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editorial

Superbugs but no drugs: steps in averting a post-antibiotic era

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The post-antibiotic era: grim prospects for a possible future

The discovery of antibiotics has transformed medical practices and saved countless lives. Yet, the misuse and overuse of these 'miracle drugs' have inadvertently led to the spread of antimicrobial resistance (AMR) (Fig. 1). Along with the emergence of multidrug-resistant (MDR), extensively-drug-resistant (XDR) and pan-drug-resistant pathogens, the world is on the verge of a post-antibiotic era, which would plunge medicine back into the dark ages. In this gloomy scenario, treatable infections and routine surgery would become life threating. If not seriously addressed, this silent epidemic is projected to kill 10 million people per year by 2050 with an economic burden of US$100 trillion. While AMR continues to rise, the discovery of new antimicrobials has drastically declined. Between 2000 and 2015 only five new antibiotics entered the market compared with 20 antibiotics marketed between 1940 and 1962. This has been further compounded with big pharma such as Novartis, AstraZeneca, Sanofi and Allergan recently pulling out of antibiotics R&D. Antibiotics discovery and regulatory approval are lengthy, expensive and difficult endeavors. At the same time, these medications are inexpensive, often used for short term and are useless once resistance develops, thus providing poor returns on investment. Small biotech companies have also struggled as in the case of Achaogen, which recently went bankrupt just 1 year after receiving FDA approval for its novel antibiotic plazomicin. Global momentum was mobilized and, in 2016, WHO

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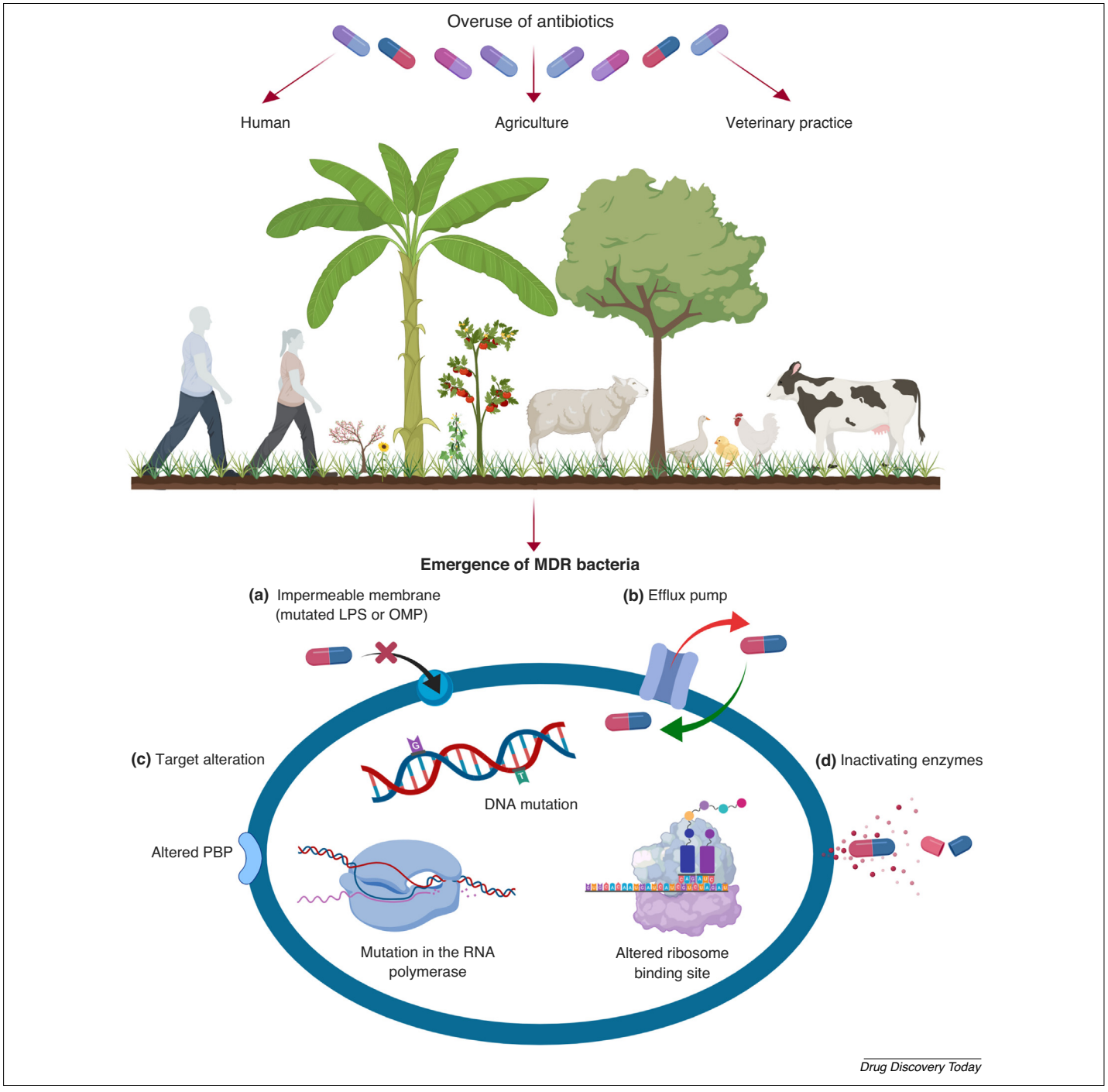

