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Fighting Antibiotic Resistance: Insights Into Human Barriers and New Opportunities

Antibiotic Resistance Constantly Rises With the Development of Human Activities. We discuss Barriers and Opportunities to Get It Under Control

Aubin Pitiot[1] | Camille Rolin[1,2] | Carole Seguin-Devaux[1] | Jacques Zimmer[1]

[1]Department of Infection and Immunity, Luxembourg Institute of Health, Esch-sur-Alzette, Luxembourg | [2]University of Luxembourg, Esch-sur-Alzette, Luxembourg

Correspondence: Jacques Zimmer (Jacques.Zimmer@lih.lu)

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ABSTRACT

The public health issue of bacterial multi-resistance to antibiotics has gained awareness among the public, researchers, and the pharmaceutical sector. Nevertheless, the spread of antimicrobial resistance has been considerably aggravated by human activities, climate change, and the subsequent increased release of antibiotics, drug-resistant bacteria, and antibiotic resistance genes in the environment. The extensive use of antibiotics for medical and veterinary purposes has not only induced increasing resistance but also other health problems, including negative effects on the patient's microbiome. Preventive strategies, new treatment modalities, and increased surveillance are progressively set up. A comprehensive approach is, however, lacking for urgently tackling this adverse situation. To address this challenge, we discussed here the main causes driving antimicrobial resistance and pollution of the environment by factors favorable to the emergence of drug resistance. We next propose some key priorities for research, prevention, surveillance, and education to supervise an effective clinical and sustainable response.

1 | An Update on the Phenomenon of Antibiotic Resistance

"Antibiotics" and "antibiotic resistance (AR)" appear 316 078 and 62 793 times into Pubmed (accessed on January 23, 2025), clearly reflecting the major issue of antimicrobial resistance (AMR) on human health [1]. By 2050, in absence of appropriate counter-measures, it was estimated that as many people would die by infections with multidrug-resistant (MDR) bacterial pathogens as by cancer (10 million premature deaths per year) [2]. The World Health Organization (WHO) has ranked AMR as one of the top three health threats of the 21st century [3] and has issued a priority list of the most infective MDR bacteria (Table 1). While an estimated 1.14 million deaths were directly attributable to AR, an additional 3.57 million deaths were associated with MDR bacteria and 21.35 million people succumbed to sepsis in 2021, also known as a silent pandemic [4]. Importantly, one in five people who died directly from AR in 2019 was a child under 5 years old often affected by previously treatable infections (e.g., *Escherichia coli*). The diversity of bacterial strains and of antimicrobial agents combined with the fast emergence of mechanisms of resistance has resulted in a huge complexity driving AMR evolution and distribution around the world [5]. Strikingly driven now primarily by the increase use of antibiotics, the resistance mechanisms and

TABLE 1 | Resistance to clinically used antibiotics and their incidence in the world.

Antibiotic class	Mode of action	Resistance mechanism(s)	Principal examples	Incidence of resistance	Bacterial priority pathogens
β-lactams	Inhibition of the bacterial cell wall synthesis	Enzymatic inactivation (hydrolytic degradation) Reduction of affinity to penicillin-binding proteins Cell wall modifications Decreased intracellular drug concentration (Efflux pumps)	Penicillins	Common	Group B Streptococci *Staphylococcus aureus* *Haemophilus influenzae*
			Cephalosporins	Widespread	*Enterobacter* spp. *Neisseria gonorrhoeae*
			Carbapenems	Rare	*Acinetobacter baumannii* *Enterobacter* spp. *Pseudomonas aeruginosa*
			Monobactams	Rare	—
Glycopeptides	Inhibition of peptidoglycan synthesis	Alternative peptidoglycan precursors	Vancomycin	Uncommon	*Enterococcus faecium*
β-lactamase inhibitors	Inhibition of β-lactamase enzymes	Increased expression/diversity of beta-lactamase enzymes (extended-spectrum beta-lactamase bacteria) Mutations in β-lactamase active sites	Clavulanic acid	Rare	—
Metronidazoles	Inhibition of DNA synthesis	Enzymes converting antibiotic to nontoxic derivatives	—	Uncommon	—
Fluoroquinolones	Inhibition of DNA replication	Target-site gene mutations Decreased intracellular drug concentration (Efflux pumps)	Levofloxacin	Uncommon	*Salmonella* spp. *Shigella* spp. *Neisseria gonorrhoeae*
Aminoglycosides	Inhibition of protein synthesis	Enzymatic inactivation (hydrolytic degradation, chemical modification) Target modification (mutation or replacement by alternative resistant target) Decreased intracellular drug concentration (Efflux pumps)	Streptomycin	Widespread	—
Tetracyclines			Doxycycline	Widespread	—
Macrolides			Erythromycin	Moderate	Group A Streptococci *Streptococcus pneumoniae*
Fusidic acid			—	Rapid when used alone	—
Lincosamides			Lincomycin	Moderate	—
Sulfonamides	Inhibition of folate synthesis	Target modification (mutation, or replacement by alternative resistant target)	Sulfacetamide	Widespread	—
Trimethoprim			—	Moderate	—
Ansamycins	Inhibition of RNA synthesis	Mutation in the β-chain of RNA polymerase Increased expression of RNA polymerase binding proteins	Rifampicin	Common	*Mycobacterium tuberculosis*

Note: The incidence of the resistance mechanisms extends from rare (few clinical cases per year) to widespread (more than 10% of clinical strains) [6]. When applicable, prioritized bacteria found in the last column are present in the 2024 updated WHO Bacterial Priority Pathogens List from each group (critical, high, or medium priority) [7].

their pervasiveness has evolved against all classes of antibiotics (Table 1).

AR is usually addressed as a "One Health Approach" recognizing that "the health of Humans, animals, plants and the wider environment are closely interlinked and interdependent" [8, 9]. While AR is a global pandemic, its causes, consequences, and needs differ largely between countries [4, 10]. It is especially true for low and middle-income countries (LMIC), characterized by a high burden of infectious diseases that will account for 80% of the estimated deaths in 2050. The fight against AR should thus be therefore multifaceted, tailored, and address all health sectors to achieve reliable and durable control of drug resistance. In this essay, we aim to focus on the direct roles of Human activities on AR in order to advice on human-specific priorities to tackle this phenomenon.

