Communication

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One Earth-One Health Concept to Combat Bacterial Resistance Having Dual Mutation Pattern, Based on the Self-Regulation of Ecosystems

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Abstract

Antibiotic resistance (ABR) has emerged as a grave threat to human health, and the One Earth-One Health (OE-OH) concept was proposed for addressing this challenge in 2024. To elucidate and refine this concept, a dual mutation pattern of bacterial resistance was put forward adhering to the principle of parsimony, involving the integration of Lamarckian and Darwinian evolutionary theories, and niche construction theory. Subsequently, the theoretical underpinnings of this concept were clarified based on the self-regulation and perpetual reconstruction of ecosystems, and a fundamental mathematical model was presented for the renewal of antibiotic resistance genes (ARGs) with the evolution of ecosystems. From this concept, it deduced that ABR and ARGs likely emerge 3.5 billion years ago and are now ubiquitous across the globe. Moreover, the self-regulation of the Earth's ecosystem on the generation, dissemination, and elimination of ABR and ARGs, involving various biotic and abiotic factors, was sorted out for enhancing an understanding of this concept. As an external intervention on this self-regulation, the use of antibiotic has been posed a concern transcending the self-regulatory capacity of ecosystems. Thereby, several crucial measures are proposed from the OE-OH concept, emphasizing the key role of utilizing the self-regulation of ecosystems in addressing ABR.

Keywords:OE-OH; one health; mutation; ecosystem; antimicrobial agent; antibiotic; microbe; plant; climate; environment; combination; parsimony; Occam; Lamarck; Niche; Darwin

1. Introduction

Antibiotic resistance (ABR) has emerged as a serious threat to global public health and economic development, and the COVID-19 pandemic has further exacerbated this crisis [1–3]. It was showed that ABR has rapidly spread from diverse settings where antibiotics are used into surrounding environments [4,5]. Moreover, antibiotic resistance genes (ARGs) can be extensively detected in a wide range of water and soil environments [4–7], with their presence even being on the north slope of Mount Everest [8]. In light of these alarming trends, the World Health Organization (WHO) has projected that, without any intervention, antibiotic resistance would lead to 10 million deaths annually by 2050 [9,10]. In response to this crisis, FAO, UNEP, WHO, and WOAH have developed the One Health Joint Plan of Action (2022–2026) (OH JPA), and appeal working together for the health of humans, animals, plants and the environment [7,11].

As is widely acknowledged, the use of antibiotics, particularly their overuse and abuse, has given rise to the crisis of ABR. However, it is worth exploring whether these reports can accurately reflect the actual situation of ABR. On the one hand, many studies, driven by the interests and focus of researches, tend to concentrate more on the spread and evolution of ABR among microorganisms

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and/or in the environment, while neglecting or studying less on the self-regulatory capacity of the Earth's ecosystem in weakening and eliminating ABR and ARGs [12–15]. This self-regulatory capacity encompasses the complex interactions among humans, plants, animals, microorganisms, and the environment, as well as the functional redundancy and removal of ARGs [4,16–18]. On the other hand, it is also worth contemplating whether the mere detection of ARGs implies that ABR has been transmitted to the sampling site. These two aspects have prompted a more profound re-evaluation for the strategies and measures aimed at addressing ABR. Based on the discoveries of various laws on drug combination preventing ABR [19,20] and the effects of numerous plant metabolites in reversing ABR [12,21,22], the One Earth-One Health (OE-OH) concept for preventing ABR was put forward at the 6th International Caparica Conference in Antibiotic Resistance 2024 (IC²AR 2024) [12,23].

The One Health (OH) concept posits that antibiotic resistance (ABR) encompasses multiple facets, including humans, animals, plants, and the environment, emphasizing the pivotal role of humans in combating ABR. In contrast, the OE-OH concept places greater emphasis on the self-regulatory capacity of the Earth's ecosystem and its sub-ecosystems in relation to ABR. Specifically, it accords equal importance to the generation, spread, weakening and elimination of ABR by the ecosystem, and regards the production and use of antibiotics as an intervention within the ecosystem's ABR dynamics. Herein, the theoretical underpinnings of this concept, together with some innovative prospective insights, reasoning, deductions, and inductions concerning ABR and ARGs from the OE-OH concept, are presented as follows. Based on these, some distinctive strategies for combatting ABR are subsequently proposed and elaborated.

2. The OE-OH Concept

2.1. A Dual Mutation Pattern of Bacterial Resistance

In accordance with the principle of parsimony [24,25], also known as Occam's Razor, the mutation theory of bacterial resistance can be reconsidered. We believe that bacterial resistance predominantly engages in proactive evolution by adaptive mechanisms, and which is designed to avert the unnecessary expenditure of energy and resources that are typically associated with random mutations. This assertion aligns with Lamarck's theory which has also garnered support from recent research endeavors [26]. However, there may also be minor imprecise mutants during the course of proactive resistance mutations. Simultaneously, some mutants carrying ARGs can also emerge through the occasional and non-adaptive random mutations, and be passively screened by natural selection in accordance with Darwinian evolution. From these, ARG-carrying mutants originate from two distinct types of mutations, shown on Figure 1. The dual mutation pattern of bacterial resistance, characterized primarily by proactive evolution and occasionally by passive selection, exhibits a striking congruence with the Niche construction theory as it pertains to ecosystems [27,28].

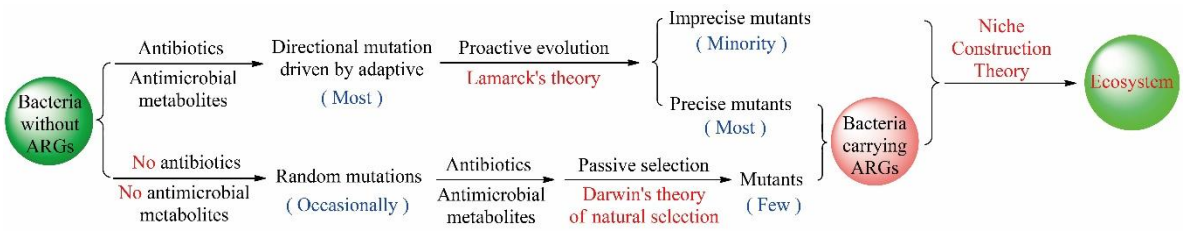

Figure 1. Dual mutation pattern of bacterial resistance through proactive evolution and passive selection.

2.2. Theoretical Underpinnings of the OE-OH Concept Based on Ecosystems

Inspired by the dual mutation pattern illustrated in Figure 1, it can be inferred that antimicrobial metabolites produced by microbes (some of which are termed antibiotics now), microbial resistance and ARGs likely emerge concurrently with the formation of the microbial ecosystems. This is because they arise from the competition among microorganisms within ecosystems and are renewed as ecosystems undergo reconstruction [29–32]. Namely, ARG-carrying bacteria likely first emerged

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when certain microbial ecosystems were formed 3.5 billion years ago [33,34], and have been continuously spreading and renewing ever since (Figure 2). Simultaneously, the Earth, including soil, various environments and all the organisms that inhabit it, can be regarded as a giant ecosystem composed of countless sub-ecosystems that operate through similar mechanisms. Therefore, the robust self-regulatory capacity and perpetual reconstruction of ecosystems, particularly those of the Earth's one [13–15], form the theoretical underpinnings of the OE-OH concept. From this perspective, various aspects related to microbial resistance can be reexamined. Moreover, even although the proactive mutation is the primary pattern of microbial resistance to antibiotics, a large number of antibiotic-resistant microbes can still be found prior to exposure to antibiotics. This is due to the substantial accumulation of ARG-carrying pathogens in the Earth's ecosystem over a long period of time.