FIGURE 1

Multifaceted mechanisms of multidrug resistance. Overuse of antibiotics in humans, animals, plants and the environment impose a selection pressure that promotes the emergence of multidrug resistant (MDR) bacteria. **(a)** Membrane permeability to antibiotics can decrease owing to mutations in the outer membrane protein (OMP) or lipopolysaccharide (LPS). **(b)** Bacterial membranes can have MDR efflux pumps that extrude antibiotics outside the cell. **(c)** Antibiotic target alteration can be caused by mutations in the antibiotic binding site including penicillin-binding protein (PBP), DNA, RNA polymerase or ribosome. **(d)** Some bacteria can produce inactivating enzymes that cause degradation of the antibiotics.

declared a list of priority pathogens for drug development. Recent international initiatives across governments, nongovernmental organizations, academia and the pharma industry were created. Partnerships such as the Global Antibiotic R&D Partnership (GARDP), Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global AMR and Development Hub were established. Antibiotic stewardship programs aimed at proper treatment, preventing overuse, AMR surveillance and minimizing AMR development were created by WHO and Centers for Disease Control and Prevention (CDC). All of these efforts are essential in dealing with AMR; yet gaps still exist practically in the lack of global coordination and the limited late-stage funding of

clinical development and sustainable commercialization. In the past decade, the European Union (EU) and the USA have banned the use of antibiotics as growth promoters in animal feed. Although this is a promising step toward responsible antibiotic use, loopholes still exist. The US Environmental Protection Agency (EPA) is currently in the process of allowing the spraying of 440 000 kg of antibiotics to treat citrus diseases despite serious objection [1]. Furthermore, regulations to curb antibiotic misuse are lacking in most of the developing world. With today's high mobility of humans, animals and crops, AMR pathogens can easily spread globally. The New Delhi metallo-beta-lactamase (NDM) resistance gene was first reported in Sweden from a patient hospitalized in India and has since spread globally reaching as far as the High Arctic [2]. In a recent global study, two-thirds of the world's rivers were found to contain high and unsafe levels of antibiotics. Recent evidence suggests that climate change might also be a driver of the AMR problem [3]. Another twist of antibiotic overuse, especially during infancy, is disruption of the human microbiota balance potentially contributing to modern-day chronic diseases.

Microbial natural products: the exhausted resource that keeps giving

Traditionally, most antibiotics were discovered as natural byproducts of microorganisms such as molds and the bacteria *Streptomyces*. Over 60% of antibiotics in clinical use today are natural products or their derivatives. Despite early success, this approach has failed in recent years to produce new antibiotics owing to the high rate of rediscovering already known antibiotics. Although, on the face of it, microbial natural products appear to have been exhausted, recent work using clever approaches suggests otherwise. Work exploring insect microbiota has identified bacteria that produce cyphomycin – effective against drug-resistant fungi [4]. iChip® technology enabled culturing previously unculturable bacteria yielding the novel antibiotic teixobactin [5]. Exploring previously unexplored and hard-to-access locations such as deep-sea vents or Arctic seas also holds the promise of finding novel antibiotics. Genomic analysis of *Streptomyces* revealed a wealth of natural metabolite biosynthesis genes that are not expressed or 'cryptic' under laboratory conditions. Activating cryptic pathways from older-strain collections could reveal new antibiotics. DNA sequencing, bioinformatics and heterologous expression have led to the discovery of malacidins without the need for cultivation of the producing microorganism [6]. Another elegant approach is the use of synthetic-bioinformatic natural products (syn-BNPs), which chemically synthesized humimycins based on the primary sequence of the biosynthetic bacterial genes without the need for gene expression or bacterial cultivation altogether [7]. Such innovations clearly demonstrate that natural sources are still an attractive avenue for novel antibiotic discovery.

