What if a 'Trojan horse' strategy could help address antimicrobial resistance?

Antimicrobial-resistant infections are predicted to become the second biggest cause of death worldwide by 2050. Despite increasing investment in the development of new antimicrobials, awareness campaigns on antimicrobial misuse and abuse, and monitoring of antimicrobial use and resistance in animals, humans and the environment, antimicrobial resistance continues to grow and the last three decades have not seen even one novel antimicrobial class reach the market. Could the answer lie in a 'Trojan horse' strategy to disrupt a natural physiological process common to all bacteria?

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In Homer's telling of the fall of Troy, following an unsuccessful 10-year siege, the Greeks offered the Trojans a large wooden horse. Once the gift was inside the city walls, out came an army, led by Odysseus, who destroyed the city and ended the war. While it may seem far-fetched to use an old Greek myth as an analogy for the fight against antimicrobial resistance (AMR), the market dearth of new antimicrobials, despite millions of euros invested, means bold new strategies are needed.

The Trojan horse that could be 'offered' to antimicrobial-resistant bacteria is gallium. This metal-based nanoparticle strategy exploits an essential living requirement for all living beings: iron acquisition. As an essential micronutrient, during an infection iron is used as a pawn in a tug of war between humans and bacteria: our organism sequesters iron in red blood cells, as well as in heme, ferritin and lactoferrin molecules; in parallel, bacteria secrete iron chellators (siderophores and heme carriers) that bind host ferric iron (Fe(III)) and transport it to the bacterial cell. Using gallium (Ga(III)) as an antimicrobial would mean tricking the bacteria into believing they have acquired iron. Gallium is an iron-mimetic metal, of similar electric charge, ion diameter and biochemistry to iron. It can enter bacterial cells through iron membrane receptors, like a Trojan horse, and then replace iron in physiological processes. However, unlike iron, it cannot be reduced to divalent gallium. Therefore, it inhibits essential cell biochemical processes that depend on iron as a co-factor, quickly becoming toxic for the bacteria and leading to its death.

Gallium is not a novel promise. This FDA-approved drug for cancer treatment was shown more than 10 years ago to successfully inhibit the virulence of *Acinetobacter baummannii*, a nosocomial bacterial pathogen that has become resistant to virtually all known antimicrobials, including 'last resort' ones. Since then, gallium's antimicrobial activity has been demonstrated for other multidrug-resistant (MDR) bacteria considered by the World Health Organization (WHO) to be critical priority pathogens for the development of new antimicrobials. These include *Pseudomonas aeruginosa*, Enterobacterales species and *Mycobacterium tuberculosis*, responsible for tuberculosis, the second most deadly communicable disease (after COVID-19), causing 1.5 million deaths per year. More specifically, gallium was effective in a pilot phase Ib trial involving 20 patients with cystic fibrosis and chronic *P. aeruginosa* lung infections.

The exploration of bacterial iron acquisition as a novel antimicrobial strategy is not limited to the Trojan horse effect of gallium. Cefiderocol (developed by Shionogi) is a broad-spectrum siderophore-cephalosporin combination drug that showed activity against carbapenem-resistant pathogens for the treatment of complicated urinary-tract infections in double-blind clinical trials. In 2020, the European Medicines Agency (EMA) authorised its use as a 'reserve' against Gram-negative infections with limited treatment options. It is currently the only iron-acquisition antimicrobial authorised in the EU. Two other siderophore-cephalosporin products, GSK-3342830 (by GSK) and GT-1 (by Geom Therapeutics), are no longer in active development. The translational gap between the available evidence from preclinical research on iron-acquisition strategies as a target of antimicrobial drugs and the lack of follow-through in clinical trials could partially reflect known issues of fragmentation of EU health research and market failures.