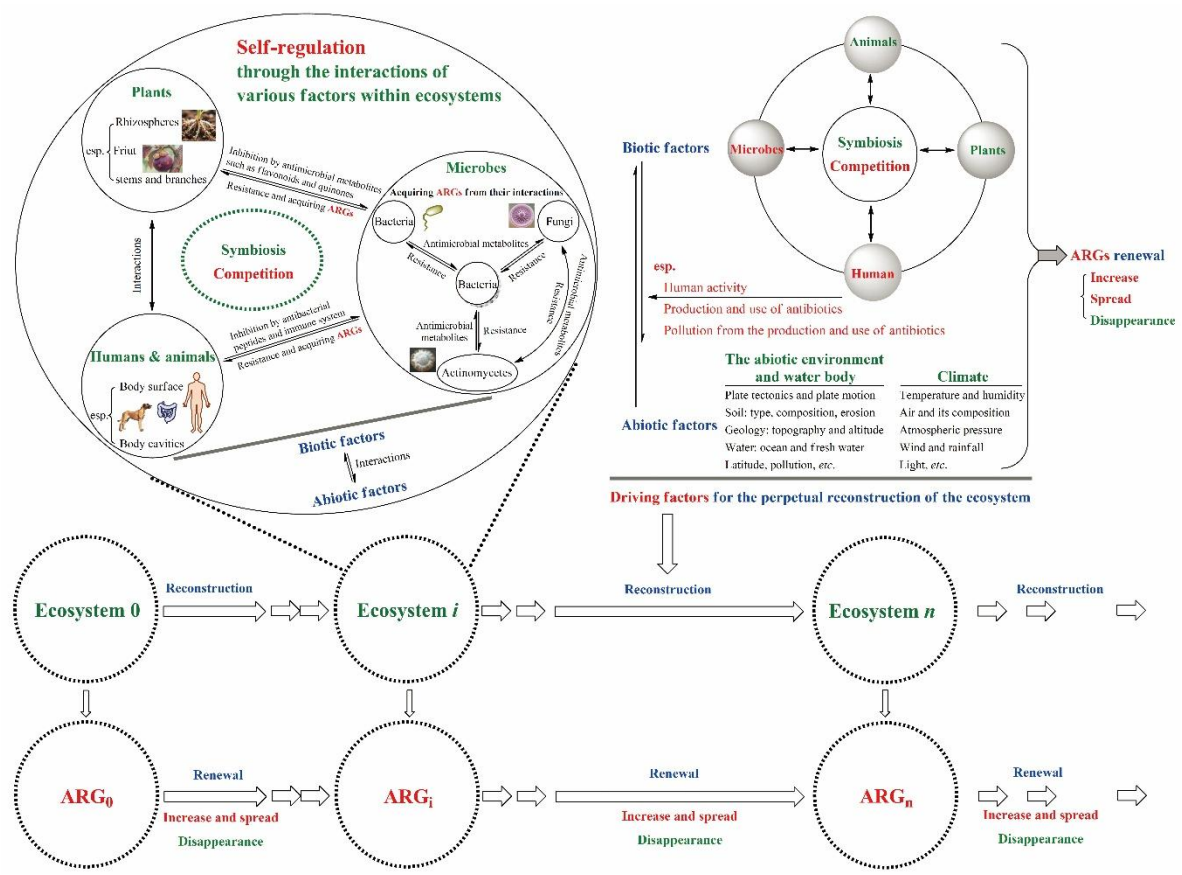

Figure 2. Schematic for the theoretical underpinnings of the OE-OH concept based on the robust self-regulatory capacity and perpetual reconstruction of ecosystems. The ecosystem can be the entire Earth's ecosystem or its various sub-ecosystems; ecosystems 0, *i*, and *n* indicate the ecosystem at different time points during its evolution, and their antibiotic resistance genes (ARGs) correspondingly renew with the perpetual reconstruction of the ecosystem.

2.3. A Fundamental Mathematical Model for the ARGs Renewing with the Ecosystem

The OE-OH concept envisions the Earth as a giant ecosystem, intricately woven from a myriad of sub-ecosystems that operate through similar mechanisms. The amount of ARGs within an ecosystem can be articulated through a fundamental mathematical model as follows.

$$ARG_i = ARG_0 + (ARG_1^{In} + ARG_2^{In} + \cdots\cdots + ARG_i^{In} + \cdots\cdots + ARG_n^{In}) + (ARG_1^{De} + ARG_2^{De} + \cdots\cdots + ARG_i^{De} + \cdots\cdots + ARG_n^{De})$$

$$ARG_n = ARG_0 + \sum_{i=1}^{n} ARG_i^{In} + \sum_{i=1}^{n} ARG_i^{De}$$

Where ARG_i and ARG_n are the amount of ARGs at two time points (Figure 3) of the ecosystem which can be the Earth's one or its various sub-ecosystem, and time point i can be equal to n; ARG_0

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can be the amount of ARGs at any time point while time points i and n are more than or equal to time point 0, and especially the amount of ARG_0 is zero before the microbial ecosystem emerged on the Earth; ARG^{In} is the increased amount of ARGs in the ecosystem, for example ARG_1^{In} is that from time point 0 to 1; ARG^{De} (defines as negative value) is the decreased amount of ARGs in the ecosystem, for example ARG_1^{De} is that from time point 0 to 1; $\sum_{i=1}^{n} ARG_i^{In}$ is the sum of the increased amount of ARGs from time point 1 to n, and $\sum_{i=1}^{n} ARG_i^{De}$ is the sum of the decreased amount of ARGs from time point 1 to n.

