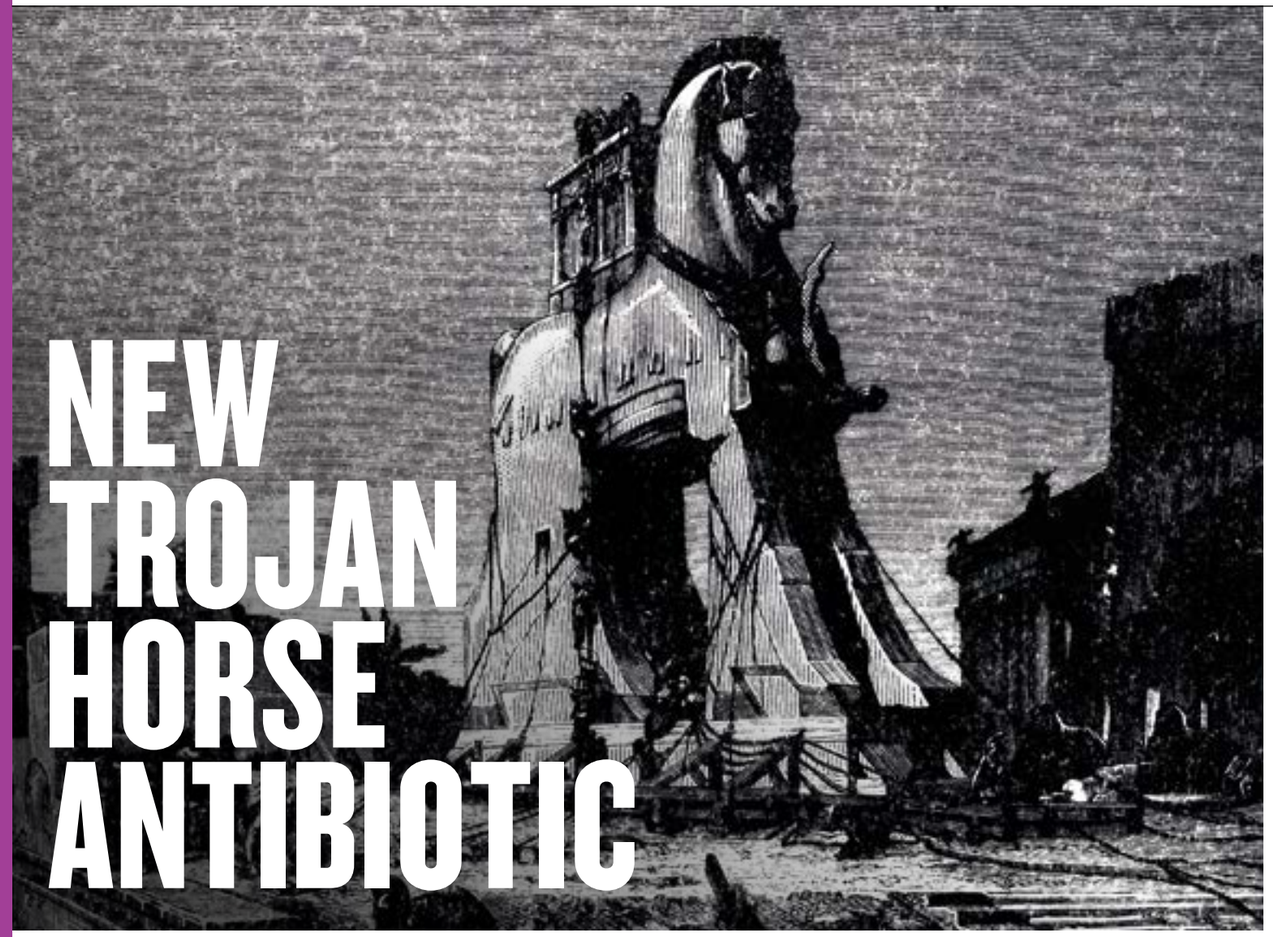


# NEW TROJAN HORSE ANTIBIOTIC

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

Warnings about the ever-increasing threat of antimicrobial resistance (AMR) have been coming thick and fast in recent years. Most 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 90,000 here in the UK, adding almost £3bn to the cost of healthcare.

The OECD's simple remedy for the looming crisis is to promote better hand hygiene, curb the over-prescription of antibiotics, and test patients quickly to see whether they have bacterial or viral infections. It also claims that any investment in a package of such measures would pay for itself within just a year.

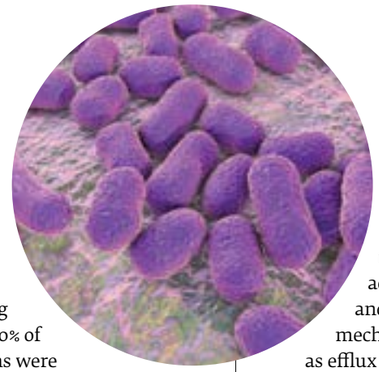
## New antibiotic

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 from "pursuing the development of novel treatments to combat this evolving threat".

It has been developing a new antibiotic called cefiderocol and its initial results were published in *The Lancet Infectious Diseases* journal in October.

Leading the Shionogi effort is its senior medical director, Dr Simon Portsmouth, who is not one to shrink from the danger posed by the spread of AMR. "This is clearly a real threat and already patients are dying with untreatable infections," he says, pointing to another report published in *The Lancet Infectious Diseases* in November. The piece from the European Centre for Disease Prevention and Control estimates the number AMR cases across Europe in 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 irrefutable, 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."

The new antibiotic fights infections by infiltrating and breaking down the defences of the bacteria – a process that Portsmouth likens to a Trojan horse. "In infection, the immune system removes 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 defence either 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*, cefiderocol was pitted against urinary tract infections (UTIs), which are the most common source of multiple drug-resistant Gram-negative infection. "The patients with complicated UTIs are a good population to study with monotherapy in a double-blinded manner," says Portsmouth. "This has been the common regulatory pathway for recent antibiotics undergoing streamlined development."

The results were encouraging. Portsmouth and his team hoped cefiderocol would at least match the performance of the well-established antibiotic imipenem and its sidekick cilastatin among a group of 452 patients randomly assigned either drug, but it actually scored a 73% success rate compared to imipenem's 55%. "We were pleased to see improved 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.

## The future

What's the next step in cefiderocol's promising development? "Further trials are ongoing in patients hospitalised with pneumonia and in carbapenem-resistant infections of the lung, urinary tract and blood stream," says Portsmouth. "We plan to submit a new drug application to the US Food and Drug Administration, followed by a marketing authorisation application to the European Medicines Agency and other countries." Anyone who wants to follow its progress can do so at clinicaltrials.gov under the identifiers NCT02714595 and NCT03032380.

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 among a big group of patients, including some who had not responded to other antibiotics," says Portsmouth. "Further trials in more difficult-to-treat AMR are ongoing, but overcoming the threat of AMR will require more than just new antibiotics. That said, it is reassuring that we're making progress with the development of these drugs." BMS

### SIMON PORTSMOUTH

- ✔ **1992** – Graduated in medicine from the University of Sheffield
- ✔ **2003** – Became an HIV specialist at St Mary's Hospital London
- ✔ **2008** – Worked on HIV-associated Kaposis's sarcoma and got an MD
- ✔ **2008** – Became a Fellow of the Royal College of Physicians
- ✔ **Present** – Moved into drug development for HIV and hepatitis C
- ✔ **Present** – Now working for Shionogi on cefiderocol and a new influenza antiviral.

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