2 | Antibiotics, Driving Force, or Conceivable Solution to AR?

2.1 | Research Pipeline on Antibiotics

At first sight, the AR situation might worsen because there are too few truly new antibiotics in the pipeline of the pharmaceutical industry [11, 12]. In 2024, among the 27 antibiotics addressing priority pathogens in clinical trials, only six presented innovative characteristics. The others harbored modifications from already approved drugs [13] leading to the rapid development of resistance, usually in 0–6 months after antibiotics introduction [14]. The low number of new molecules can be ascribed to the lack of substantial benefit in front of the very high cost of the lengthy discovery, the high number of hurdles before registration by health authorities and the development of alternative antibiotic product classes. Antibiotics are quite cheap and are usually prescribed for a short period until the clearance of the acute infection [15]. Conversely, innovative anticancer treatments (e.g., checkpoint inhibitors, adoptive cell therapy, etc…) are sold at very high prices and are usually versatile, rendering them more cost-effective to pharmaceutical industries than antibiotics.

This pessimistic picture has however recently improved. For instance, the use of artificial intelligence allowed the recent discovery of a new class of antibiotics (tethered macrocyclic peptides) able to alleviate the usual antibiotic pressure. New efficient combinations of recent and old drugs should facilitate treatments by clinicians [16] such as the association of meropenem with two inhibitors of β-lactamases. Moreover, the early-stage clinical pipeline has been expanded between 2020 and 2024 with novel antibacterial pharmacophores that should result in novel biological activities [17]. Finally, antibiotics characterized by new mechanisms of action are constantly discovered and should replenish the current portfolio of antibiotics or combinations [18–20].

2.2 | Adverse Events Associated With Antibiotics

Like most therapeutic approaches, antibiotics can lead to potentially dramatic adverse events (Figure 1). Allergic reactions and particularly cutaneous eruptions and anaphylaxis to beta-lactams antibiotics (e.g., penicillin) are common and can sometimes cause fatal consequences [21]. Likewise, nephrotoxicity of certain antibiotic classes (e.g., aminoglycosides, vancomycin, beta-lactams, and tetracyclines) can be worsen by repeated administrations [22]. Additionally, some medications have negative influence when combined with antibiotics; antidepressants could accentuate resistance and contribute to the spread of AR given the widespread use of these medications [23].

Importantly, antibiotics with broad-spectrum action attack and destabilize some of the bacterial microbiome present in the intestine, the respiratory tract, the female genito-urinary system, and the skin [24] causing dysbiosis and potentially leading to unwanted side effects (e.g., diarrhea). To prevent or resolve this side-effect of antibiotic therapy, intake of probiotics [25, 26], or transfer of a new microbiota by fecal transplantation from a healthy donor to the diseased patient's digestive tract [26, 27] have been identified as appropriate treatments. However, both therapies likely transfer resistance genes from the initial bacterial treatment to pathogenic bacteria in the recipient host and thus participate in the spread of AR [26]. Noteworthy, an altered microbiota (caesarian birth) or disturbed by overuse of antibiotics (especially during the first 3 years of life) might be largely responsible for the factors leading to the development of inflammatory and autoimmune diseases (e.g., celiac disease, eosinophilic esophagitis, diabetes) [28, 29], which in turn aggravate the microbial disequilibrium. Antibiotics not only have harmful effects on the gut-brain axis [28, 30] but also favor cancer development. According to the large retrospective study of Roderburg et al. [31], the intake of high doses of antibiotics especially from the penicillin and cephalosporin families significantly increases the incidence of cancer. Ultimately, tumors themselves harbor a microbiome that can be an ally or a foe for the immune response and/or the anticancer treatment: antibiotics administered up to one year before checkpoint inhibitor therapy negatively influence the success rates of the latter [32]. The systematic use of antibiotic(s) should be therefore carefully controlled to slow down AR and decrease the number of unwanted side effects.

2.3 | Human Activities as Factors of Antibiotic Resistance

With the limited number of new antibiotics discovered every year and the reliance on the existing ones to treat infections, AR has been constantly growing. Bacteria easily develop various strategies to withstand the antibacterial effects of antibiotics, metals, and chemicals, notably through structural modifications and modulation in their metabolic pathways [33]. Those strategies are coded by antibiotic/metal resistance genes (ARG and MRG), usually present in plasmids, and nowadays found in the majority of bacterial strains [34].

Of concern, the clustering of resistance genes in complex resistance regions (CRR) results in co-selection, a phenomenon occurring regularly in various microbial communities and providing simultaneous selection of resistance genes [35]. Close genes providing protection against different antibiotics, chemicals, and/or heavy metals are co-expressed in the same plasmid. This genetic background drives the co-resistance: one antibiotic (or chemical,