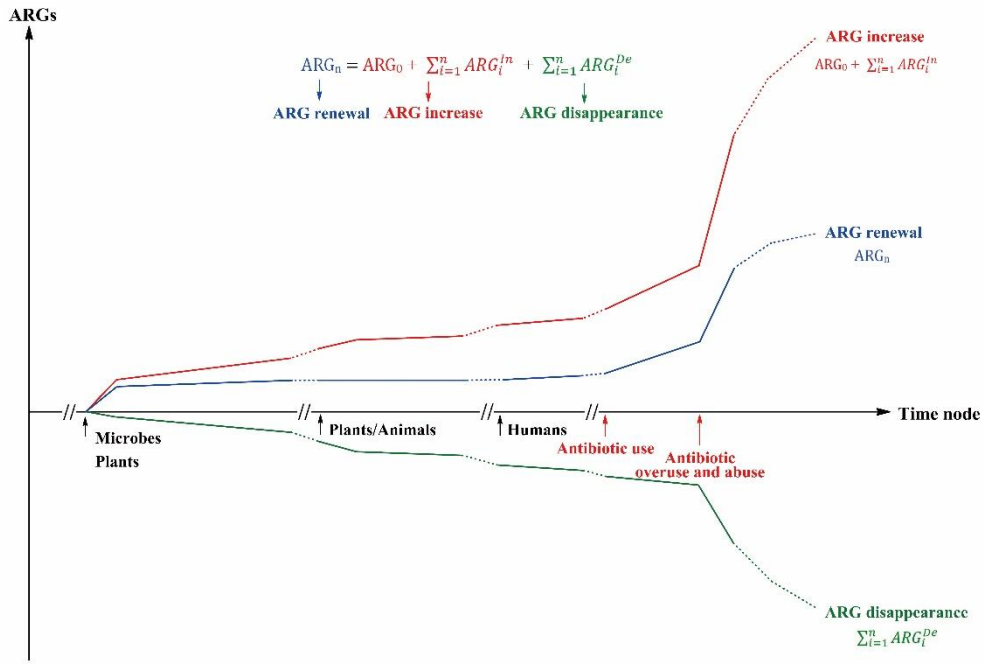

Figure 3. Schematic for the amount of ARGs (ARGs, *y*) within an ecosystem changing with different evolutionary time nodes (Time, *x*), according to the fundamental mathematical model. The ecosystem can be the entire Earth's ecosystem or its various sub-ecosystems, and the time nodes include the emergence of microbes, plants, animal, and humans, and the use of antibiotics by humans.

3. ARG Analyses from the OE-OH Concept Based on Ecosystems

3.1. ARGs Emerging Before Humans and Existing Everywhere

Antimicrobial metabolites are a category of natural products that generate from the competition for ecological niches among microorganisms within ecosystems or in response to survival stress [29–31]. From the evolutionary history of the Earth, it is known that microbes emerge about 3.5 billion years ago, and by that time, diverse ecosystems teeming with microbial communities had already taken shape [33,34]. After a long period of evolution, there are sufficient reasons to infer that the structural skeletons of most clinical antibiotics can be biosynthesized by environmental microorganisms. This can be confirmed by the fact that the structural skeletons of clinical antibiotics were mostly discovered from soil microorganisms [29]. In other words, microorganisms that carry the genetic information for biosynthesizing the structural skeletons of most clinical antibiotics, including microbial strains belonging to the same or different genera and species, are widely distributed in various sub-ecosystems of the Earth. Even synthetic quinolone antimicrobial agents bear a resemblance in structural framework to naturally occurring compounds such as plant-derived flavonoids and benzofuranones [12,35]. This is also a reason that natural products with antibacterial activity can be continuously discovered from environmental microorganisms. Likely, the genetic information of microorganisms producing these natural products has existed on the Earth before the emergence of humans [36], while only was discovered and excavated after entering into the 20th century.

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It is reported that today's pathogenic microorganisms originate from the soil [37,38]. Therefore, clinical pathogens should be widely distributed across various ecosystems on the Earth and likely emerged prior to the existence of humans (Figure 3). Since antimicrobial metabolites generated before 3.5 billion years ago, it is reasonable to deduce that, due to microbial competition within ecosystems, the ARGs of pathogenic microorganisms evolved in response to the survival stress from antimicrobial metabolites (some of which are now used as antibiotics) produced by other environmental microbes may had been already emerged at that time.

Box 1. The OE-OH concept based on the self-regulation of the Earth's ecosystem for ABR and ARGs.

$$ARG_n = ARG_0 + \sum_{i=1}^{n} ARG_i^{In} + \sum_{i=1}^{n} ARG_i^{De}$$

Factors for the generation and spread of ARGs (ARG^{In})

Abiotic factors

The abiotic environment and water body

Plate tectonics and plate motion, geological disaster

Soil components, dust and air [6,37,85–89]

Hydrographic system and water flows [5,90,91]

Ocean and its currents [53,61,92]

The melting of ice and snow in the Arctic, the Antarctic and high mountains [8]

Climate

Rainfall, wind, global warming, and drought [39,93]

Biotic factors influenced by climate change and climate extremes [60,94–96]

Factors for the weakening and elimination of ARGs (ARG^{De})

Abiotic factors

The abiotic environment and water body

Plate tectonics and plate motion, geological disaster

Soil components, dust and air [6,85,97]

Dilution and/or elimination of antibiotics and ARGs [55,81,98, 99]

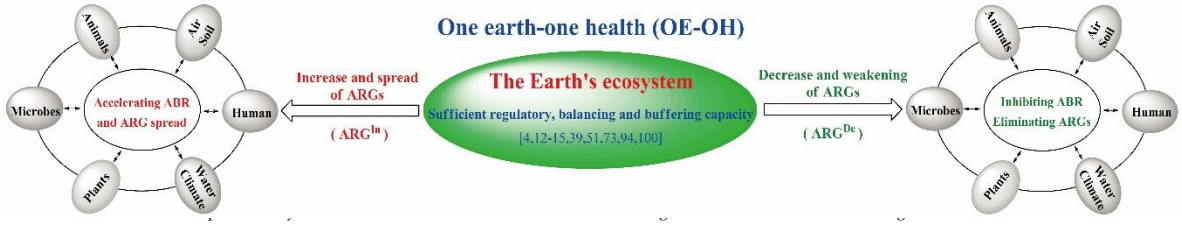
Dilution, decrease and disappearance of the selective pressure [48]

The killing and clearance of ARGs and antibiotic-resistant pathogens [81,82,100–102]

Climate

Rainfall, wind, global warming, and drought [39,93,100]

Biotic factors influenced by climate change and climate extremes [48,94,95]



Horizontal transfer of ARGs according to genetic compatibility and ecological connectivity [51]

Plants

The decrease in plant diversity [62]

The ARGs enrichment in the rhizosphere of plants [108]

The activation to ARG expressions by plant antibacterial metabolites [18]

Animals

Activities and migration

Foraging and excretion [109–115]

The activation to ARG expressions by antimicrobial peptides [18]

Human and human activity

Daily activities, migration, travels, diet, and excretion [3,37,109,110,112,114,116–118]

The activation to the ARG expressions by antimicrobial peptides [49]

Population gathering and domestic sewage [4,58,59]

The use and abuse of antimicrobial agents in medical activities, livestock, poultry farming, and aquaculture, *etc.* [4,48,53]

The use of air and environmental disinfectants [119]

The pollution of air and water from the production and use of antibiotics and environmental disinfectants [3,4,54–57,119]

The impacts of human activities on all biotic and abiotic factors that generate and spread ABR and ARGs in the Earth's ecosystem [60–65]

The killing and inhibition of other microbes to pathogens within ecosystems [4]

Plants

The increase in plant diversity [62]

The degradation of antimicrobial agents by plants [84,121,122]

Sensitization of antimicrobial resistance by plant antibacterial metabolites [12,123]

The killing and clearance of plant antibacterial metabolites to drug-resistant pathogens [4,72]

