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ROAD

Combining therapies and combining research - the strategy for retaining antibiotic security

By Professor Anthony Coates

The World Health Organization recognises antimicrobial resistance (AMR) as one of the most pressing global threats to medicine. Without effective antibiotics, much of the success of modern medicine, such as the levels of unprecedented survival rates from major surgery or super effective, chemotherapy treatment, would be totally compromised. With our defences running out, where is the innovation and investment in the next generation of antibiotics? Who is stepping up to take on the challenge?

Too easy, for too long?

Antibiotics have been the cornerstone of modern medicine since the 1940s. However, concerns are growing as to their sustained effectiveness due to the alarming emergence of drug-resistant 'superbugs'. Antimicrobial resistance (AMR) is a complex issue of global concern that has the potential to void advances in modern medicine. If we can't defend ourselves from basic bacterial infections, we render other areas of medicine redundant.

Dr Marc Sprenger, director of WHO's Antimicrobial Resistance Secretariat has previously warned that unless intervention is made, the burden of deaths from AMR could balloon to 10 million lives each year by 2050. That's a staggering one death every three seconds. With the world on the cusp of a post-antibiotic era, WHO has established the Global Antimicrobial Surveillance System (GLASS), a sort of tsunami early warning system, to constantly monitor the situation.

If not big pharma, then who?

WHO recently published a global priority pathogen list. A hit-list of the most harmful and potentially uncontrollable infections, against which we most urgently require an effective safeguard. The list is intended to spur governments to put in place policies that incentivise basic science and advanced R&D through both publicly funded agencies and the private sector investing in new antibiotic discovery.

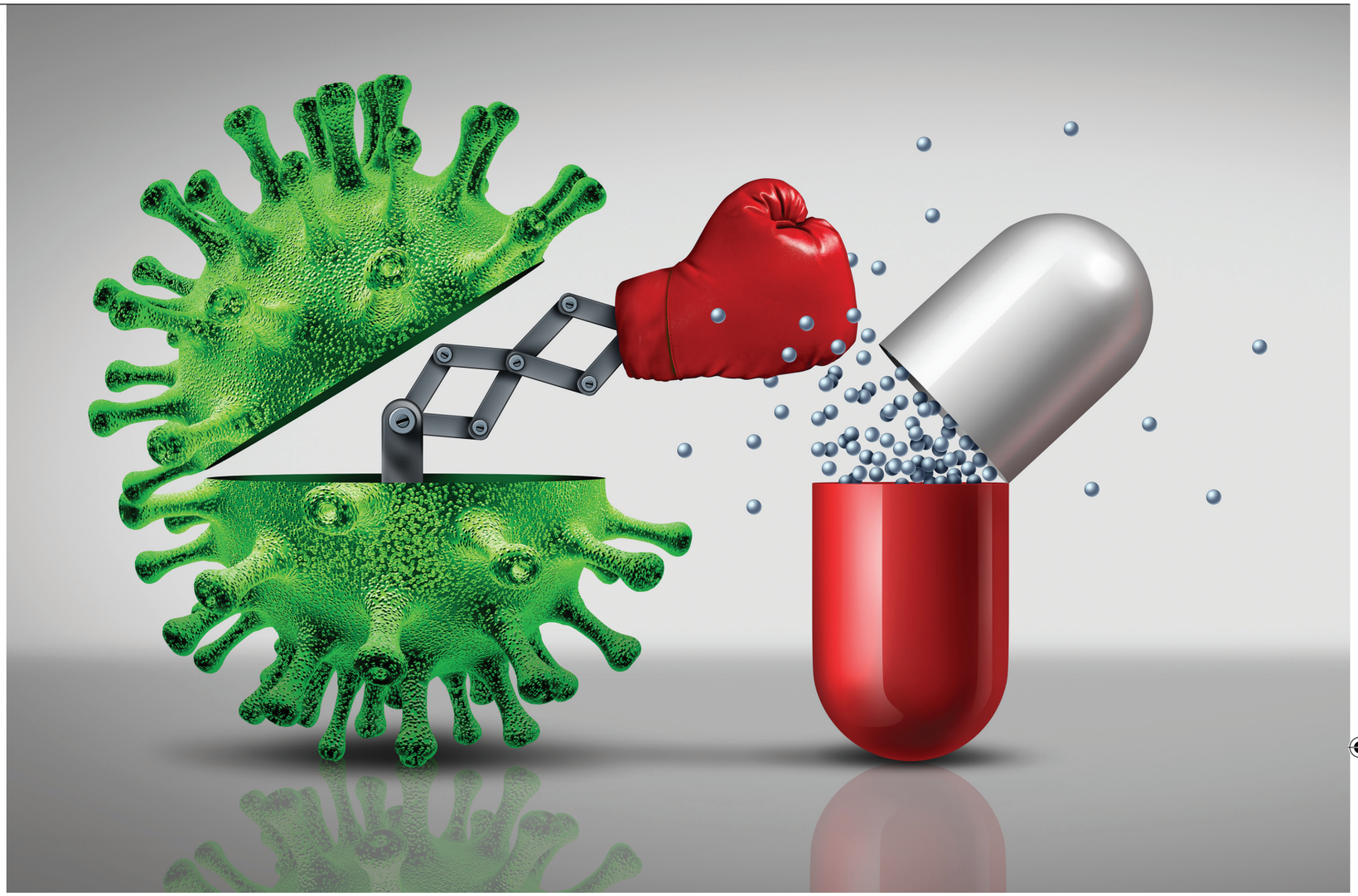
Yet 'big pharma' has mostly ruled itself out of the antibiotics game, favouring a focus on more incremental increases in innovation in chronic disease areas, rather than the more unpredictable leaps needed to keep up with the development of bacterial mutation. The high risk of creating a new chemical entity deters large pharmaceutical operations. This leaves the fight for antibiotic survival, arguably one of the most urgent fields of drug development, to smaller, more nimble biopharmaceutical companies.