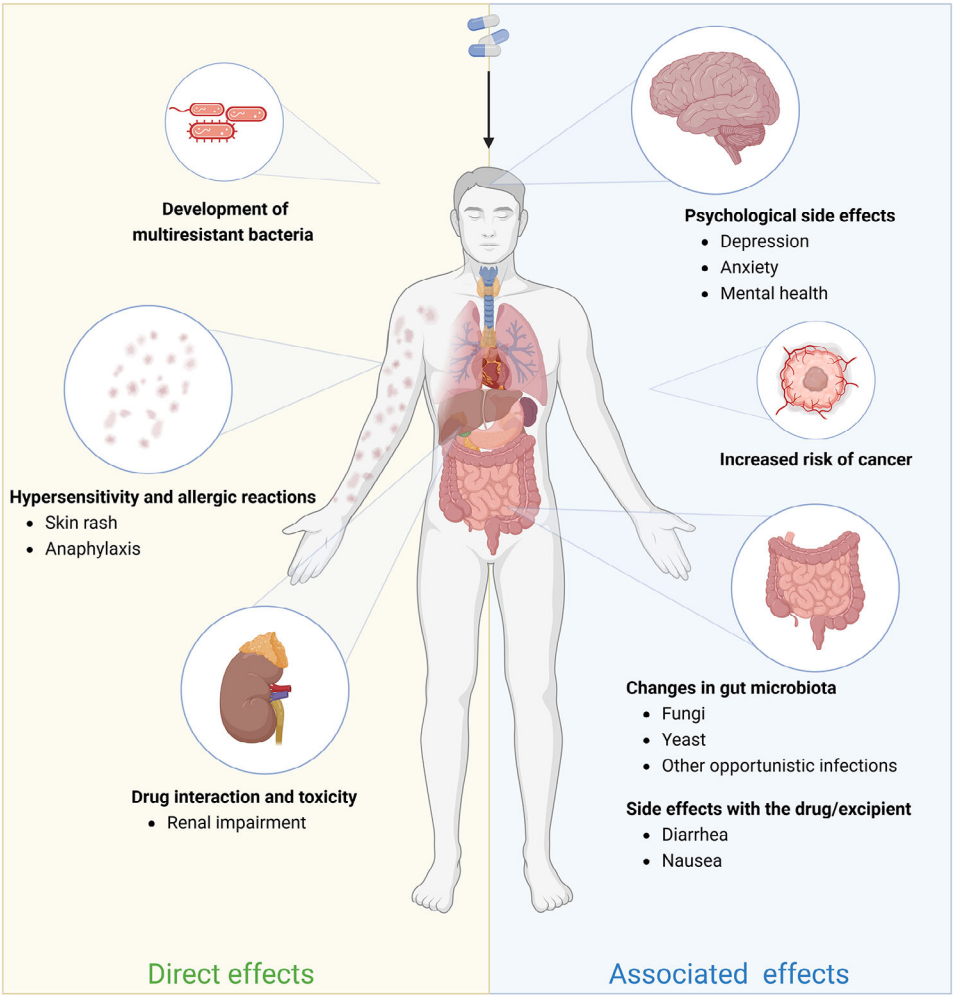

FIGURE 1 | Adverse events associated with antibiotics. Antibiotic use in patients is associated with direct and associated adverse effects. Direct effects include the development of multiresistant bacteria, allergic reactions, and nephrotoxicity. Associated effects comprise psychological disorders, increased risk of cancer as well as modifications of the gut microbiome.

or metal) is sufficient to select and maintain simultaneously every other resistance linked together, sometimes on mobile genetic elements, with the selective pressure tied down to antibiotics and other anti-microbial agents such as heavy metals (e.g., copper) and biocides (e.g., methanol) [36, 37].

Although the natural and genetic causes (e.g., mutation, genetic transfers, co-selection) [38] are the biological reasons behind AR, the social and economic environment (societal pressures, repetitive and improper habits, pollution) as well as the physical environment (climate change) play a substantial role in strengthening their emergence [39, 40]. In LMIC (e.g., sub-Saharan Africa and South Asia), despite their lower antibiotic consumption, higher burden of MDR bacteria, and increased deaths are now observed. The presence of critical bacteria, poor sanitation and hygiene, difficult access to antibiotics, and poor laboratory infrastructures are driving more deleterious resistance effects in the bacterial population: the commensal bacterium *E. coli* is now rapidly evolving to an MDR bacterium in those developing countries [41, 42].

The global efforts born from the COVID pandemic has raised more awareness concerning the risks caused by AR and has set in motion new infection-control measures. This had led to the launch of the 10–20–30 global target focusing on the reduction of 10% of AMR-attributable deaths, 20% of inappropriate antibiotic use in humans, and 30% of antibiotic use in animals by 2030. However, other human determinant factors can be responsible of the increasing numbers of MDR bacteria (Figure 2) [43].

2.4 | Antibiotic Resistance: Human Inappropriate or Overuse of Antibiotics

Since their apparition in the armamentarium of doctors, antibiotics have been used effectively against a wide range of infections decreasing their mortality rate. However, their efficacy, their cheapness and their easy access worldwide (available without prescription in many countries, or through online markets) only encourages the medical personnel and the general population to overuse them [44]. Multiple studies have investigated the correlation between antibiotic consumption and the dissemination of MDR bacteria studies [45]; the most recent show a 46% increase of the global antibiotic consumption between 2000 and 2018 rising from 9.8 Dose Delivered Daily (DDD) per 1000 persons per day to 14.3 [46], respectively.