Animals

The killing and clearance of animal body to drug-resistant pathogens including the immune system, antibacterial peptides, beneficial microorganisms, *etc.* [124]

Foraging and the sensitization of the intestinal microbial ecology to drug-resistant pathogens [4]

Human and human activity

The killing and clearance of human body to antibiotic-resistant pathogens [49,50,71,125] including the immune system, antibacterial peptides, beneficial microorganisms, *etc.*

Diet and the sensitization of gut microbial ecology to antibiotic-resistant pathogens [12,126]

Degradation, reduction and removal of antibiotics in waste residues and water from medical activities, livestock, poultry farming, and aquaculture, etc. [81,83,84]

Disinfection and inactivation of antibiotic-resistant pathogens

All other possible human activities on biotic and abiotic factors that clear antibiotics and decrease ARGs within the Earth's ecosystems [64,81,124,127]

As the Earth's ecosystem and its diverse sub-ecosystems evolve and undergo reconstruction driven by a variety of biotic and abiotic factors (Box 1) [39], new ARGs are constantly emerging. new antibiotic resistance genes (ARGs). Moreover, ARGs are continuously spreading and renewing across every corner of the Earth (Figure 3). Therefore, it can be inferred that microorganisms responsible for producing the structural skeleton of certain antibiotics, along with pathogens carrying corresponding ARGs, are are located in specific ecosystems. When antibiotics are isolated from soil or marine

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microbes, it is likely that these pathogens have already encountered these antibiotics during the evolutionary process of the Earth's ecosystem. Through proactive adaptive mutations and the acquisition of heritable ARGs, these pathogens have also developed resistance to these antibiotics. This may explain why ARG-carrying pathogens can sometimes be detected shortly after the introduction of new antibiotics to the market [40], or before they appear to have come into contact with the corresponding antibiotics, sometimes even before the antibiotics are officially approved [41]. Namely, these pathogens have, in fact, been exposed to the corresponding antibiotics long ago.

Given this, it is foreseeable that ARGs can be found not only in extreme environments such as Mount Everest and the Mariana Trench but also in the Antarctic and Arctic regions of the Earth. This notion is also supported by recent researches [42–46], and means that ARGs are likely to be detected in varying degrees from every ecological niche containing microbes if the detection methods are sufficiently sensitive. Moreover, it is reasonable to assume that a certain amount of ARGs existed in various ecosystems and across the Earth prior to the production and use of antibiotics by humans (Figure 3).

3.2. ARGs by the Self-Regulation of Ecosystems Before the Use of Antibiotics

Since the emergence of microbes on Earth, diverse ecosystems composed of microbial communities have gradually taken shape and continuously evolved along with the incorporation of new organisms and the elimination of existing ones. Throughout the Earth's evolutionary history, the information of antibiotic resistance genes (ARGs) has been in a state of constant renewal, driven by the ongoing reconstruction of ecosystems. This renewal process encompasses the emergence and dissemination of new ARGs, as well as the weakening and elimination of existing ones, and which is also supported by recent researches [4,6,47–51].

As shown in Box 1, a wide range of biotic and abiotic factors, including the abiotic environment, water bodies, climate, microbes, plants, animals and humans, can impact the renewals of ARGs within the Earth’s ecosystem and its various sub-ecosystems. Owing to the sufficient self-regulation, self-balancing and buffering capacities of the Earth’s ecosystem [12–15], the evolution of ABR and ARGs has historically maintained a balanced and controllable state prior to the industrial production and use of antibiotics by humans. However, the situation has become increasingly worrying due to the extensive use of antibiotics, particularly their overuse and abuse in clinical settings, livestock, poultry farming, and aquaculture. This was also reflected in the rapid increase in ABR and the widespread dissemination of ARGs after the industrial production and use of antibiotics.

3.3. Impact of Antibiotic Use on ARGs by the Self-Regulation of Ecosystems

In the 20th century, many secondary metabolites with antimicrobial activities at low concentrations were discovered from environmental microorganisms, particularly actinomycetes, fungi, and bacteria, across diverse habitats such as land, oceans, and the body surfaces and feces of animals and humans [29,31]. Some of these metabolites and their derivatives have been developed as clinical antibiotics. In fact, the genetic information of microorganisms producing these antibiotics, together with the corresponding ARGs carried by pathogens resistant to these antibiotics, was already generated long ago, and can be considered as the products of competition among various microorganisms during the Earth's evolutionary history. Although most of the clinical antibiotics currently in use are structural derivatives of these natural antibiotics, they share similar structural skeletons with corresponding naturally sourced antibiotics. Consequently, the information of their corresponding ARGs carried by pathogens has existed in nature for a long ago. Moreover, pathogens carrying these resistance genes have spread globally, with some disseminating through soil and others colonizing specific parts of the human body [37].

From the above, the widespread use of antibiotics across various domains, including medical practices, livestock breeding, poultry farming, and aquaculture, can be considered as a human intervention on the evolution of ARGs within the global ecosystem [52]. Besides general human activities, as well as the interactions between the human body and microbes, have been driving the

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spread of ARGs (Box 1) prior to the use of antibiotics, several key activities associated the industrial production and use of antibiotics by humans have led to a sharp increase in ABR and the rapid spread of ARGs. These activities are as follows: 1) The use, overuse and abuse of antibiotics in medical practices, livestock, poultry farming, and aquaculture, *etc*. [4,48,53]; 2) The pollution of the Earth's environment caused by wastewater discharged from the settings of antibiotic production and use [3,4,7,53–57]; 3) The excessive aggregation of human population and the large amounts of domestic sewage generated under conditions of antibiotic overuse and misuse [4,58,59]; 4) The impacts of other human activities on all biotic and abiotic factors that contribute to the generation and spread ARGs within the Earth's ecosystem [60–65].

Theoretically, the wider the application scope of antibiotics and the greater their usage, the larger the intervention intensity on ecosystems. When the intervention intensity keeps within a specific and controllable range, the Earth's ecosystem and its myriad sub-ecosystems have sufficient self-regulation capabilities to restore or reestablish a new balance (Box 1). But if the intervention intensity exceeds the self-regulation capacity of ecosystems, the balance of these ecosystems will inevitably be disrupted, endangering larger ecosystems and even the entire Earth's ecosystem [66]. Therefore, our endeavors to discover new antibiotics seem to have the potential to solve the problem of antibiotic shortage caused by ABR, however they are merely a passive defense strategy even if the development of new antibiotics can be accelerated with the assistance of artificial intelligence (AI) [67]. Although AI has the potential to predict microbial resistance to existing antibiotics and facilitate a proactive defense in the future, the struggle between humans and microbes is at most evenly matched. More significantly, the damage to various ecosystems caused by the overuse and abuse of antibiotics, together with the impact and deterioration of new ecosystem reconstruction on human living conditions, should arouse sufficient attention in this struggle.

