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Antibiotic resistance

Why is resistance to antibiotics on the rise?

Why are some bacteria resistant to antibiotics?

Some bacteria have structural or functional properties that make them intrinsically resistant to antibiotics to which other bacteria are sensitive. Over time, the genes encoding these properties have become transferable to sensitive strains, resulting in acquired resistance. The mechanisms range from a lack of target sites to which antibiotics bind, to the inactivation of antibiotic agents and the pumping of antibiotics out of cells. In addition to acquiring these traits, the widespread use of antibiotics can select resistant strains through spontaneous mutation that then spread through replication.

Acquired resistance is promoted by the use of antibiotics, which can kill all but the resistant bacteria, allowing the resistant strains to multiply.

However, both intrinsic and acquired resistance can be spread through plasmids, transposons or integrons, even across species. This type of horizontal gene transfer means resistant genes already present in the environment can spread even in the absence of antibiotic overuse.

Worse, many antibiotic-resistant traits can be packaged together, creating bacteria capable of resisting multiple antibiotics, so-called 'superbugs'.

Is antibiotic resistance a modern phenomenon?

Doctors have struggled with antibiotic resistance since introducing the first effective anti-bacterial drugs, sulphonamides. As early as the 1950s, 10 years after penicillin entered circulation, resistance was connected to the overuse of antibiotics in the medical profession.

However, concerns were curbed with the introduction of streptomycin in the late 1940s, tetracyclines and chloramphenicol by the 1950s and complex combination antibiotics in the early 1960s.

After all, the introduction of novel drugs ensured there was always a different treatment for newly resistant strains.

But concerns over the resurgence of antibiotic resistance have gained momentum since the 1970s. Today, fears over antibiotic resistance are at all-time highs as resistance rates, particularly in hospitals, escalate.

Why has antibiotic resistance increased?

Certain environments are fertile ground for antibiotic resistance. Heavy-metal-laced soils or chemically rich environments, the result of industrialisation, can spawn toxin-resistant bacteria.

However, in truth, the crux of the problem is antibiotic over-prescription in animals, plants and humans. This overuse went uncurbed for decades; after all, there were always new antibiotics. If streptomycin was ineffective, patients were switched to tetracyclines, when those did not work, vancomycin could be used.

Between 1935 and 2003, 14 new classes of antibiotic entered the market. Today the few antibiotics in Phase I–III trials are mostly follow-up compounds, with few novel mechanisms for treating infections.

Unsurprisingly, the supply of new antibiotics no longer meets the growing problem of resistant strains. One 2018 study found the median number of deaths attributable to antibiotic-resistant bacteria doubled between 2007 and 2015 in Europe.

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There are a number of very valid commercial critiques that limit the investment proposition of new antibiotics and recently led to a US company having an antibiotic approved by the FDA and filing for bankruptcy within a year. The best way to address these critiques is to develop an antibiotic for a new indication with no pre-existing competition. This is Destiny Pharma's approach. Andy Smith, Edison healthcare analyst

Why are we not discovering new antibiotics?

Antibiotics are not as profitable today as they were in the 1960s. With an ageing population, chronic long-lasting oncological, neurological and cardiovascular diseases provide consistent, sometimes lifelong, profits for pharmaceutical companies until loss of exclusivity. An average course of antibiotics can last, at best, 12 days, curing the disease in the process.

Along with short lifespans, antibiotic resistance creates a cycle of economic weakness. The lack of new antibiotics means doctors reserve new drugs for resistant infections, which further

depresses sales. As a result, the large pharmaceutical companies that drove the antibiotic boom are no longer investing in new antibiotics at scale.

However, as antibiotic-resistance rates worsen, governments and charities are trying to mitigate development risks by expediting regulatory approval and making incentives available.

The Organisation for Economic Co-operation and Development estimates that each year countries are investing around $550m in grant funding for antibiotic development. That is still less than Drive AB's estimate of c $1.5bn required annually over the next 30 years to meet the production rates of the early to mid-1990s.

But antibiotic development is not a desert by any means. In September last year, 48 new antibiotic treatments for serious bacterial infection were in clinical development.

Which are the notable antibiotic-drugs?

Shionogi's cefiderocol was recently accepted for review by the European Medicines Agency with an accelerated assessment due to its potential in antibiotic-resistant disease. Meanwhile, Destiny Pharma's novel antibiotic against sensitive and resistant Gram-positive strains has been endorsed by the FDA for a new indication.

Basilea's ceftobiprole, although not a new class of antibiotic, has entered the Phase III TARGET study for the treatment of acute bacterial skin and skin structure infection, and recently released top-line data. In addition, the company's ERADICATE study is expected to report results in H221.

One of the other commercial issues depressing the antibiotic sector is that new antibiotics are frequently studied in old indications where generic antibiotics are used as a first-line treatment. This further depresses the potential for new antibiotics.

In the preclinical space, Nosopharm recently discovered symbiotic bacteria with antibiotic properties, whereas new antibiotic teixobactin has been shown to be effective against antibiotic-resistant bacteria in mice. Mouse studies from the Universite de Rennes have also found a compound that seems to be effective in Gram-positive microbes as a bacterial toxin.

In addition, other antibiotic specialists continue to develop drugs and platforms, including Entasis Therapeutics, Tetraphase Pharmaceutical and Melinta Therapeutics.