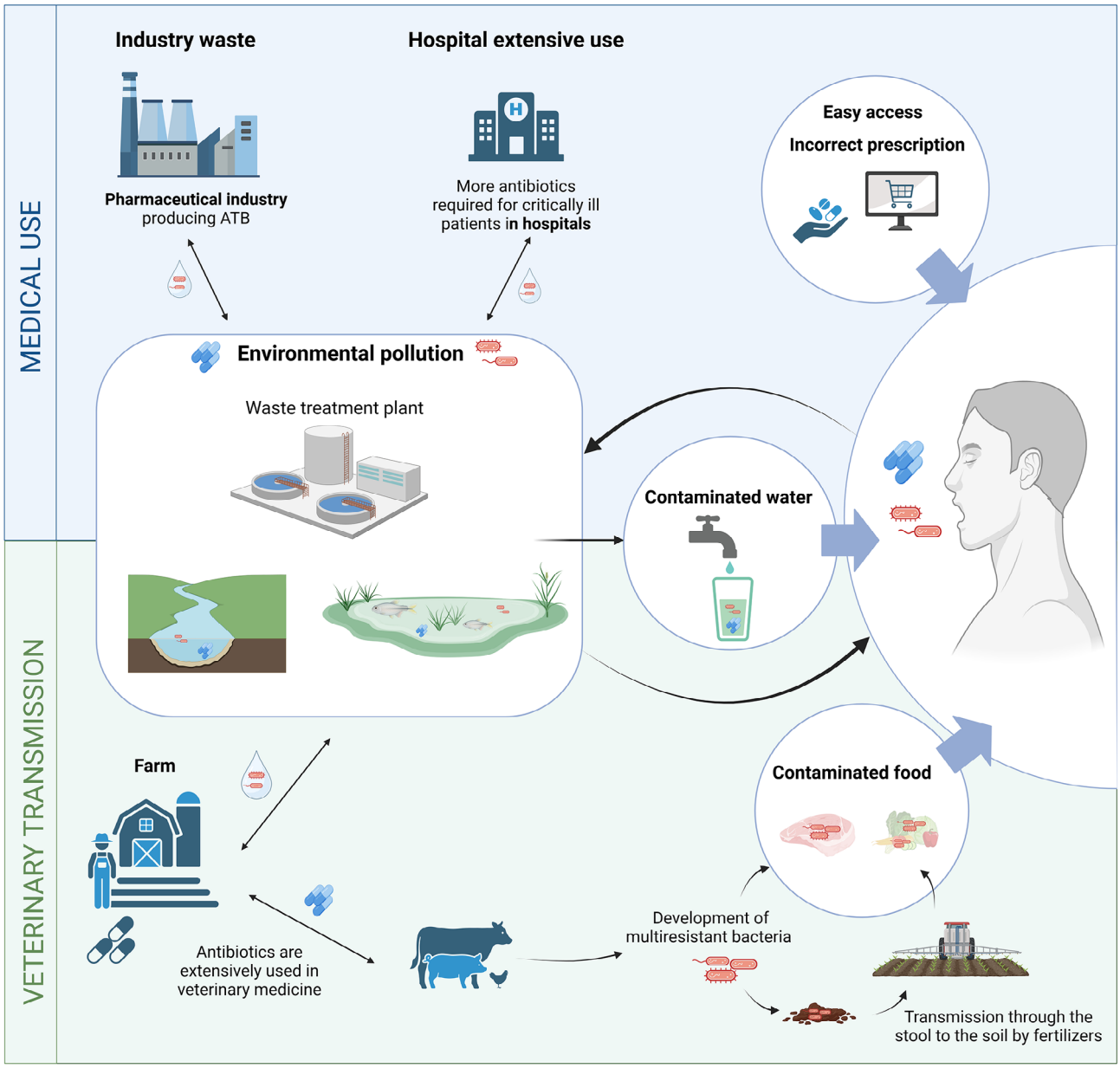

FIGURE 2 | The direct contribution of antibiotics use in the development of AMR. The direct impact of antibiotic on antibiotic resistance (AR) starts by their administration to humans (medical use (blue)) or animals (veterinary transmission (green)). Overuse of antibiotics (ATB) in clinic comes from their easy access, their empiric and excessive utilization by medical doctors, as well as their extensive prescription in hospitals to treat critically ill patients. Through their use, multi-resistant bacteria can develop in hospitals, industries and homes. Bacteria, as well as antibiotics, are released usually through waste, can transit through waste treatment plants (WTPs), where conditions are reunited to increase AR, and can lead to environmental pollution, with contaminated water easily reaching individuals through running water, and agriculture. Additionally, the extensive use of antibiotics in farming also leads to the development of multi-resistant bacteria in livestock animals. Bacteria and ATB are then transmitted to individuals, either directly through the consumption of contaminated meat, indirectly with the contaminated harvest due to the transmission from the stools to the soil, and waste from agricultural practices followed the same cycle as general waste. Antibiotics and drug resistant bacteria found in humans can start the same cycle again.

Unfortunately, the recorded data on the usage of antibiotics varies widely between countries reflecting limited national data collection and often relying on multiple and incomplete sources (e.g., paper-based medical records, insurance). For example, while the lower use of antibiotic in Europe is a direct consequence of regulations and antibiotic stewardship programs, their disparate availability is the main reason in Africa [47]. Around 30%–50% of antibiotics are incorrectly prescribed both in communities and in hospitals in terms of choice of the drug or treatment length [48]. Importantly, an outstanding 60% of antibiotics are not delivered through medical prescription. The wave of irrational and ineffective use of antibiotics during the COVID-19 pandemic intensified the spread of MDR pathogens [49, 50]. This situation is even more severe in LMIC. A recent study showed that nearly 50% of healthcare patients in those countries receive antibiotics often without purpose, usually due to the presence of few regulations on antibiotics prescription, poor training of medical doctors, and limited diagnostic methods [51].

If courses on AR and stewardship are available in many medical universities, graduated clinicians are, within certain limits, free to prescribe antibiotics [52]. Furthermore, when the diagnosis of an infection is only partial or incomplete, an empiric broad-spectrum antibiotics approach is applied leading to the spontaneous development of molecular mechanisms of resistance [53]. This is especially true for critically ill patients, where antibiotics are used urgently without clear diagnosis. In addition, the close contact between sick patients creates a fertile environment for the spread of MDR strains while favoring the exchange of genetic material [54].

2.5 | Antibiotic Resistance: Armed Conflicts and Wars

Wars are places of poor hygiene and crowding, often leading to poor health and extensive cross-contamination. In all conflict zones (e.g., Iraq, Afghanistan, …) "doctors without borders" operatives have reported higher levels of MDR bacteria (up to 70% in Trauma center) than in countries at peace [55]. A recent work observed high rates of resistance genes against antibiotics in Ukrainian war patients, far from the controlled incidence of resistance described prior to the conflict [56], highlighting the severity of AR in warn-torn countries.

The exacerbation of AR during ongoing conflicts is at first caused by the disruption of normal healthcare systems and services: the exodus of healthcare professionals, destroyed infrastructures, and difficulty to access correct drugs and treatments only increases the risk of medical errors or incorrect prescription, and the subsequent rise of MDR bacteria in the population. The sporadic hygiene measures (e.g., lack of clean water) in those areas facilitate the contamination of the population. Furthermore, combat-related wounds and injuries caused by pieces of metal (bullet, shrapnel) are more susceptible to infection. Their treatments usually necessitate an extensive use of generic antibiotics associated with an increased risk of AR. The mixing of the wounded soldiers with the general population in common areas such as hospitals accelerates the transmission and the spread of MDR bacteria regionally and globally [57, 58]. Finally, the displacement of populations caused by wars only accentuates the phenomenon: refugee camps have limited access to resources and the overcrowding and unhygienic environment favor the transmission of MDR bacteria.

Although it has become imperative to fight AR locally in such favorable environment, notably through the surveillance of MDR bacterial strains, conclusions drawn from the majority of armed conflicts of the 20th and 21st century suggest that such straightforward measures will be difficult to implement, even with the role of international aid organizations [57].