Therefore, if the overuse and abuse of antibiotics are not controlled, the approval and application of new antibiotics will only accelerate the spread of ABR and ARGs. This will lead to the continuous destruction of larger and more ecosystems centered on the application environment. Moreover, various ecosystems containing more pathogens carrying ARGs will be restructured, ultimately posing a threat to the survival and development of humans. Thus, it is imperative to implement scientific and rational measures to control the spread of ABR and ARGs, for maintaining the balance of the Earth's ecosystem and its various sub-ecosystems.

4. Measures Combating ABR from the OE-OH Concept Based on Ecosystems

As previously stated, the use of antibiotics can be regarded as an intervention on ecosystems from the OE-OH concept. Thereby, a counteracting intervention aimed at preserving the balance of ecosystems should be taken for effectively combating ABR (Figure 4) [68]. Simultaneously, the self-regulation and self-balance capabilities of ecosystems can be fully understood and utilized for the risk evaluation on some measures taken for the research and development, application and management of antibiotics. Learning from the approach of problem management [69,70], some distinctive measures from the OE-OH concept, with the support of literature, are suggested as follows:

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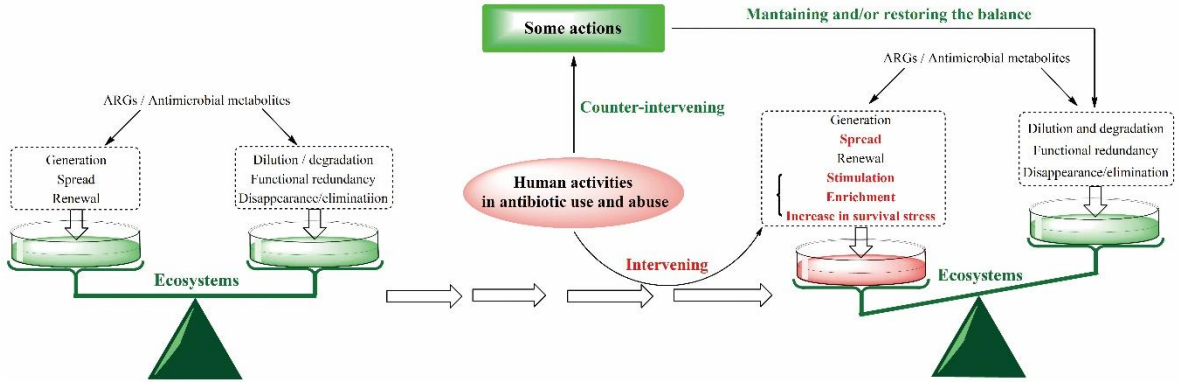

Figure 4. Analysis schematic of some imperative actions taken to offset the imbalance risk of ecosystems caused by the antibiotic use exceeding the self-regulation and balancing capacity of ecosystems, for combating the ABR from the OE-OH concept.

4.1. Minimizing Antibiotic Use, While Fully Utilizing the Regulatory Role of Plants

From the OE-OH perspective, the bodies of humans or animals themselves can be regarded as ecosystems with sufficient self-regulation capabilities. For instance, their immune systems [49], antimicrobial peptides [71], colonized probiotics, and the competition among microorganisms within the body's ecosystem can eliminate infected pathogens, including those are antibiotic-resistant. Meanwhile, many plants, such as traditional Chinese medicine and ethnic medicines, also have the potential to regulate the balance between the bodies of humans or animals and microbes [12,72,73]. This has been evidenced in China during the COVID-19 pandemic [74]. Therefore, it is entirely feasible to reduce the use of antibiotics through utilizing the self-regulation and self-balance abilities of both humans and animals themselves, as well as the regulatory effects of plants on these abilities. Furthermore, even in cases where the bodies of humans and animals are infected, the balance between them and microbes can still be regulated or restored by plants. This can help to mitigate the progression of microbial infections and, to the greatest extent possible, avoid the unnecessary use of antibiotics.

4.2. Minimizing Antibiotic Emissions, While Fully Utilizing the Self-Regulation of Ecosystems

From the OE-OH perspective, microbial resistance predominantly follows the proactive pattern of adaptive evolution, occasionally the passive one of random mutation by natural selection. As the Earth continues to evolve and develop, ARG-carrying pathogens that are widely distributed can be activated, screened, and enriched under the stress of antibiotics. Consequently, the emission of antibiotics into the surrounding environment not only stimulates the overexpression of ARGs in pathogens and enriches the information of ARGs, but also enables susceptible bacteria to proactively evolve into resistant pathogens. Therefore, it is crucial to minimize the emission of antibiotics and ARGs.

Alternatively, from the OE-OH perspective, the transmission processes of antibiotics and ARGs also involve their dilution, redundancy, or disappearance by various ecosystems. Therefore, when effective control is challenging and emissions are unavoidable, the weakening and elimination capacities of ecosystems to antibiotics and ARGs can be fully utilized [73,75–77]. At this moment, scientific and rational measures should be adopted, based on the risk management [78], to implement graded emissions for keeping the emissions of antibiotics and ARGs within the controllable and balanced range of ecosystems, minimizing the damage caused by excessive accumulation of antibiotics and ARGs to the original ecosystem.

4.3. Avoiding the Excessive Aggregation of Population

From the OE-OH perspective, the entire Earth's ecosystem possesses a robust self-regulation capacity to manage the generation, dissemination, enrichment, dilution, weakening, and elimination

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of ARGs, thereby maintaining its equilibrium. However, the overuse and abuse of antibiotics by humans will lead to a continuous enrichment of ARGs and stimulate their proliferation in the environment, resulting in an increasing diversity and abundance of ARGs. If the population becomes excessively concentrated at this moment, it will significantly surpass the capacity of various biotic and abiotic factors (Box 1) to weaken and eliminate ARGs, as well as the self-regulation ability of ecosystems, leading to an excessive accumulation of ARGs in ecosystems centered around the population gathering areas. Therefore, it is crucial to avoid excessive population aggregation [76]. Specifically, the scale of cities should be kept within reasonable limits, and the urban layouts should be appropriately decentralized. This can also be indirectly proved by the transmission patterns of the COVID-19 pandemic.

4.4. Accelerating the Antibiotic Reserve Based on the Understanding for Microbial Defense Mechanisms

From the OE-OH perspective, we can gain a comprehensive understanding of the proactive defense mechanisms of microbes in ecosystems, for developing new antibiotics that are less likely to encounter resistance. Additionally, it is also encouraged to develop new antibiotics with high specificity and minimal disruption to the gut microbes and organismal ecosystems. Meanwhile, it is essential to thoroughly explore the unknown ARGs within ecosystems. By doing so, we can utilize AI technology to predict potential ABR. Based on the potential mechanisms of microbial resistance, the development of new antibiotics that are difficult for pathogens to develop resistance should be expedited to ensure a sufficient reserve of these new antibiotics. In addition, from a policy standpoint, the protection period of patents for new antibiotics can be extended, for reducing the unnecessary use of new antibiotics.

