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editorial

A route out of resistance

Antimicrobials have been one of the biggest success stories in medical history, but the emergence of drug resistance is threatening our ability to successfully treat infections. New approaches, interdisciplinary frameworks and policies have an important role in preventing entry into a post-antimicrobial era.

In his 1945 Nobel lecture, Alexander Fleming cautioned that despite the promise of antibiotic therapy "there is the danger that the ignorant man may easily under dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." Seventy years later, and despite decades of successful treatment, our prized antimicrobial toolbox is becoming obsolete and untreatable infections in the clinic are part of the new normal.

Despite news outlets proclaiming a resistance apocalypse, the vast majority of infections today remain treatable. However, the future threat of widespread antimicrobial resistance (AMR) is real and should be taken seriously. Drug-resistant infections are associated with 50,000 deaths per year in the US and Europe alone, and worldwide incidences are likely much higher. A recent analysis projected that if pathogens were to become resistant to all available drugs, annual infectious disease deaths could reach 10 million by 2050, and end up costing US$100 trillion in lost economic output[1].

In light of such statistics, many groups have publically called for action against the emerging AMR threat, identifying several research and policy shortcomings that remain to be addressed[2,3]. For example, in a Comment in this month's issue, Carolyn Shore and Allan Coukell from The Pew Charitable Trusts discuss a roadmap for new antibacterial development aimed at tackling resistance. Over the past year, Pew convened a meeting with academic and industry scientists to propose a series of concrete steps to jumpstart new antibacterial development, including an injection of targeted funding to build a new infrastructure for sharing expertise and data and ensuring that results are converted into translational ideas.

The Pew proposal outlines key questions that remain unanswered in antibiotic development, in particular arguing for expanded research in understanding guiding principles for designing drugs that can penetrate bacteria and are resistant to efflux. The roadmap also calls for the creation of diverse chemical libraries to engage novel microbial targets and investment in validating non-traditional antimicrobial approaches such as host modulation, new biologics (for example, monoclonal antibodies) and microbiome supplementation. Non-traditional use of small molecules to target virulence or resistance mechanisms rather than essential pathways may also help rescue the clinical usefulness of drugs for which widespread resistance has already emerged. New protocols and scientific benchmarks will likely be needed to assess the viability of these approaches.

Beyond therapeutics, there is a need for new diagnostics that can identify resistance profiles before treatment is initiated. DNA amplification- and sequencing-based technologies hold promise for sensitive and fast detection of mutations associated with drug resistance, but to date, these platforms work for only a few drugs in which resistance mutations have been validated. A challenge will be to tailor these methodologies at the point of care to faithfully detect drug resistance for compounds with complex mechanisms of action in a variety of clinical specimens and pathogens.

Although the Pew roadmap focuses on accelerating drug development, there are fundamental questions regarding the emergence of resistance that also deserve attention. In particular, AMR can arise through different mechanisms depending on the pathogen and nature of infection; therefore understanding the physiological and ecological bases of these resistance acquisition events, especially within infection-relevant contexts, will be key to designing appropriate resistance management guidelines. Also, while there are energetic costs to microorganisms in producing resistance factors, the importance of resistance-associated fitness costs during infection remains unclear. Notably, in this month's issue, an Article by Weiss and colleagues shows that while colistin resistance can be lost *in vitro* when antibiotic treatment is stopped, resistant bacteria are enriched *in vivo* and can kill mice even in the absence of drug. Thus, reversing resistance is not simply a case of removing drug pressure, and more work is needed to understand how specific pathogens and resistance mechanisms can impact the ability of resistant strains to persist in the population.

New policies to restrict indiscriminate antimicrobial use are also needed to extend the life of our current drugs. Over-prescription remains a major concern, as unintended use of antibiotics can have drastic effects on our microbiota and enrich for resistant microorganisms. Agricultural use of antibiotics to increase livestock yield can also select for resistant bacteria, and recent reports of the colistin resistance gene MCR-1 being found in our food supply has stoked fears that colistin use in animals could threaten the clinical usefulness of this last-line drug against several multidrug-resistant pathogens.

The Pew roadmap and the growing number of similar calls for action highlight the need for new interdisciplinary frameworks to integrate different expertise and steer research programmes in more coordinated directions. Funded by public–private partnerships, these initiatives would support grants, establish organizational structures and databases, and, importantly, create economic incentives for industrial participation in developing new drugs. While clearly warranted by the potential scale of the AMR problem, calls for new initiatives come easily and have been made on previous occasions. However, the reality of actually securing additional funds (Pew estimates implementation of their roadmap would cost US$200 million over five years) and establishing new integrated structures for research and drug development is not to be underestimated. If such plans are to be realised, it will require commitment from all parties involved. Ultimately, our ability to successfully translate ideas to the clinic depends on governments being forward-thinking and committing tangible investments to tackle this increasingly important problem. ❐

References

1. *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations* (The Review on Antimicrobial Resistance, 2014); http://go.nature.com/QVqY2M
2. ISDA *Clin. Infect. Dis.* **52**(suppl. 5), S397–S428 (2011).
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Correction: A route out of resistance

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The original version of this Editorial incorrectly credited the need for new diagnostics to identify resistance profiles to the Pew roadmap, which makes no such suggestion. We apologize for any confusion this may have caused; all versions of the Editorial have been modified to rectify this error.