Author: Luisa Antunes, Scientific Foresight Unit (STOA)

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Potential impacts and developments

When Alexander Fleming discovered penicillin in 1928, medicine entered a modern era, in which communicable diseases once responsible for child mortality, such as tuberculosis, pneumonia and diarrhoea, could finally be treated, contributing to a progressive improvement in life expectancy and quality. The emergence of bacteria resistant to all known antimicrobials could now push us back to a pre-antibiotic era, where people die from minor infections. The WHO has thus declared AMR to be a top 10 global public health threat.

Developing effective antimicrobials, raising health professional and public awareness to reduce the abuse and misuse of existing antimicrobials, strengthening surveillance, and investing in infection prevention and universal access to high-quality healthcare are some of the policy measures that the European Commission and WHO have indicated as an effective AMR response that integrates human, animal and environmental health ('One Health').

Effectively tackling AMR would reduce the mortality burden due to AMR infections. AMR directly caused 1.27 million worldwide deaths in 2019, estimated to rise to 10 million by 2050, surpassing cancer. In the EU alone, AMR is responsible for 33 000 yearly deaths, a trend which continues to increase, especially in eastern and southern countries, and is linked in part to lower investment in public healthcare.

A second impact would be reduced economic burden on EU national healthcare systems, which exceeds €1.1 billion yearly. COVID-19 showed how a health emergency can place extraordinary pressure on healthcare professionals and divert necessary attention from leading diseases (e.g. cardiovascular disease, dementia and cancer). The OECD estimates that applying simple policy measures proposed by the WHO (hygiene, antimicrobial stewardship, diagnostics and awareness campaigns) would save, in a year, about €3 for every €2 invested.

The emergence of 'superbugs' is a slow-motion pandemic, driven by the ease of lateral gene transfer in microbial communities and international spread through travel, including tourism and the food industry. Its cross-border nature calls for multidisciplinary, international coordination. Investing in universal antimicrobial access and access to safe water and sanitation would reduce the 5.7 million deaths worldwide due to treatable bacterial infections (e.g. cholera, dysentery, typhoid) in low- and middle-income countries and prevent dissemination of AMR.

Anticipatory policy-making

The EU supports research and development (R&D) projects on new therapeutics, vaccines and diagnostic tools through the FP7 and Horizon 2020 framework programmes and partnerships with Member States and industry. The EU-IMI partnership project GNA NOW is investing over €30 million in the discovery of new antimicrobials by 2024. The Health Emergency Preparedness and Response Authority considers AMR one of the top three priority cross-border threats and has allocated €580 million to the procurement of therapeutics against priority pathogens.

As part of the Pharmaceutical Strategy for Europe, the European Commission is currently revising EU pharmaceutical legislation, with expected adoption by the end of 2022. It includes 'orphan' medicinal products, used to treat rare diseases, a field typically underinvested in by the pharmaceutical industry. MDR tuberculosis and cystic fibrosis are examples of such diseases, for which new drugs and vaccines are urgently needed.

The discussion on antimicrobial R&D financing models usually centres around either 'push' or 'pull' incentives, which pay, respectively, for the inputs and outputs of R&D. Push incentives reduce the R&D cost for companies, whereas pull incentives reward successful R&D. A novel incentive model is 'de-linkage' (e.g. the UK's 'Netflix' subscription and the US PASTEUR Act), where governments pay an annual subscription for new antimicrobials, regardless of use. Another recent strategy involves transferrable exclusivity extensions, which have faced criticism due to higher medicinal costs. A proposed solution has been the creation of a European public infrastructure to accompany the entire drug cycle independently of market failures.

Lastly, research into infection prevention and surveillance could be more effective than the development of new antimicrobials. Vaccines contribute to disease mitigation and eradication, with low resistance. With the innovation in RNA technologies and medical AI, we could soon see new vaccines against cystic fibrosis pathogens and tuberculosis, relieving pressure on AMR. Developments in diagnosis, such as wastewater monitoring, metagenomics and AMR gene sequencing, could further help to hinder AMR infections at their inception.

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