Are we overlooking the obvious? Bacterial evolution is at the heart of antimicrobial resistance

The Global Burden of Disease study projects that deaths from antimicrobial resistance (AMR) will increase from 1·1 million in 2021 to 1·9 million by 2050,[1] underscoring the urgent need to preserve effective antibiotics. The Review by Charlotte Ho and colleagues[2] in *The Lancet Microbe* highlights the value of non-antibiotic approaches in combating AMR; however, an often overlooked aspect is the rapid evolutionary adaptation of pathogens. Sustainable solutions against AMR need to incorporate strategies that account for these adaptive changes.

From an evolutionary perspective, the most effective way to prevent AMR is to reduce the use of antimicrobials, thereby reducing drug-related selection of bacterial pathogens.[3] Even when antimicrobial therapy is absolutely necessary, evolutionary principles can help to further optimise therapy, for example, by selecting antimicrobial drugs with low resistance rates (ie, drugs that elicit resistance through mutations at only a few genomic sites or those for which resistance always requires multiple independent mutations) or high costs of resistance (ie, the expression of evolved resistance comes with a trade-off, leading to a decrease in the expression of other fitness-related traits), or both.[3,4]

One example of a highly promising trade-off is collateral sensitivity: the evolution of resistance to one drug directly causes increased sensitivity to a second drug (eg, ciprofloxacin-resistant *Pseudomonas aeruginosa* shows high sensitivity to aminoglycosides).[5] Another evolution-informed strategy is to combine antimicrobial drugs with one another or with other non-antimicrobial substances, either simultaneously or in sequence. Ideally, this approach should align with points outlined in the previous paragraph, aiming to create highly selective environments that make bacterial adaptation difficult or even impossible.[3,4] The potential of combining antimicrobials with other non-antimicrobial substances has been neglected in the past and might offer new options for combating AMR in the future.

Finally, a key strategy is to optimise therapy by taking into account the human microbiome, whose integrity and functionality can be compromised by antimicrobial therapy, potentially causing other types of severe diseases in affected individuals. Such disruptions can facilitate AMR through the horizontal transfer of resistance genes; however, the microbiome could also be harnessed by promoting protective or highly competitive microbes, or both, thereby helping to eliminate or control the abundance of harmful pathogens.[4-6]

These examples highlight the need for a well defined translational strategy that integrates these evolutionary insights into diagnostic and therapeutic practices. Such an approach can reshape the management of AMR by embedding evolutionary principles directly into patient care, guiding the development of sustainable antibiotic therapies.

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