2.6 | Antibiotic Resistance: Veterinary Use

Globally, it is estimated that around two-thirds of all prescribed antibiotics are for animals, not necessarily to cure infections, but mainly to be used as growth supplements and help the breeding of animals. In the United States, up to 80% of delivered antibiotics are given to livestock directly integrated as food supplements [59, 60]. In high-income countries, despite the launch of strict regulations, antibiotics continue to be used in excess and often without adequate veterinary supervision. With increased demand for food animal production and intensification of production with cheap prices, LMIC maintained a high and unchecked veterinary use of antibiotics [47].

Those routine administrations, in particular at sub-therapeutic concentrations, spread AR to the livestock and predispose to the emergence of MDR pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *E. coli* resistant to colistin or carbapenems in animals [61–63]. ARG, MDR bacteria, and even antibiotics present in livestock easily escape into surrounding populations and spread in the environment through stools and urine (e.g., 40%–80% of the dose of antibiotics taken by animals can be released) [64]. In addition, they can be transmitted to humans by direct contact with the animals or be ingested through meat and dairy from antibiotics-filled animals [65], crops and fruits grown on contaminated soil (Figure 2) [66, 67].

2.7 | Antibiotic Resistance: Environmental Pollution

Accumulating evidence demonstrate the contribution of Human environmental pollution to the emergence and increase of AR. Bacteria are known to adapt quite readily to encountered chemicals, biological material, and/or metal from the environment [36, 68, 69]. As such, pollution of soils by antibiotics, biological and chemical products, microplastics or even biocides can lead to the occurence of co-selection [70, 71]. Pollution is especially worrying due to the 3.5 million tons of chemicals pesticides used across the world [72]. Due to their low biodegradability by conventional treatment systems, these components are easily dispersed through fertilizers or running water. Thus, wastes from all facilities involved in agricultural practices (e.g., biogas plants), goods production (e.g., pharmaceutical manufactures), hospital effluents but also everyday waste from individuals contribute to the spread of antibiotics, ARG, and AR [64]. The shifting of goods production to LMIC (e.g., China and India), where few environmental laws regulate the full treatment of wastes from thousands of manufactures have largely contributed in the recent years to AR through the contamination of communal water and sewers with antibiotic and chemical residues [73].

Hospital wastewater spawned from all healthcare services contains low concentrations of conventional and emerging micropollutants as well as subdoses of antibiotics contributing much more to AR development than municipal wastewater (4–50 times). Studies have shown that the increase of ARG and bacteria in the environment is a direct consequence of the excessive concentration of microplastics in already polluted landfill leachate and surface water bodies. Microplastics promote both the formation of bacterial biofilm (pools of high ARG exchange between bacteria) [74] and the adsorption of antibiotics and chemicals molecules at their surface contributing to a heightened selective pressure on the environment [75]. Even years later, the concentration of antibiotics and ARGs remains very high, especially in an environment enriched with heavy metals [76].

Wastewater treatment plants (WWTP), developed to cleanse the water, promotes the development of MDR bacteria. The high concentration of microorganisms mixed with sub-inhibitory concentrations of antimicrobials from human and veterinary medicines and supplemented with antimicrobial substances leads to a selection pressure furnishing exchange of ARGs together with mobile genetic elements (e.g., plasmids, transposons, etc.). The treated waters containing low but significant amounts of bacteria and ARGs are then discharged directly to the environment [77]. Stabilized sewage sludge derived from WWTP, likely containing MDR bacteria, ARGs and antibiotic residues (1 ng to 100 mg/kg in dry matters), are sometimes used as compost, further contaminating the soil environment [78].

The exposure of all bactericidal agents, chemicals, metals and MDR bacteria raised by various Human activities, even in small concentrations, has therefore a vast impact on microorganism's biodiversity and the circulating pool of ARGs [79].

2.8 | Antibiotic Resistance: Climate Change

Apart from the direct impact of our pollution on the environment, AR is also closely related to the worsening of climate change. The globally rising temperatures and higher humidity enhance the survival and multiplication of many bacterial species but reduce the biodiversity that potentially limits the proliferation and outgrowth of MDR pathogens [80]. The higher frequency of natural disasters such as intense and long-lasting flood episode could likewise contribute to the growth and the spread of such bacterial strains, as well as weaken infrastructures needed to decontaminate including the WWTP [81, 82]. This is well illustrated in the review by Zambrano [83] who presents the problem as an issue of "global interconnectedness" where climate change, modifications of landscape, continuous introduction of antibiotics, other drugs, heavy metals and further pollutants into the environment modify the initial "natural" communities and subsequently favor AR.

3 | Entering the Next Stage of the Fight Against AR

While the complete abolishment of antibiotics is not a conceivable solution, a reduction of their daily use coupled with their responsible and rational prescription by the medical community could slow down the emergence of AR and the apparition of resistant bacterial strains. The early ban of antibiotics for growth purposes in 1986 made Sweden one of the countries with the lowest occurrence of MDR bacteria in the EU [84]. In France, the launch of a national health plan led to a 75% decrease of fluoroquinolones and cephalosporins in animal husbandry, followed by a drop of AR strains (*E. coli* resistant to 3rd generation cephalosporins was reduced from 16% to <2% in poultry) [85].

With the "One Health action plan against AR" launched in 2017, the European Union (EU) aims to be an example in this process for the rest of the world [86]. The Global Action Plan (GAP) shared by the WHO to address the current AR crisis and acting as inspiration for national antibiotic plans all over the world was reviewed in 2021, addressing its successes, challenges, best practices [87], and discussing on the tailored responses needed at a local level to fight AR [4, 10]. The plan has been divided into five main objectives: (i) increasing awareness on AR through training, education, and communication; (ii) strengthening the knowledge on AR through surveillance and research; (iii) reducing infection incidence with directly applicable methods (e.g., sanitation and hygiene); (iv) optimizing antimicrobial molecules in human and animal health; and (v) developing sustainable investment and economy for new medicines, diagnostic tools, and so forth. Here, we discerned some of the successful strategies already in implementation for Humans (Figure 3) [88, 89].

