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# EU research alliance fights back against resistant super-bacteria

Antimicrobial resistance is a growing health threat across the world, but EU-funded scientists are working together to boost research and find new treatments.

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Bacterial infections are a major health challenge, killing around 100 Europeans a day as they become increasingly resistant to common antibiotics. To address this, researchers like Dr Rienk Pypstra are working together to create more effective treatments.

The problem with bacteria – one of the simplest life forms – is that they evolve very quickly.

“With diabetes or heart diseases, for example, the human body is not evolving at a speed that means we have to have new treatments every three or four years,” said Pypstra, an expert in drug development and head of Infectious Diseases at UK specialist pharmaceutical consultancy tranScrip.

But it is different with infections, he warned, because “pathogens have such a short duplication time and are present in such big quantities that you see natural evolution at a very high speed”.

Pypstra coordinated the eight-year EU-industry co-funded COMBACTE-CARE research project, which ended in 2023. Working with an academic consortium, hospitals and laboratories across the EU, it laid the groundwork for research into antimicrobial resistance and development of better treatments.

Given the fickle nature of pathogens, the task was far from simple.

“Whenever we develop a new antibiotic, after a couple of years, pathogens emerge that have found a way to escape, and they start to proliferate, and they take over.”

Antimicrobial resistance is now considered one of the greatest global public health challenges. In laboratory conditions, some bacteria can double every 20 minutes and start developing resistance to antibiotics in about 10 days.

In the European Economic Area (EU countries plus Iceland, Liechtenstein and Norway), antimicrobial resistance is estimated to be responsible for 35 000 deaths every year, according to data by the European Centre for

Disease Prevention and Control. Without a concerted effort to address resistance, there are fears this could rise to around 390 000 by 2050.

**New treatments**

The public-private research project that Pypstra coordinated was part of efforts to produce new treatments for multidrug-resistant bacterial infections.

The aim was to find treatments for ailments, including complicated urinary tract infections, abdominal infections (often contracted following major surgery), and hospital-acquired lung infections, such as ventilator-associated pneumonia.

All those can be caused by bacteria resistant to a class of antibiotics known as carbapenems.

“For a long time, carbapenems were the ‘last-resort antibiotics’,” Pypstra said. “Then some bacteria emerged that could break down these carbapenems, and some of those are even resistant to the latest drugs.”

With resistance increasing, the World Health Organization now lists various carbapenem-resistant bacteria as priority pathogens, requiring research and development of new drugs.

One particular problem is a specific subclass of carbapenem-resistant infections caused by bacteria which produce enzymes that accelerate the breakdown of carbapenems and render them ineffective.

To tackle those bacteria, doctors were previously using older toxic agents or combining two specific antibiotics. But while the latter approach has had some success, it was fraught with difficulties.

The optimal dose of the two antibiotics was unclear, and they were often given to patients as separate intravenous infusions, on different time schedules. This made it less effective and complicated for medical staff.

Along with the usual safety and efficacy trials and non-clinical studies to find the optimal dose of each antibiotic in the combination, researchers also had to overcome some “manufacturing difficulties” as the two drugs are chemically very different, Pypstra said.

Their research led to a novel treatment that was recently granted marketing authorisation in the EU by the European Commission.

**Public-private partnership**

The development of new treatments in this field was supported by the Innovative Medicines Initiative (IMI), a public-private partnership between the EU and the European pharmaceutical industry.

Pypstra said it was important to show that such a partnership can work because antimicrobial resistance needs “other sources of funding besides the private market”.

With antibiotics, investment returns for drug manufacturers are limited and slow, often discouraging antibiotic research and development. Unlike many new drugs, antibiotics are not used as quickly and broadly as possible upon release, for several reasons.

Firstly, resistance spreads gradually, so initially there is not much need for widespread use of new antibiotics.

Secondly, antimicrobial stewardship – a globally accepted approach to reduce misuse of antibiotics – dictates that new antibiotics are kept in reserve.

“You don’t want to suddenly start using them broadly, because then you will very quickly select new mechanisms of resistance,” Pypstra explained. “You keep the best drugs on the shelf.”

But public-private partnerships aim to put the overall return on investment for drug companies on a par with other therapeutic areas, he said.

**Collaborative network**

Pypstra said that collaboration between academic centres and industry has proved very successful.

Collaborations of this kind have since evolved into a clinical trial network called Ecraid (European Clinical Research Alliance on Infectious Diseases), which builds on the work by IMI COMBACTE projects and on other EU research projects.

With 19 organisations across six countries, including from 600 to 700 hospitals across Europe, it offers a single point of access to a pan-European clinical research network for infectious disease.

The network's aim is to conduct trials for infectious diseases, including antimicrobial resistance, explained Ecraid's chief executive, Professor Marc Bonten, an infectious disease epidemiologist at UMC Utrecht in the Netherlands.

"The clinical evaluation of new antibiotics is extremely challenging because trials are on patients with acute infections that must be treated immediately," Bonten said.

This means there is little time for doctors to enrol patients in regular trials for new antibiotics. But a series of so-called perpetual observational studies conducted by the network could help address these time constraints.

These clinical studies, which enrol patients on a perpetual basis, collect data on antimicrobial-resistant bacterial infections in hospitals. They include patient risk factors, type of infection, bacteria involved, treatments used and patient outcomes.

"These observational data will allow epidemiological analysis, but the main goal is to create an infrastructure that will help us to do clinical trials more efficiently," Bonten said.

The studies are carrying out many of the processes needed for clinical trials, such as enrolling patients and collecting appropriate data.

This means that in the future, trials of new antibiotics and treatment combinations can plug into the network without having to start from scratch. In addition, they will also have background epidemiological data to compare their results against.

"The goal is to deliver and create an infrastructure in which randomised controlled trials can be embedded very efficiently," Bonten said.

"So, for any new antibiotic in the field of ventilator-associated pneumonia, complicated urinary tract infection or acute respiratory infection, we now have a tested system of hospitals across Europe that can enrol patients for trials."

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