The chemical tool box: an essential aspect of first-in-class antibiotic discovery

The field of chemistry has been instrumental in antibiotic development. Not only in the creation of synthetic antibiotics but also in modifying naturally occurring antimicrobials producing next-generation antibiotics. Most synthetic libraries are biased toward mammalian targets rather than bacterial targets. Chemicals that inhibit essential bacterial targets have failed owing to bacterial membrane impermeability. Fortunately, computational models were developed to predict the physicochemistry required for compound penetration into bacteria. The use of direct evolution has recently been applied to cytochrome P450, which normally synthesizes β-lactam antibiotics allowing it to produce γ- and δ-lactams [8]. This exciting new application could pave the way for industrial-scale production of newer classes of antibiotics not found in nature. Nanoparticles such as 'structurally nanoengineered antimicrobial peptide polymers' represent promising antibacterial agents with high potency against MDR bacteria with little toxic effect on mammalian cells. Positively charged compounds with specific frameworks derived from antibiotics can disintegrate the bacterial cell envelops leading to bacterial death without resistance development. Today's advances in artificial intelligence and machine learning are powerful tools in guiding drug discovery. Although such applications are new, recent work has demonstrated that artificial intelligence can guide and optimize antibiotic development [9].

Alternatives to antibiotics: old therapies and new technologies

Alternatives to antibiotics have shown promise but are still far from being clinical applications. Bacteriophages are viruses that kill bacteria and were once used to treat infections in western countries; they are still used today in some European countries and Russia. Phages are selective against specific pathogens; however, bacteria can develop resistance and this field lacks adequate large-scale clinical trials to evaluate efficacy and safety [10]. The interest of several biotech/pharma companies in phages as successful treatments, where other treatments have failed, are signs of renewed interest in this old and abandoned field. Immune-mediated therapies such as antibacterial monoclonal antibodies have been developed to treat infections but suffer high production cost. The CRISPR/Cas system has been used for selectively removing AMR genes from specific bacteria, thus re-sensitizing them. This promising technology is highly specific and can be specially adapted to many bacteria and AMR genes, yet it is still a pre-matured area owing to the lack of a suitable delivery vehicle.

Public awareness and global action: joining forces for the future of human health

One of the success stories of challenges we face in the 21st century, such as plastic pollution or climate change, is raising public awareness. This awareness has led to changes in daily habits of the public and has contributed to policy changes toward solutions. Although the AMR problem has recently gained media and public attention, it still lags behind other global challenges. Evidence-based efforts that raise public awareness to AMR and antibiotic overuse without scaremongering are vitally important. Interdisciplinary incentives and unified international efforts are pivotal to address this global challenge. Many view the current framework for antimicrobial discovery, approval and commercialization as broken. A coherent plan that addresses the shortcomings of antibiotic development at all stages is essential for a robust and sustainable antibiotic pipeline. This includes experts from disciplines spanning basic sciences, medicine, the pharma industry, economics and policymaking. The use of innovations in

chemistry, biology, synthetic biology, bioinformatics, direct evolution and artificial intelligence needs to be further expanded in antimicrobial discovery. Chemical synthetic libraries need to expand their chemical space to encompass bacterial physicochemistry. Alternatives to antibiotics such as phage therapy and nanoparticles should be investigated in clinical settings. Development of first-in-class small molecules with nothvel mechanisms-of-action is urgently needed. New antimicrobials cannot alone address AMR because pathogens will develop resistance. Thus, implementing treatment protocols such as combination drug therapy to minimize resistance development should be considered. AMR is a global problem and should be tackled with a unified global effort. New technologies to report resistance prevalence and better stewardship programs are globally needed. Funding and the lack of resources remain major obstacles in achieving these goals but, by the same token, this could be an opportunity for new job creation and economic stimulation. At last, as the world leaders gather to address the fourth industrial revolution strategic sustainable goals, the world's efforts and resources should unite to ensure the future health of the global population.

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