3.1 | Investing on Research and Prevention

3.1.1 | Improvement of Innovative Diagnosis Tools

One solution to reduce antibiotic use is to better diagnose bacterial infections, especially during primary care. This principle is successfully applied in the Scandinavian region, which benefits from a higher number of diagnostic tools than any other country, such as rapid antigen detection kits, systematic culture, and susceptibility testing of bacteria [90]. The launch of an antigen-detection test to rapidly discriminate *Streptococcus* infection in case of a sore throat has decreased the antibiotic's prescription as compared to empirical therapy [91]. More rapid diagnostic instruments would allow the delivery of the right treatment to prescribe promptly [92, 93].

3.1.2 | Development of Sustainable Technologies to Limit Release of ATB and MDR Strains in the Environment

In high-income countries, hospital and industrial wastewater are discharged into municipal wastewaters and are either treated together in sewage treatment plants as "co-treatment" or pretreated as industrial waste before being discharged. Both solutions are inadequate and are usually ineffective against emerging micro-pollutants [94]. Large scale hospital wastewater treatments include tertiary processes of activated sludge system and membrane bioreactor requiring both high energy supply needs for aeration, high operational costs, and further posttreatment to degrade the concentrated micro-pollutants in smaller volume in case of membrane process. These techniques are nevertheless unable to guarantee safe hospital wastewater treatment and prevent the spread of disease outbreaks.

In low-income settings, hospital wastewaters can directly be discharged into lakes and rivers by draining systems [95]. The development of sustainable technologies able to remove all antibiotics, MDR bacteria and ARGs from hospital or nursing homes are therefore required. Despite the serious public health risks, not enough research has been conducted on this topic. Several alternatives posttreatments or separate disinfection technologies have been proposed to remove completely micro-pollutants from hospital wastewater such as granular and powered activated carbon adsorption, advanced oxidation processes, ozonation, UV, or phytotherapy [94]. There is nevertheless no single technique able to eradicate all pathogens or ARGs. More evidence is now

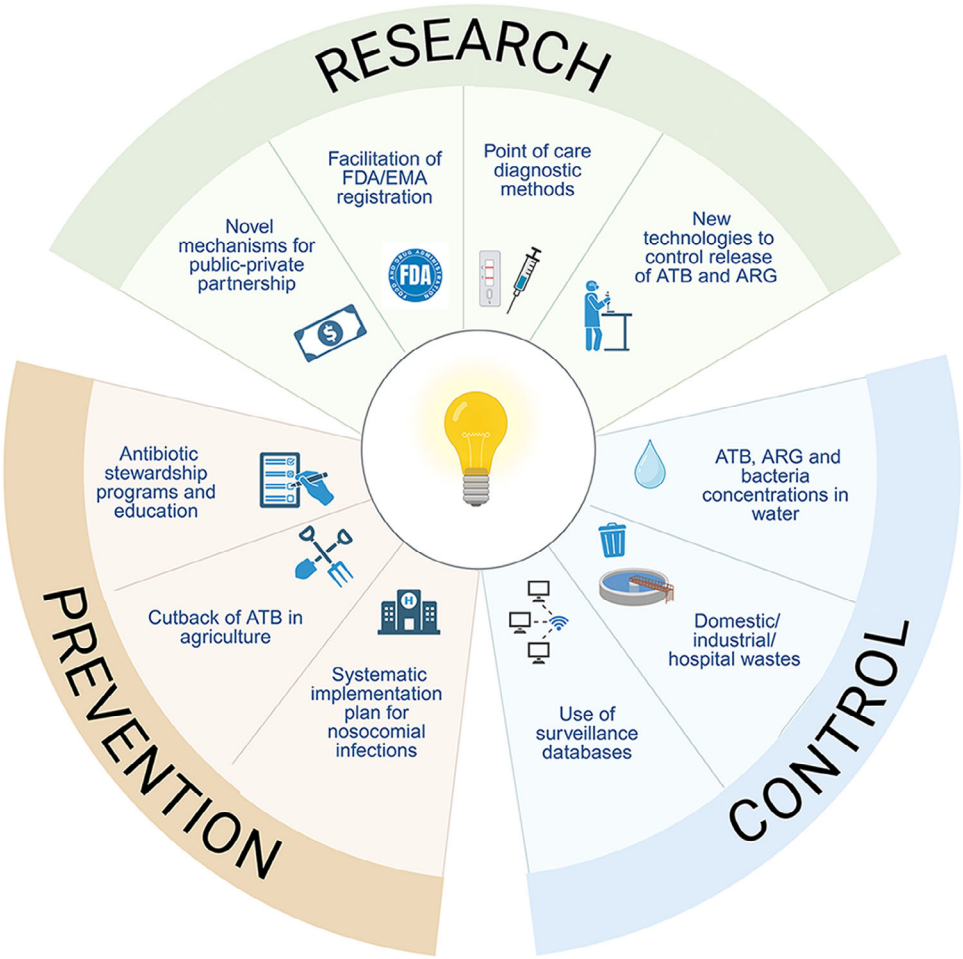

FIGURE 3 | Solutions to overcome antibiotic resistance. Antibiotic resistance could be tackled by enhancing research, requesting better funding, as well as promoting the development of preventive measures, such as a larger system of MDR bacteria surveillance, and global initiatives with a continuous education of the public.

needed to guide the future processes of sustainable elimination, easily adaptable for low resource-settings.

3.1.3 | Finding of New Anti-Infective Therapeutics

To overcome the failed attempts of the last generations of antibiotics to circumvent the development of resistance mechanisms, new therapeutic strategies are under investigation and development as summarized in Table 2 [96].

Antimicrobial peptides (AMP), derived from natural products (e.g., colistin) are known for their broad spectrum activity and their high bactericidal activity [97]. Although the ones found in nature lack potency, selectivity against bacteria and safety, structure-activity-guided computational studies and high-throughput screening of AMP-based libraries has helped to streamline the pipeline of new lead compounds [98]. Those synthetic AMP with improved resistance profiles pave the way toward more potent, stable and less toxic compounds with a large chemical space for optimizations. Their incorporation to nanotechnologies or combination with other antimicrobial drugs should synergize their effects [99].

