organism carrying New Delhi metallo-beta-lactamase (a superbug) was reported from a Sydney hospital in collaboration with a French laboratory, Taylor notes.

Antibiotic resistance is becoming more common, but for pharmaceutical companies the "superbug" bacteria requiring treatment are less appealing targets for drug development than conditions that require long-term medication, such as statins (cholesterol-lowering drugs) and anti-depressants, beta-blockers or anti-rheumatics, Taylor says.

Why invest in antibiotics when the returns on drugs for high cholesterol or heartburn are so much more lucrative? asks [Richard Day](#), director and professor of Clinical Pharmacology at the University of New South Wales' Faculty of Medicine. And the figures back him up.

Pfizer's cholesterol pill Lipitor remains the best-selling drug worldwide. Its annual sales in 2010 were US\$12.9 billion, and its closest competitors are Plavix, a blood thinner from Bristol-Myers Squibb and Sanofi-aventis; Nexium, the heartburn pill from AstraZeneca; and Advair, the asthma inhaler from GlaxoSmithKline.

"Pharmaceutical company decisions over the last two decades have led to the situation today where antibiotics play only a minor part in companies' portfolios of new medicines," notes Medicines Australia chief executive Brendan Shaw. To highlight the pharmaceutical companies' issues, he points to a 2009 study by the London School of Economics and Political Science that revealed the barriers to developing antibiotics – and some of the obstacles are government created. The companies have long lead times, costs and commercial risks involved in developing new medicines, consequently they must make long-term decisions about which potential cures they will commercialise years in advance of those medicines reaching the market, notes Shaw.

While some of the problems faced by pharmaceutical companies simply reflect the nature of antibiotic medicines – such as the short-term nature of a medicine's effectiveness – Shaw outlines other disincentives and public health dilemmas. "Governments have restricted the use of antibiotics generally, and kept new antibiotics as a treatment of last resort, to try to limit the growth in the superbugs' antibiotic resistance," he says. "While justified on public health grounds, it limits the size of the market for a company developing a new medicine."

Financial realities have also played their part in dissuading the pharmaceutical industry from investing in new antibiotic medicines. The long-term availability of less expensive generic antibiotics has meant that governments have typically used these as the benchmark for assessing new antibiotics. "Driving down the cost of new antibiotics by referencing them to the price of older cheap generic antibiotics might help reduce health expenditure in the short term. However, over the course of a couple of decades it has meant that companies are no longer able to justify the costs of developing new antibiotics," Shaw says. What might be seen as efficient in the short term is actually inefficient for the overall economy and society in the long term, he points out.

The knock-on effect will be seen in 15 to 20 years, Shaw predicts. "Governments have failed to recognise that the decisions about the different therapeutic treatments they will pay for today will impact in years to come." He has suggested one-off incentives – including extending patent terms, tax credits and commercialisation funds – could help in providing financial incentive for antibiotic development, once they have been proven to be effective.

## Countering Resistance

In response to the looming crisis in antimicrobial resistance, the Australasian Society for Infectious Diseases and the Australian Society for Antimicrobials convened an [Antimicrobial Resistance Summit](#) in Sydney in February. The meeting brought together an interdisciplinary group of experts from the medical, veterinary, agricultural, infection control and public health sectors to establish priorities and a joint plan of action.

Part of the multi-faceted strategy involves "antibiotic stewardship" programs that focus on monitoring the antibiotics that are prescribed in hospitals to encourage best practice. Clinicians often need to prescribe antibiotics for an infection before it is tested to identify the most appropriate antibiotic, says [Mary-Louise McLaws](#), a professor at the University of New South Wales and head of the NSW Hospital Infection Epidemiology and Surveillance Unit of the School of Public Health and Community Medicine. An antibiotic stewardship program assists the clinician by providing information that should maximise the likelihood that the most appropriate antibiotic is given before the test comes back.

Antibiotic stewardship is part of a wider course of action to reduce the rate of spread of antibiotic resistance that includes a comprehensive national resistance monitoring and audit system, co-ordinating education and stewardship programs and implementing infection prevention and control guidelines, McLaws says.

In Europe, a multinational surveillance program of bacteria isolated from specimens examined for clinical diagnosis of infection, known as "clinical isolates", includes superbugs and provides trending data, says Taylor. "There is a global program on TB [tuberculosis] and multi-drug resistance, as that is a very important disease," he says. "Similarly there is one for gonorrhoea that originated from and continues in Australia." Both conditions are common globally, and are only found on humans and transmitted directly between humans, so the impact of antibiotic misuse in their treatment is seen in the development of antibiotic resistance, and treatment failures.

Unlike Europe, Australia does not have a substantial broad-based surveillance program because the federal government will not fund it, Taylor says. "The information needs to be collected systematically and from defined populations at risk so the data can be used to predict likely efficacy of treatment."

In contrast to many of his colleagues, Taylor is largely optimistic. "For the common infections, excellent antibiotics are still available and others are coming off patent," he says, adding: "The search for new classes of molecules that can be modified to increase antimicrobial potency is ongoing but most are dead-ends."

When asked if the world may face a superbug plague of apocalyptic proportions, he says: "That is one perspective and may be relevant to TB and gonorrhoea. But there is too much hyperbole about superbugs. In our community, the place where they spread most commonly is in hospitals; or in the case of New Delhi, across the streets on sewerage outflow. It is important that those with the information use it wisely and do not spread unnecessary fears from a sense of desperation that government is not listening," Taylor emphasises. "[Medical practitioners need to] act responsibly, measure the extent and impact of the problem and report their findings."

Lobbying governments about what is essentially a public health problem and developing guidelines to reduce the spread and impact in our community is also crucial, Taylor says. "The answer lies in excellent diagnosis, excellent care and excellent pharmacy support, as well as continuing education of the medical profession and the community at large."

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