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REVERSING A DYSTOPIAN FUTURE

NEW STRATEGIES TO DISCOVER ANTIBACTERIAL AGENTS

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NEW ANTIBIOTICS STRATEGIES (REVERSING A DYSTOPIAN FUTURE)

Resistance to antibiotics currently causes 700,000 deaths a year. If we don't find and implement solutions quickly, this number will shoot up to ten million a year by 2050, more than deaths due to cancer. The situation, given its importance and how hard it is to get the message across, is very similar to the climate emergency or crisis.

Although there are measures that can be put in place to minimize the problem, we're going to need new antibiotics with non-traditional mechanisms of action. However, new molecules are scarce and companies are no longer investing in this type of research among fears of limited returns. Faced with this situation, experts propose offering incentives to encourage public-private collaboration.

To discuss the importance of this problem, the latest advances and the difficulties of solving it, a group of top international experts met for a session of B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate led by experts in the field from the Barcelona Institute for Global Health (ISGlobal).

CONCLUSIONS

- There are many similarities between the problem of antimicrobial resistance and the climate crisis, both in their impact and how hard it is to get the message across. The economic consequences could be similar to a more than 2°C rise in global temperatures.

- We are going to need new drugs based on novel strategies with new mechanisms of action. Noteworthy proposals include searching in the oceans, precision antibiotics like monoclonal antibodies, the use of bacteriophages, nanotechnology and peptides that cause bacteria proteins to aggregate and collapse.

- It is very difficult to take new antibiotics to market, especially those with a new approach. Companies don't see the market opportunities and propose incentives to encourage public-private collaboration.

- It is important to boost current funding structures to promote the research and development of new molecules and to come up with new mechanisms, surely through public institutions or public-private partnerships, which will cover the lack of innovative proposals in the earliest phases of research.

1. THE RESISTANCE PROBLEM

Antibiotics resistance causes an estimated 700,000 deaths each year. If this continues, the number will reach ten million annual deaths by 2050. These were the figures published in 2014 by a committee of experts led by Lord Jim O'Neill under the umbrella of the British government.

"We need a global plan to tackle this situation," warned Jordi Vila, head of the Microbiology Department at Hospital Clinic Barcelona, director of the Antimicrobial Resistance Initiative at ISGlobal and co-leader of this B·Debate session. The main mechanism behind resistance is selective pressure. The genomes of bacteria are always changing randomly and some of these changes can give them advantages in fighting a certain type of antibiotics. When that type is used, and especially if not administered correctly, the most resistant bacteria tend to survive (be selected) and will later have an easier time spreading.

"**There are different ecological niches we have to take into account when using antibiotics**," explained Vila, referring to veterinary uses, both in animals and the food chain; and use in developing countries, in the community and in hospitals. "It is a complicated situation with many interactions among these niches and they can be spread through food, migratory birds, international travel, etc."

This global problem also has significant economic consequences. **If nothing is done to stop the situation, according to the 2014 report, the impact on countries' gross national product could be between 2% and 3.5%.** This is the same as the estimated impact of the ominous two-degree increase in temperatures due to global warming.

For Laurence Roope, a researcher at the University of Oxford Health Economics Research Centre, **there is a clear similarity between antibiotics resistance and climate change or the climate crisis**. Both in their characteristics and consequences, and in the challenge they pose in terms of informing the public and raising awareness. In both cases there is a 'tragedy of the commons', in which **individuals, acting rationally, end up destroying a limited shared resource**. Plus, according to Roope, "indiscriminate use of antibiotics, like carbon, has future costs. There isn't much incentive for people to change their behavior now because the consequences are much further down the line and are inevitable unless other people also reduce their consumption; and the models are complex and, to a certain extent, uncertain." However, "given the possible consequences, and just as preventive measures are the right move for climate change, they should also be applied in the case of resistance."

Roope posits that the economic consequences could help bolster the message, both to reduce consumption of antibiotics and incentivize the development of new molecules. But this field is problematic for companies, because they are "a product that is difficult to develop and should be used as little as possible," which is why he proposes that "**profit should not be tied to volume sold, as antibiotics have value as a treatment option, beyond how often they are actually used.**" He also reminded the audience that, right now in the world, more people still die because they don't have access to antibiotics than due to antibiotic resistance.

Apart from researching new antibiotics, some strategies could come through repositioning old molecules, as noted Jesús Rodríguez-Baño, president of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). "**Some aspects of old drugs weren't studied in depth enough, and could also be used for different types of infections**," he noted. Or they could come from a combination of drugs, as explained Javier Garau, head of internal medicine at Clínica Rotger Quironsalud in Palma de Mallorca. However, "sometimes this concept is abused, out of fear of not covering everything. **We need more studies on the most promising combinations**."

However, as Jordi Vila noted, **"no matter how many measures we implement, we'll never get to zero resistance. We're going to need new antibiotics**." Luis Martínez-Martínez, head of the Microbiology Service at Hospital Universitario Reina Sofía in Córdoba, warned that there are fewer and fewer new molecules being discovered, and even for them resistances are appearing. Plus, "**only one in five antibiotics that start phase I clinical trials are ever approved**."

Ursula Theuretzbacher, founder of the Center for Anti-Infective Agents in Vienna, Austria, gave her analysis of current research into new antibiotics. The cons: the vast majority of those being tested in the clinical phase are variations of old ones, so they are susceptible to cross resistance (the same mechanism causes resistance to several similar antibiotics). The pros: more than half of the pre-clinical studies involve a less traditional approach. And "we need new targets, new mechanisms of action."