Bacteriophages have recently regained interest in modern medicine thanks to their efficacy against biofilm, their synergy with antibiotics, and their safety toward the microbiota. In Eastern Europe, bacteria-specific phages with optimized lytic activity used in cystic fibrosis patients showed encouraging results in the treatment of both *Mycobacterium abscessus* and *Acinetobacter baumannii* lung infections [100] as well as against wound and corneal infections reaching bacterial eradication with limited side effects. Several challenges still need to be addressed, such as selectivity, phage concentration at the site of infection, immunogenicity, stability, manufacturing processes, and especially the apparition of resistance toward the treatment [101]. Nevertheless, improving phage therapy by synthetic-based technologies, by creating chimaeras or mutants to expand spectrum of activity [102] or by isolating the mechanisms involved in bacteria direct killing can inspire a new range of therapeutic strategies [103]. For example, endolysins degrading the microbial cell wall have been explored as combination therapy with antibiotics, reaching phase III clinical trials against methicillin-resistant *Staphylococcus aureus* [104].

Monoclonal antibodies and antibody-based drugs are safe and promising therapeutics offering the possibility to target specifically the pathogenic bacteria while preserving the commensal

TABLE 2 | Alternative strategies to replace antibiotics and limit the phenomenon of AR.

Strategy	What is it?	Prevention or treatment	Main benefits	Resistance?
Bacteriophage therapy	Viruses specific of bacteria	Prevention/treatment	Highly selective and specific Multiplication through treatment requiring one dose	Emerging: Alterations of envelope determinants used by phage adsorption
Antimicrobial peptides	Cationic peptides; part of innate immunity	Treatment	Destabilization of membranes Enhance immunity as immuno-modulators	Emerging: Modulation of membrane Presence of efflux pumps Proteolytic enzymes
Nanoparticles	Materials (organic or inorganic) within the nanometer scale range	Treatment	Self-therapeutic agents and drug-delivery vehicles	Rare: Aggregation of the nanoparticles by virulence factors
Monoclonal antibodies/derived molecules	Molecules derived from natural immunoglobulins	Prevention/treatment	Specific neutralization and induction of effector functions	Rare: Mutations of the target or loss of its expression
Inhibitors of quorum-sensing (QS)	Inhibition or silencing of bacterial QS, leading to decrease of virulence gene expression, and biofilm formation	Treatment	Inhibition of virulence factors without damage to the normal microbiota	Common: Multiplicity and redundancy of QS systems Presence of efflux pumps
Probiotics	Ingestion of live and beneficial bacteria to prevent a diseased state	Prevention/treatment	Maintenance of normal gut microbiome	Emerging: Acquisition of resistance mechanisms from probiotic bacteria
Bacteriocins (e.g., lantibiotics)	Bacteria-produced toxins used to inhibit growth of other bacterial strains	Treatment	Large spectrum of effects Active at low concentrations	Rare: Changes in bacterial cell-surface charge and membrane fluidity
Fecal microbiota transplant	Administration of a new intestinal microbiota from a healthy donor	Prevention/treatment	Modulation of diseases associated with dysbiosis	Not described
Vaccines	Live-attenuated, killed microorganisms or microbial subunits	Prevention	Reduction of resistance-conferring mutations Multiple immunogenic epitopes	Rare: Increase of genetic variability in the targeted antigens
Essential oils	Plant-derived products with health-promoting properties	Treatment	Allows bacteriostatic or bactericidal effects even at low concentration	Not described

communities [105]. Three molecules directed against bacteria are already in clinics, and several others, usually neutralizing secreted virulence factors or toxins, progress through clinical development [106]. One major challenge is to develop antibodies recognizing broad and conserved epitopes across different bacterial strains. Additionally, both the modulation of surface proteins, and production of mucus/proteases can affect their binding [107]. The addition of deliverable molecules to an antibody could circumvent some of those barriers. One such molecule was designed to release a rifampicin analogue, through lysosomal proteases cleavage subsequent to its phagocytosis by *Staphylococcus aureus* [108]. Antibodies are currently engineered to enhance affinity, half-life, downstream effector functions, or opsonic activity [109].

Nanostructures are polymeric/inorganic elements (formed from silver, gold, copper, etc.) that offer various advantages by both being drug-delivery systems, and inherently exerting antibacterial activity. Nanoparticle formulations can provide different antimicrobial mechanisms and interfere with cellular processes with improved drug delivery or prolonged drug release. They show a synergistic potential of combining several antibiotics to maximize efficacy against MDR with minimized toxicity [110]. As multi-functional therapeutics, they might enable the attack on many fronts in combination therapy with antibiotics, chemicals, or antibodies, to reduce the development of resistance [111, 112].

Anti-biofilm therapeutics are necessary to fight against the multidimensional complexes formed by bacteria during chronic infection. Biofilms increase resistance to antibiotics and host immune responses and pose extreme clinical challenges. Hence, novel multifaceted therapeutic approaches, such as quorum sensing inhibitors should refill the antimicrobial armamentarium to prevent, eradicate, or increase the penetration of antimicrobials inside biofilms [113].

It is worthy to note that alternative therapeutics have a limited spectrum compared to antibiotics. However, they are more likely to reach clinical success, not harming the commensal communities and limiting adverse side effects in the long term. These novel therapeutic approaches will nevertheless require substantial efforts and time since they will not follow the conventional development path of antibiotics.

3.1.4 | Increase the Surveillance of MDR

The surveillance of the incidence of MDR is an integral component of regulation. It needs to be complete, exhaustive, and continuous to facilitate the evaluation of the different interventions at both global and local event. International initiatives have thus been developed to assess MDR worldwide, englobing the premier surveillance system, the Study for Monitoring Antimicrobial Resistance Trends (SMART) [114], and the Global Antimicrobial Resistance and Use Surveillance System (GLASS), whose goal is to provide international guidance on how to sample and standardize data on MDR [115].