4.5. Encouraging Antibiotics Used in Combination with Plant Antimicrobial Ingredients

From the OE-OH perspective, the increased application of new antibiotics will accelerate the spread and enrichment of ABR and ARGs if the overuse and abuse of antibiotics are not controlled. Therefore, it is imperative to use antibiotics rationally. Among various strategies for the rational use of antibiotics, combination therapy has the advantages of cost-effectiveness in enhancing the efficacy of antibiotics, reversing microbial resistance, and extending the life cycle of antibiotics, buying more time for the development of new antibiotics. This can be also proved by the clinical practice of combination therapy, such as the combination of sulfamethoxazole and trimethoprim, β-lactamase inhibitors and β-lactam antibiotics, and multiple anti-tuberculosis drugs. Therefore, combination therapy is highly commendable [12,52]. However, it is noteworthy that an inappropriate antibiotic combination would instead increase the risk of ABR, due to the effect preventing resistance is associate with the fractional inhibitory concentration index, as well as the proportion and concentration of two antibiotics in the combination [19,20,79].

Antibiotics are derived from the competition among microorganisms. Both bacteria/fungi producing the structural skeleton of antibiotics and pathogenic bacteria are classified as microbes. As a result, their individual defense mechanisms are familiar to each other, making it easier for pathogens to develop resistance to antibiotics in the combination. However, the antimicrobial ingredients of plants originate from the interaction between microorganisms and plants within ecosystems, and the defense mechanisms between plants and microbes are less familiar to each other. Simultaneously, plant-derived antimicrobial components generally exhibit weaker antibacterial activity and smaller stresses on microbial survival compared to antibiotics. Therefore, it is more challenging for microbes to develop resistance to them [20]. Moreover, the combination of plant-derived antibacterial components and antibiotics often has a wide range of synergistic effects [12], and the impact on gut microbes is also milder. Therefore, plant-derived antibacterial components are ideal candidates for combination therapy with antibiotics.

4.6. Simulating the Elimination of Antibiotics and ARGs in Ecosystems

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From the OE-OH perspective, ecosystems have robust capacity to regulate ABR, encompassing the dilution, weakening and elimination of ARGs. Therefore, it is highly encouraged to simulate the elimination of antibiotics and ARGs in ecosystems based on a thorough understanding of their self-regulation mechanisms [68,80]. For instance, employing bacterial ecology to combat ARG dissemination [4], utilizing photocatalysis-enhanced constructed wetlands to remove ARGs [81], simulating sunlight-induced inactivation of tetracycline-resistant bacteria [82], and leveraging bacteria-microalgae-fungi symbionts or plants to remove antibiotics [83,84]. Additionally, these ecological simulation methods and technologies can also, to the greatest extent possible, avoid the potential adverse effects on ecosystems that may be caused by the measures taken.

5. Methods

5.1. The OE-OH Concept

The OE-OH concept was put forwards from the previous results and the sufficient self-regulation ability of the Earth's ecosystem in the evolution of ABR [12,23]. Here this concept has been further defined, improved and clarified using logical, reasoning and deductive methods based on the principle of parsimony [24,25], involving the understanding integration of Lamarck's theory, Darwinian evolution, and Niche construction theory. It includes dual mutation patterns of bacterial resistance, theoretical underpinnings of the OE-OH concept based on ecosystems, and basic mathematical model for the ARGs renewing with the ecosystem. The literature supporting the reasoning and deduction, together with all other literature, was unsystematically searched from PubMed database and Google academic search engine, using various relevant keywords. Furthermore, some highly persuasive references in the obtained literature were also tracked.

5.2. Analyses of ARG Generation, Spread and Elimination from the OE-OH Concept

From the OE-OH concept, the generation, spread and elimination of ARGs along with different time nodes of the Earth's evolution were analyzed using reasoning, deductive and inductive methods based on the self-regulation of ecosystems, together with the supporting of literature also searched from PubMed database and Google academic search engine. These especially include the emergence and distribution of ARGs emerging before humans, the ARG regulation by ecosystems such as its generation, spread, weakening and elimination of ARGs before the industrial production and use of antibiotics, the sharp increase in ARGs after the industrial production and use of antibiotics together with which impact on the self-regulation and self-balance of ecosystems for ARGs.

5.3. Measures Combating ABR from the OE-OH Concept Based on Ecosystems

Regarding the use of antibiotics as an intervention on ecosystems, some important measures for the research and development, application and management of antibiotics are suggested, from the OE-OH prospective, for maintaining the balance of ecosystems regulating on ARGs, learning from the approach of problem management [69,70].

6. Conclusions and Outlook

The OE-OH concept was defined and clarified, which includes a dual mutation pattern of proactive evolution (most) and passive selection (few) for bacterial resistance mutation, the theoretical underpinnings of the OE-OH concept based on ecosystems, and a fundamental mathematical model for the renewal of ARGs within the ecosystem. Derived from this concept, it deduced that ABR and ARGs emerge 3.5 billion years ago and exist in every corner of the Earth prior to the production and use of antibiotics by humans. Additionally, the amount of ARGs was schematically presented in accordance with different time nodes of the Earth's evolution. Subsequently, the self-regulation of the Earth's ecosystem on the generation, spread, weakening and elimination of ABR and ARGs, involving a variety of biotic and abiotic factors, has been

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systematically sorted out for facilitating a comprehensive understanding of the OE-OH concept. Regarded as an intervention on ecosystems, the industrial production and use of antibiotics, particularly their overuse and abuse, have led to a sharp increase of ARGs, posing a concern that transcends the ecosystem's self-regulatory capacity. Based on this, several crucial measures derived from the OE-OH concept are proposed to redress the imbalance in ARG generation and elimination within ecosystems, combatting ABR. These measures place a strong emphasis on simulating and leveraging the self-regulatory mechanisms of ecosystems, while also advocating for the minimization of antibiotic use and emissions, preventing excessive population aggregation, and encouraging antibiotics used in combination with plant-derived antimicrobial ingredients.

Drawing on the OE-OH concept, the following research directions are proposed for future exploration. (1) Conducting in-depth investigations into ARGs in problem-oriented samples from both designed terrestrial and marine environments. This not only can help to elucidate the dissemination of ARGs, but also can provide additional evidence for understanding the Earth's evolution, plate tectonics, and human migration; (2) Referred to Lamarck's theory and Niche construction one, emphasizing the interactions among various factors in host ecosystems and strengthening researches on the proactive defense mechanisms of microbe, for developing new antibiotics with strong selectivity that cause minimal disruption to human ecosystems such as the gut microbiota; (3) Emphasizing the self-regulation of ecosystems, strengthening researches on the regulation of plant on the ecosystem of human body preventing microbial infection, and encouraging the research and development of antibiotics in combination with plant-derived antimicrobial ingredients; (4) Increasing efforts to study the dilution and degradation of antibiotics in ecosystems, as well as the weakening and elimination of ARGs, and developing methods and technologies that simulate the ecosystems' elimination of antibiotics and ARGs; (5) Based on the self-regulatory capacity of ecosystems in the elimination of antibiotics and ARGs, conducting researches on the schemes of population distribution and urban settlements for combatting ABR. Finally, it is essential to implement the OH Joint Plan of Action from the OE-OH perspective emphasizing the key role of utilizing the self-regulation of ecosystems in addressing ABR.

