Warnings about the ever-increasing threat of antimicrobial resistance (AMR) have been coming thick and fast in recent years. Must recently, in November, a report from the Organisation for Economic Co-operation and Development (OECD) called Stemming the Superbug Tide warned that over the next 30 years antibiotic-resistant infections could kill around 2.4m people around the world, including 50,000 in the UK, adding almost £3bn to the cost of healthcare.

Simon Portsmouth explains the latest trials of a hopeful new antibiotic and looks at the ongoing fight against drug-resistant bacteria.

**New antibiotic**

Of course, another weapon in the arsenal is to develop newer and more robust antibiotics. But this approach doesn’t come quite so quickly or cheaply – it can take up to a decade, with the costs running into millions, even billions.

While the funding and licensing environment for antibiotics may not be quite so attractive to pharmaceutical companies, that hasn’t deterred the US arm of the Japanese firm Shionogi in Japan, and Portsmouth’s job has since been to perfect the new drug’s efficacy and push it closer to commercial reality.

Shionogi’s response began several years ago, with the development of cefiderocol in Japan, and Portsmouth’s job has since been to develop it further, and to push it closer to commercial reality. "It was designed for Gram-negative AMR," he explains. "It is a siderophore, with the iron chelating molecule that leads to active transport into the cell. Previous siderophores haven’t reached human trials due to the rapid emergence of adaptive resistance, which isn’t the case with cefiderocol."

The new antibiotic fights infections by infiltrating and breaking down the defences of the bacteria – a process that Portsmouth likens to a Trojan horse. "Infection, the immune system removes the iron to starve bacteria of this essential metal," he says. "Bacteria produce siderophores naturally to scavenge free iron. Cefiderocol with a siderophore side chain highjacks or mimics this system to get transported into cells across the outer membrane and so overcomes some mechanisms of resistance, such as efflux pumps and porin channels – which are bacteria’s natural defences against pumping drugs out or preventing their transport across the cell membrane. Once inside the cell, the structure of cefiderocol is stable to carbapenemases and works like any other cephalosporin antibiotic by binding to and inhibiting penicillin-binding proteins."

**The trial**

For the trial covered in The Lancet Infectious Diseases journal in October, the future looks positive for cefiderocol, as efflux pumps and porin channels – which are bacteria’s natural defences against pumping drugs out or preventing their transport across the cell membrane. Once inside the cell, the structure of cefiderocol is stable to carbapenemases and works like any other cephalosporin antibiotic by binding to and inhibiting penicillin-binding proteins."

The future looks positive for cefiderocol, so does that make somebody at the heart of the response to AMR feel optimistic? "The trial showed efficacy over a very good comparator antibiotic and able to demonstrate the favourable safety profile," says Portsmouth.

Some side-effects were noted, but they were more or less in line with the team’s expectations. The most common was diarrhoea, though its frequency was no worse than with imipenem, they state. "We were pleased to see improved efficacy over a very good comparator antibiotic and able to demonstrate the favourable safety profile," says Portsmouth.

**The evidence for the rising menace of AMR is irreffutable, but instead of further alarming reports what’s needed now is action from governments, healthcare agencies and the pharmaceutical industry around the world.**

Simon Portsmouth 

**References**: 1. 2015 and the resulting deaths. "About 70% of the 33,000 deaths were attributable to Gram-negative infections," says Portsmouth. "In Europe the deaths for AMR exceeded those for TB, HIV and influenza combined." The OECD report estimates that antibiotic-resistant infections are killing more than 2,000 people in the UK every year and almost 30,000 in the US.

**Breaking down defences**

The evidence for the rising menace of AMR is irreffutable, but instead of further alarming reports what’s needed now is action from governments, healthcare agencies and the pharmaceutical industry around the world.

Shionogi’s response began several years ago, with the development of cefiderocol in Japan, and Portsmouth’s job has since been to perfect the new drug’s efficacy and push it closer to commercial reality.

"It was designed for Gram-negative AMR and designed to overcome β-lactamase activation and entry to the cell," he says. "Cefiderocol was designed to have stability against all known carbapenemases and was a response to AMR. It is a siderophore, with the iron chelating molecule that leads to active transport into the cell. Previous siderophores haven’t reached human trials due to the rapid emergence of adaptive resistance, which isn’t the case with cefiderocol."

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