One major purpose of the population-level surveillance programs is to gather information on resistant organisms and prescription routines [116]. This allows detecting and responding faster to infectious outbreaks. While current phenotypic routine approaches provide a limited characterization of the pathogen, genetic and genomic approaches are gradually included in the surveillance programs, allowing a much more precise monitoring and modelling of AMR evolution and transmission [117]. Genomic AMR surveillance is based on whole-genome sequencing, which can be applied not only to isolated microorganisms (microbial genomics), but also to entire microbial communities (metagenomics) [116]. They can contribute to the detection of new emergent strains, the identification of sources, transmission pathways and mobile ARG responsible for AMR [117]. They also characterize the genetic basis of resistance, which in turn can help predict the resistance dissemination [118]. Interestingly, microbial epidemiological data can also be correlated with phylogenomic data to constitute phylodynamic studies, a powerful approach to elucidate evolutionary mechanisms [116].

However, the current state of surveillance varies greatly between countries with some highly structured systems in high-income countries, but low and far from being representative surveillance sites in LMIC. Moreover, challenges in the implementation of genomic approaches in routine surveillance include lack of harmonization and standardization, high running costs, shortage of trained biinformaticians with prolonged turnaround times for sequencing [117, 118]. Among these, the definition of a framework for use, the development of new training competencies, and the harmonization of surveillance between different stakeholders are important aspects to tackle [117, 118].

3.1.5 | Control ATB and Bacteria in Bodies of Water

The directive of the European Parliament concerning urban wastewater treatment was amended in 2022 to revive the reindustrialization of the pharmaceutical industry in Europe and center the responsibilities of water treatment toward national authorities. This directive promotes the responsible use of antibiotics in human and veterinary medicines and requires harmonized methodologies for measuring AR in urban wastewaters and, when relevant, in the collecting systems. National public health authorities should measure AR at least twice a year for agglomerations of above 100 000 people. These data would help reducing the use of specific classes of antibiotics and updating restrictions in animals [119].

The outcomes and evaluations of the first national health plans in Europe, showed that multifaceted interventions, focusing on multiple issues at the same time, and including educational materials for medical prescribers were the most effective [120].

3.2 | Educating the Specialists and the Public

3.2.1 | Reinforce the Role of Governmental Agencies and Facilitate Their Procedures

One key aspect of the fight against AR is the necessary involvement of governmental and international agencies, as well as collaborations between national committees, in order to initiate a common policy concerning the regulation of antibiotics, the use

of new therapeutics, and the surveillance of AR [114, 121]. In 2022, EU member states all approved the limitation of antibiotics in livestock, exclusively to medical purposes leading already to a net positive impact today [122].

If the access to antibiotics is strictly regulated in some countries (e.g., France, USA, …), self-medication is common in most regions (Asia, Africa, South and Central America) where antibiotics, delivered without prescription and regulation, are easily available. Thus, laws prohibiting illegal selling of antibiotics to Humans and their overuse in animals and harmonized rules should be enforced worldwide [52, 123].

Numerous heavy administrative procedures by the Federal Drug Agency (FDA), the European Medicines Agency (EMA) or the other national health agency hinder the development and the commercialization of new drugs and alternative therapeutic approaches against bacteria. An evolution of the regulatory guidance in place, or the development of new initiatives, such as the clinical trials network, could facilitate and accelerate their clinical development [124]. Strategies to decrease the risks and the hurdles before registration of any new antibiotics could be developed in a close collaboration between the academic, the pharmaceutical sector and the health agencies, as incentives to initiate clinical trials and accelerate or ensure the registration of the drugs when clear endpoints are achieved. The extended duration of patents might be considered to revive the attractiveness of the pharmaceutical industry.

3.2.2 | Tailor the Education and Communication Campaigns

One important axis, improved over the years, is the importance for individuals to understand the concept and potentially deadly issue of AR. Education needs to be adapted to everyone, with the communication or information campaigns specifically addressed, either to the general population, the medical or the non-medical prescribers.

Antimicrobial stewardship programs include the publication of guidelines, the promotion of educational conferences on topics related to antibiotics and/or infectious diseases, interviews with medical experts, communications through TV, radio, and newspapers [125]. These campaigns are critical to teach the public on how to use antibiotics correctly (e.g., follow the treatment until the prescribed endpoint) or to perform diagnostic tests. They are correlated with a decrease in antibiotic use and a lower amount of MDR bacteria, without adverse effect on mortality [126].

The education and how the public retains information on AR should be different according to population subgroups, specific to age or qualification levels. Children and young adolescents could benefit from pedagogic and/or ludic activities informing about the AR problem (e.g., e-bug.eu), as well as the use of social media and online videos followed easier by the younger generations [127]. For future and present healthcare professionals and farmers, an upgrade of the initial and a continuous formation, focusing more on microbial virulence, antibiotics, and prevention of infection would encourage the promotion of measures to reduce the necessity of using antibiotics. The implementation of the education plan "ASSURE" elective in Pennsylvania showed an increase of confidence of medical students to correctly prescribe antibiotics by working with national/international programs on the concept of AR [128].

4 | Conclusion

As the global consumption of antibiotics is expected to increase by 200% by 2030 [4], AR is now posing a pervasive threat to health systems and Humans. However, AR spread in resource limited- and high-income settings is quite distinct requiring the design of tailored measures to fight AR for an efficient post-antibiotic era.

Here, we offer a state of the art of measures that have already made an impact on AR spreading. Our opinion is that the reduction of antibiotics and the development of alternative targeted therapeutic approaches need completion with cutting-edge surveillance methods of antibiotics and MDR pathogens in the environment, as well as education programs for all prescribers and non-prescribers. Importantly, the understanding of Human determinant factors involved in the acceleration of selective pressure leading to increasing numbers of AR bacteria remains unclear and needs more evidence to tackle the problem.

It is a priority to improve market attractiveness and diminish the hurdles until registration of alternative drugs. Pushed by the development of new specific diagnostic tests, more targeted therapies could alleviate AR pressure while using more conventional antibiotics for undiagnosed emergencies in hospitals. Others [129] have previously emphasized the urgency to design novel mechanisms of funding for the future translational pipeline, to upscale the early-stage process or to find novel strategic mechanisms of investments for Health. Ultimately, a large effort is necessary in low-income countries to implement "the right antibiotics at the right moment" [130] as well as new sustainable technologies to treat the environmental pollution by antibiotics and MDR.

Finally, as emphasized in this essay, only international, concerted, collaborative and multivalent measures supported by investments can be truly effective in the fight against AR.

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed for this essay.

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