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References

1. Murray, C.J.L.; Ikuta, K.S.; Sharara, F.; Swetschinski, L.; Aguilar, G.R.; Gray, A.; Han, C.; Bisignano, C.; Rao, P.; Wool, E.; et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **2022**, *399*, 629–655.
2. Wang, C.; Mantilla-Calderon, D.; Xiong, Y.; Alkahtani, M.; Bashawri, Y.M.; Al Qarni, H.; Hong, P.Y. Investigation of antibiotic resistome in hospital wastewater during the COVID-19 pandemic: is the initial phase of the pandemic contributing to antimicrobial resistance? *Environ. Sci. Technol*. **2022**, *56*, 15007–15018. doi: 10.1021/acs.est.2c01834.
3. Mohapatra, S.; Yutao, L.; Goh, S.G.; Ng, C.; Luhua, Y.; Tran, N.H.; Gin, K.Y. Quaternary ammonium compounds of emerging concern: classification, occurrence, fate, toxicity and antimicrobial resistance. *J. Hazard. Mater*. **2023**, *445*, 130393. doi: 10.1016/j.jhazmat.2022.130393.

 doi:10.20944/preprints202506.2442.v2

4. Wang, D.; Zhou, X.; Fu, Q.; Li, Y.; Ni, B.J.; Liu, X. Understanding bacterial ecology to combat antibiotic resistance dissemination. *Trends Biotechnol.* **2025**, *43*, 1566-1582. doi: 10.1016/j.tibtech.2024.12.011.
5. Wang, B.; Ma, B.; Zhang, Y.; Stirling, E.; Yan, Q.; He, Z.; Liu, Z.; Yuan, X.; Zhang, H. Global diversity, coexistence and consequences of resistome in inland waters. *Water Res.* **2024**, *253*, 121253. doi: 10.1016/j.watres.2024.121253.
6. Hu, X.; Fu, Y.; Shi, H.; Xu, W.; Shen, C.; Hu, B.; Ma, L.; Lou, L. Neglected resistance risks: cooperative resistance of antibiotic resistant bacteria influenced by primary soil components. *J. Hazard Mater.* **2022**, *429*, 128229. doi: 10.1016/j.jhazmat.2022.128229.
7. Gao, F.Z.; He, L.Y.; Liu, Y.S.; Zhao, J.L.; Zhang, T.; Ying, G.G. Integrating global microbiome data into antibiotic resistance assessment in large rivers. *Water Res.* **2024**, *250*, 121030. doi: 10.1016/j.watres.2023.121030.
8. Fu, C.X.; Chen, C.; Xiang, Q.; Wang, Y.F.; Wang, L.; Qi, F.Y.; Zhu, D.; Li, H.Z.; Cui, L.; Hong WL, et al. Antibiotic resistance at environmental multi-media interfaces through integrated genotype and phenotype analysis. *J. Hazard Mater*. **2024**, *480*, 136160. doi: 10.1016/j.jhazmat.2024.136160.
9. Naddaf, M. 40 million deaths by 2050: toll of drug-resistant infections to rise by 70. *Nature* **2024**, *633*, 747–748. doi: 10.1038/d41586-024-03033-w.
10. Mancuso, G.; Midiri, A.; Gerace, E.; Biondo, C. Bacterial antibiotic resistance: the most critical pathogens. *Pathogens* **2021**, *10*, 1310.
11. FAO, UNEP, WHO, WOAH. One Health Joint Plan of Action (2022–2026). Working together for the health of humans, animals, plants and the environment. Rome, **2022**. doi: 10.4060/cc2289en.
12. Yuan, G.; Lian, F.; Yan, Y.; Wang, Y.; Zhang, L.; Zhu, J.; Fatima, A.; Qian, Y. One Earth-One Health (OE-OH): antibacterial effects of plant flavonoids in combination with clinical antibiotics with various mechanisms. Antibiotics, **2025**, *14*, 8. doi: 10.3390/antibiotics14010008.
13. Lenton, T.M. Gaia and natural selection. *Nature* **1998**, *394*, 439–447.
14. Nicholson, A.E.; Wilkinson, D.M.; Williams, H.T.P.; Lenton, T.M. Multiple states of environmental regulation in well-mixed model biospheres. *J. Theor. Biol*. **2017**, *414*, 17–34.
15. Maull, V.; Pla Mauri, J.; Conde Pueyo, N.; Solé, R. A synthetic microbial Daisyworld: planetary regulation in the test tube. *J. R. Soc. Interface* **2024**, *21*, 20230585.
16. Lynch, M.; O'Hely, M.; Walsh, B.; Force, A. The probability of preservation of a newly arisen gene duplicate. *Genetics* **2001**, *159*, 1789–1804. doi: 10.1093/genetics/159.4.1789.
17. Qian, S.H.; Chen, L.; Xiong, Y.L.; Chen, Z.X. Evolution and function of developmentally dynamic pseudogenes in mammals. *Genome Biol*. **2022**, *23*, 235. doi: 10.1186/s13059-022-02802-y.
18. Smith, W.P.J.; Wucher, B.R.; Nadell, C.D.; Foster, K.R. Bacterial defences: mechanisms, evolution and antimicrobial resistance. *Nat. Rev. Microbiol.* **2023**, *21*, 519–534. doi: 10.1038/s41579-023-00877-3.
19. Xu, X.; Xu, L.; Yuan, G.; Wang, Y.; Qu, Y.; Zhou, M. Synergistic combination of two antimicrobial agents closing each other's mutant selection windows to prevent antimicrobial resistance. *Sci Rep*. **2018**, *8*, 7237. doi: 10.1038/s41598-018-25714-z.
20. Yi, H.; Yuan, G.; Li, S.; Xu, X.; Guan, Y.; Zhang, L.; Yan, Y. Drug combinations to prevent antimicrobial resistance: various correlations and laws, and their verifications, thus proposing some principles and a preliminary scheme. *Antibiotics* **2022**, *11*, 1279.
21. Górniak, I.; Bartoszewski, R.; Króliczewski, J. Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochem. Rev.* **2019**, *18*, 241–272.
22. Farhadi, F.; Khameneh, B.; Iranshahi, M.; Iranshahy, M. Antibacterial activity of flavonoids and their structure-activity relationship: an update review. *Phytother. Res*. **2019**, *33*, 13–40.
23. Yuan, G.; Yi, H.; Zhang, L.; Guan, Y.; Li, S.; Lian, F.; Fatima, A.; Wang, Y. Drug combinations to prevent antimicrobial resistance: theory, scheme and practice. *In Book of Abstracts, Proceedings of the 6th International Caparica Conference on Antibiotic Resistance. Caparica, Portugal, 8–12 September 2024*; Capelo-Martinez, J.L.; Santos, H.M.; Oliveira, E.; Fernández, J.; Lodeiro, C.; Eds.; PROTEOMASS Scientific Society: Caparica, Portugal, **2024**; Keynote Presentations 8; p. 93.
24. Van Den Berg H.A. Occam's razor: from Ockham's via moderna to modern data science. *Sci Prog*. **2018**, *101*, 261–272. doi: 10.3184/003685018X15295002645082.

