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Editorial overview: Antibiotics special issue
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While writing this Antibiotics editorial it is impossible to ignore the broader, present context of infectious diseases. The SARS-CoV2 global pandemic has made immense impacts in all facets of life—many experienced unspeakable tragedies, families have been separated, experiences and opportunities have been sidelined, life itself was less bright. Of course, the pandemic has also impacted research, teaching, our authors, our editors, and likely you, our readers. This year, we reflect with special gratitude to all those who are treating, researching, and studying infectious diseases.

In this Special Issue, we focus on bacterial resistance to antibiotics. Many readers will already be aware of the gravity of this crisis. Without significant action and intervention, antibiotic resistance is predicted to cause 10 million annual deaths worldwide by the year 2050, outpacing the predicted mortality from cancer [1]. Antibiotics are truly miracle drugs that transformed our ability to treat bacterial infections and paved the way for major medical breakthroughs such as transplants. Although they have been used for over 75 years, major questions about antibiotics remain, and there are numerous monumental challenges presented by bacteria that we must overcome in order to preserve the power of these drugs. Key challenges include the increasing occurrence of untreatable infections; the need for rapid diagnostics to identify infecting organisms and their antibiotic resistance profiles; the need to ration a dwindling supply of therapeutics; and the urgent push to develop new effective drugs and other antibacterial approaches. Similar issues played out at a breakneck speed during the SARS-CoV2 pandemic. That these issues focus collective global attention, resolve, and resources, offers hope that great progress can similarly be made in confronting the crisis of antibiotic resistance.

The spread of antibiotic resistance continued unabated throughout the pandemic. If anything, it intermingled with the pandemic response. COVID patients frequently received antibiotic prescriptions very early in their treatment, before routine test results could have been at hand, and most COVID patients ultimately lacked diagnoses of suspected or confirmed bacterial infections [2]. Overburdened healthcare providers also suffered outbreaks of antibiotic-resistant infections in several COVID treatment units [3,4].

The pandemic has emphasized the value of accurate and timely diagnostics for treating individuals and controlling infections. For bacteria, the gold standard broth microdilution MIC assay has long been used for detecting resistance. While a ‘resistant’ profile in MIC assays helps clinicians avoid treating with ineffective antibiotics, MIC assays do not sensitively detect some forms of resistance. Standard MIC assays lack the sensitivity to detect minor subpopulations of bacteria that can resist the action of an antibiotic
and continue growing. Such resistance is termed ‘phenotypic resistance’ (involving no stable genetic changes or acquisition of resistance determinants) and its incidence can be surprisingly common in clinical isolates. So, while an MIC assay may indicate the use of a particular antibiotic, phenotypic resistance may ultimately prevent its clinical effectiveness. In this issue, Akiyama and Kim offer a review of phenotypic resistance, the possible molecular mechanisms, and offer insight into how mathematical modeling can help explain these phenomena. There is an ongoing push to engineer newer assays that detect resistance using microfluidics on smaller bacterial population sizes and with rapid readouts. Such diagnostic tools are much needed, but in some cases may not survey sufficient numbers of bacterial cells to detect minor resistant subpopulations. An understanding of how the actions of antibiotics on individual cells can impact broader bacterial populations will be important to fully realize the predictive power of a new generation of diagnostic tools.

A major obstacle to the effectiveness of antibiotics is efflux of drugs from the bacterial cell. Some efflux pumps can expel thousands of structurally diverse chemical compounds. Zgurskaya et al. examine this remarkable feature and polyvalence, outlining the challenges of developing effective efflux pump inhibitors. Curiously, some of the best efflux pump inhibitors are themselves efflux substrates. How such inhibitors exert their activity is also explored. The article by Hassan et al. underscores that we have only a limited knowledge of the efflux systems used by bacteria, as the authors describe the newly discovered PACE family of efflux pumps. Although this system is effective at removing the biocide chlorhexidine from the cell, genomic and molecular analyses suggest that PACE efflux pumps emerged to pump out native polyamine substrates, highlighting endogenous physiological roles as well.

Another major challenge are biofilms whose structure, matrix, and outer surface can limit the bioavailability of antibiotics to reach bacterial cells. Bacteria in biofilms can be 1000-fold more resistant to antibiotics than when grown in planktonic form. Anderson Goncalves da Silva et al. highlight distinct strategies to overcome biofilms which include physical disruption or removal (i.e., removing implanted devices), the use of agents which disperse the biofilms, and the development of antibacterials that are unhindered by biofilms.

As mentioned previously, some bacterial strains are now resistant to all available antibiotics. To overcome the resistance of such isolates, clinicians have long combined multiple antibiotics, which can lead to synergistic efficacy. However, while this approach has sometimes been effective, the rationale for how to choose antibiotics to combine has been murky at best, and clinicians are often forced to guess. Davis et al. discuss important factors such as the role of the microenvironment in the efficacy of combinations, the development of resistance to combinations, and new technologies that will facilitate the testing of greater numbers of combinations.

It is clear that new antibiotics will be essential to meet the continuing challenge of resistance. Randall and Davies discuss how new computational tools can enhance discovery and optimization efforts that use large chemical compound libraries, novel biosynthetic gene clusters, or peptide-based molecules. Making use of such modern approaches may de-risk early discovery efforts and/or accelerate the work of chemical optimization.

In addition to new antibiotics, distinct antibacterial approaches are being explored. Novick et al. provide a broad review of diverse approaches including the intriguing topic of live predatory bacteria which have been administered to patients to seek out and destroy infecting bacteria, bacteriophages, and the use of phagemids and antibacterial drones.

Finally, recent years have seen an explosion of research and insights into the commensal bacteria that collectively form our microbiome. Seemingly by the day we are learning more and more about how the microbiome impacts all aspects of our physiology. The immense power of the microbiome can also be harnessed to exclude pathogenic bacteria in a process termed colonization resistance. Here, Shealy et al. discuss this process, including a discussion of how specific bacterial metabolites can prevent expansion of pathogens as well as how metabolic flexibility of the pathogens allows them to fight back.

Unfortunately, the crisis of antibiotic resistance will worsen before we can regain the upper hand. The actions that researchers, clinicians, and governments take now and in the coming years will have a huge impact on how soon we can shift the momentum. We are optimistic that great advances can be made, but only if sufficient resources and attention are paid to this problem. We hope this Special Issue will encourage the next generation of scientists and clinicians to join this most critical fight.

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