2. THE SEARCH FOR NEW ANTIBIOTICS

"In the search for new antibiotics with new mechanisms of action, nature is still a great place to look," noted Sara Soto, associate professor at ISGlobal Barcelona and co-leader of this B·Debate session. Specifically, "little exploration has been done in the seas and oceans, taking into account that up to 10,000 new species are discovered each year."

Additionally, as noted Domingo Gargallo-Viola, CSO of ABAC Therapeutics, "**bacteria are much more genetically diverse than mammals**. If antibiotics have traditionally targeted very conservative evolutionary aspects, how can we keep finding new broad-spectrum antibiotics?" His answer is to follow a path similar to that used in precision oncology, targeting specific pathogens.

This is the path Hasan Jafri presented. The Director of Clinical Research at AstraZeneca presented a new type of monoclonal antibodies that target *Pseudomonas aeruginosa*, one of the pathogens that have developed critical resistance. This new approach could help minimize and/or complement the use of antibiotics and Jafri calls it a "paradigm shift".

One of the advantages of this precision approach is that they are much more tolerant of our own bacteria, our microbiome, which suffers when we have to take broad-spectrum antibiotics and which, also subject to selective pressure, can act as a reservoir of resistances. In fact, it is directly associated with immunity, both given its function of 'training' the defenses and for its job as a barrier to infections. Curiously, as explained Àlex Soriano, chief of the Infectious Diseases Service at Hospital Clinic Barcelona, the feces transplants indicated to treat *Clostridium difficile* infections are associated with fewer recurring urinary-tract infections, possibly because the

transplant decreases the amount of resistant bacteria. Likewise, the rate of blood infections is much lower than in patients treated with antibiotics.

Another novel treatment is the use of bacteriophages, viruses that naturally attack and destroy bacteria. Although they have been in use for decades, especially in former Soviet states, "we don't have any scientific proof that they work yet," explained Patrick Jault, who helped launch the European PHAGOBURN project in 2013. "What we have is a path towards a potential therapy," he continues. **"In general, what we are looking for is a combination, a stable cocktail of phages that can work on a broad spectrum of bacteria, but this is difficult to produce."**

As proof of concept, Jault presented the results of a study published in 2019 in which a combination of phages was used to treat *Pseudomonas* infections in burn patients. The cocktail was less effective than the standard treatment, but it did work, "and at a much lower dose with fewer side effects," explained Jault.

A more novel approach involves the use of peptides that inhibit protein aggregation. "**Not much is known yet, but up to 70% of newly synthesized proteins aggregate (and lose function) because they are not properly formed**," explained Els Beirnaert, CEO of Aelin Therapeutics, in Belgium. This company has developed an algorithm that identifies the regions of proteins that are most susceptible to this type of aggregation. Comparing them to the human proteome, they choose the ones that could work for at least five different bacteria without affecting our proteins. With this information, they create peptides (called Pept-ins) that selectively drive the aggregation of specific proteins, leading to 'proteostatic collapse'. "We're still in the early stages of research, but this concept develops a new mechanism of action for new targets and seems to generate few resistances," explained Beirnaert.

Other advances have to do with how antibiotics get to the point of infection. **One of the great promises is the use of nanoparticles**, with many potential advantages, like the fact that they could maximize drug efficiency at much lower doses. However, as noted Eduard Torrents, group leader at the Institute for Bioengineering of Catalonia (IBEC), "**many papers have been published about this, but it hasn't reached clinical practice yet**."

Based in part on this technology, Joan Gavaldá and his team at the antibiotics resistance lab at the Vall d'Hebron Research Institute are developing two products to fight infection by resistant microorganisms that colonize medical materials like

prosthetic joints and tracheal tubes. Jointly referred to as ThermoShot, they are silver nanoparticles that allow the union of antibiotic amikacin and are susceptible to acting due to hyperthermia (through a low-intensity electric current, for example). In the laboratory, this strategy boosts antibiotic activity up to 30-fold, even with highly resistant bacteria.

3. HOW TO ENCOURAGE RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS

If the current situation continues, by 2050 more people will die of resistant bacterial infections than cancer. However, "the investment in research into new antibiotics in the United States is 15 times smaller than in cancer research," noted Laura Marín, head of Secretariat for the JPIAMR program in Sweden. In fact, "**several companies are turning their backs on antibiotics research**," warned Seamus O'Brien, director of the GARDP consortium.

In general, explained O'Brien, the limited investment in this field is due to the fact that the estimated return is much less than that of other indications. Companies "**don't see the market opportunities to justify this commitment**."

According to Joan Bigorra, deputy director of Strategy and Innovation at ISGlobal Barcelona, there should be incentives to encourage public-private collaboration, like the ones that were introduced to promote research into rare diseases without treatment. So, **the incentives should be tied to sharing "priorities, risks and financial and social benefits, and to ensuring transparent pricing**."

For Seamus O'Brien, "the public health challenges involved in antibiotics resistance require unprecedented levels of coordination and cooperation," and he also believes it is necessary to encourage public-private collaboration, as it will "have a significant impact on the development of new antibacterial interactions." However, as Laura Marín noted, the final phase of clinical trials is important but, in general, "**there is a lack of innovative proposals in the earliest phases of research**." In fact, "current lines only offer partial coverage of priority pathogens in the long term," warned Gemma Buckland-Merret, head of the Science Lead Drug Resistant Infections Programme at the Wellcome Trust in London.

Jordi Vila concluded with “mixed feelings: hopeful, given the high quality of the proposals for new molecules in the initial phases of research; but concerned because we are facing a huge hurdle in taking molecules through to the clinical development phase.”

And time waits for no one.