There are growing concerns about the lack of new drug development surrounding antimicrobial resistance. Dr Brad Spellberg, one of the co-authors of *Bad Bugs, No Drugs* and commentator of the antibiotic sector, argues that while we are entering a 'post-antibiotic age', "the concept that we've exhausted the pantry is ridiculous [and] now we have to dig deeper, think harder and more cleverly".

Thankfully research is very much alive among the more agile, super-specialist research organisations. While the commercial difficulty in creating a new chemical entity has to date deterred big pharma, one novel approach, recognised by WHO, and gaining significant traction, is combining existing antibiotics to create new super-resistant combination therapies.

Combination therapy

Antibiotic Combination Therapy was developed in 1952 for the treatment of tuberculosis. While resistance developed against streptomycin alone, combination with another antibiotic prevented the emergence of resistance. This crucial observation was followed by combination therapies for other major disease areas such as AIDS and cancer. However, antibiotics for common bacterial infections, for example, staphylococci and Escherichia coli continued to be single molecule therapies.



Very few companies are pursuing a combination therapy strategy. Helperby Therapeutics is at the forefront of antibiotic combinations for common bacterial diseases. Wholly focused on the discovery and development of new antibiotic combinations, it has already registered 128 patents for novel combinations active against highly resistant bacteria. Helperby is identified by WHO as a company with candidate therapies in clinical trial stage that are capable of fighting all three Critical Priority Pathogens.

The work that Helperby has done has been backed up by the discovery of Dr Pamela Yeh and her team at the Department of Ecology and Evolutionary Biology, University of California, Los Angeles (UCLA). They found thousands of four- and five-drug combinations of antibiotics that demonstrate highly effective bactericidal activity. They compared two-, three-, four- and five-molecule combinations. The expectation was that some of the combinations would be very effective at killing the bacteria, but the team were startled by how many potent combinations they discovered.

"There is a tradition of using just one drug, maybe two," said Pamela Yeh. "We're offering an alternative that looks very promising. We shouldn't limit ourselves to just single drugs or two-drug combinations in our medical toolbox. We expect several of these combinations, or more, will work much better than existing antibiotics."

It was previously held that the risks of combining antibiotic drugs often outweighed the benefit because of adverse interactions. But Dr Yeh's team found the direct opposite, and reported that as more drugs were combined, an elevated frequency of synergy was observed. This evidence could just be the turning point in the fight against the spread of superbugs.

Quicker, safer, cheaper

Helperby has already established that its combination technique has the potential to extend the life of last-resort antibiotics. With two candidates in phase 2 and a further one phase 2/3 ready, it has announced a collaboration with UCLA in which it will work closely to explore the commercial opportunity of additional, new combination therapies. The collaboration will include the sharing of data, expertise and research methodology.

"The 'one drug, one target' model has limited viability," said Professor Coates, CSO at Helperby. "Combination therapy is the norm in the treatment of many cancers and viral infections such as HIV and even some bacterial diseases such as tuberculosis. It is similarly a viable alternative to the development of totally new antibiotics, a process that could take many years to reach the market."

Dr Yeh recently published on the phenomenon of emergent synergy of combining two or more existing antibiotics and their efficacy against pathogenic E. coli. The rejuvenation of existing antibiotics using synergistic combinations is likely to be an integral part of the drug development strategy to combat newly emerging pathogens.

Of course, other strategies also play their part: improved antibiotic stewardship, good infection control, publicity about AMR, more effective vaccines, less use of antibiotics in agriculture, fast diagnostic testing, more professionals working in the AMR field and more investment for clinical trials. Investing in these combined strategies will keep mankind ahead of antimicrobial resistance and is crucial in order to preserve a world where simple infections do not routinely kill otherwise healthy people.

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