 doi:10.20944/preprints202506.2442.v2

25. Khandai, K.; Navarro-Martinez, C.; Smith, B.; Buonopane, R.; Byun, S.A.; Patterson, M. Determining significant correlation between pairs of extant characters in a small parsimony framework. *J. Comput. Biol.* **2022**, *29*, 1132–1154. doi: 10.1089/cmb.2022.0141.
26. Song, X.; Tang, S.; Liu, H.; Meng, Y.; Luo, H.; Wang, B.; Hou, X.L.; Yan, B.; Yang, C.; Guo, Z.; et al. Inheritance of acquired adaptive cold tolerance in rice through DNA methylation. *Cell* **2025**, S0092-8674(25)00506-9. doi: 10.1016/j.cell.2025.04.036.
27. Laland, K.; Matthews, B.; Feldman, M.W. An introduction to niche construction theory. *Evol. Ecol.* **2016**, *30*, 191–202. doi: 10.1007/s10682-016-9821-z.
28. Constant, A.; Ramstead, M.J.D.; Veissière, S.P.L.; Campbell, J.O.; Friston, K.J. A variational approach to niche construction. *J. R. Soc. Interface* **2018**, *15*, 20170685. doi: 10.1098/rsif.2017.0685.
29. Zhang, C.; Straight, P.D. Antibiotic discovery through microbial interactions. *Curr. Opin. Microbiol.* **2019**, *51*, 64–71. doi: 10.1016/j.mib.2019.06.006.
30. Booth, S.C.; Smith, W.P.J.; Foster, K.R. The evolution of short- and long-range weapons for bacterial competition. *Nat. Ecol. Evol.* **2023**, *7*, 2080–2091. doi: 10.1038/s41559-023-02234-2.
31. Nachmias, N.; Dotan, N.; Rocha, M.C.; Fraenkel, R.; Detert, K.; Kluzek, M.; Shalom, M.; Cheskis, S.; Peedikayil-Kurien, S.; Meitav, G.; et al. Systematic discovery of antibacterial and antifungal bacterial toxins. *Nat. Microbiol.* **2024**, *9*, 3041–3058. doi: 10.1038/s41564-024-01820-9. Erratum in: *Nat. Microbiol.* **2025**, *10*, 1024. doi: 10.1038/s41564-025-01957-1.
32. Callahan, B.J.; Fukami, T.; Fisher, D.S. Rapid evolution of adaptive niche construction in experimental microbial populations. *Evolution* **2014**, 68, 3307–3316. doi: 10.1111/evo.12512.
33. Sykes, R. The 2009 Garrod lecture: the evolution of antimicrobial resistance: a Darwinian perspective. *J. Antimicrob. Chemother.* **2010**, *65*, 1842–1852. doi: 10.1093/jac/dkq217.
34. Dini-Andreote, F.; van Elsas, J.D.; Olff, H.; Salles, J.F. Dispersal-competition tradeoff in microbiomes in the quest for land colonization. *Sci. Rep.* **2018**, *8*, 9451. doi: 10.1038/s41598-018-27783-6.
35. Ohemeng, K.A.; Schwender, C.F.; Fu, K.P.; Barrett, J.F. DNA gyrase inhibitory and antibacterial activity of some flavones (l). *Bioorg. Med. Chem. Lett.* **1993**, *3*, 225–230.
36. Schwartzman, J.A.; Lebreton, F.; Salamzade, R.; Shea, T.; Martin, M.J.; Schaufler, K.; Urhan, A.; Abeel, T.; Camargo, I.L.B.C, Sgardioli, B.F.; et al. Global diversity of enterococci and description of 18 previously unknown species. *Proc. Natl. Acad. Sci. U. S. A.* **2024**, *121*, e2310852121. doi: 10.1073/pnas.2310852121.
37. Heidrich, V.; Valles-Colomer, M.; Segata, N. Human microbiome acquisition and transmission. *Nat. Rev. Microbiol.* **2025**. doi: 10.1038/s41579-025-01166-x.
38. Munk, P.; Brinch, C.; Møller, F.D.; Petersen, T.N.; Hendriksen, R.S.; Seyfarth, A.M.; Kjeldgaard, J.S.; Svendsen, C.A.; van Bunnik, B.; Berglund, F.; et al. Genomic analysis of sewage from 101 countries reveals global landscape of antimicrobial resistance. *Nat. Commun.* **2022**, *13*, 7251. doi: 10.1038/s41467-022-34312-7. Erratum in: *Nat. Commun.* **2023**, *14*, 178. doi: 10.1038/s41467-023-35890-w.
39. Wang, C.; Kuzyakov, Y. Mechanisms and implications of bacterial-fungal competition for soil resources. *ISME J.* **2024**, *18*, wrae073. doi: 10.1093/ismejo/wrae073.
40. Plough, H.H. Penicillin resistance of *Staphylococcus aureus* and its clinical implications. *Am. J. Clin. Pathol.* **1945**, *15*, 446–451. doi: 10.1093/ajcp/15.10.446.
41. Kirby, W.M. Extraction of a highly potent penicillin inactivator from penicillin resistant staphylococci. *Science* **1944**, *99*, 452–453. doi: 10.1126/science.99.2579.452.
42. Liao, X.; Hou, L.; Zhang, L.; Grossart, H.P.; Liu, K.; Liu, J.; Chen, Y.; Liu, Y.; Hu, A. Distinct influences of altitude on microbiome and antibiotic resistome assembly in a glacial river ecosystem of Mount Everest. *J. Hazard Mater.* **2024**, *479*, 135675. doi: 10.1016/j.jhazmat.2024.135675.
43. Arros, P.; Palma, D.; Gálvez-Silva, M.; Gaete, A.; Gonzalez, H.; Carrasco, G.; Coche, J.; Perez, I.; Castro-Nallar, E.; Galbán, C.; et al. Life on the edge: microbial diversity, resistome, and virulome in soils from the union glacier cold desert. *Sci. Total Environ.* **2024**, *957*, 177594. doi: 10.1016/j.scitotenv.2024.177594.
44. Roy, S.; Dawson, R.A.; Bradley, J.A.; Hernández, M. Prevalence and dynamics of antimicrobial resistance in pioneer and developing Arctic soils. *BMC Microbiol.* **2025**, *25*, 50. doi: 10.1186/s12866-025-03745-7.
45. Bisaccia, M.; Berini, F.; Marinelli, F.; Binda, E. Emerging Trends in antimicrobial resistance in polar aquatic ecosystems. *Antibiotics* **2025**, *14*, 394. doi: 10.3390/antibiotics14040394.

 doi:10.20944/preprints202506.2442.v2

46. Na, G.; Zhang, W.; Gao, H.; Wang, C.; Li, R.; Zhao, F.; Zhang, K.; Hou, C. Occurrence and antibacterial resistance of culturable antibiotic-resistant bacteria in the Fildes Peninsula, Antarctica. *Mar. Pollut. Bull.* **2021**, *162*, 111829. doi: 10.1016/j.marpolbul.2020.111829.
47. Rasouly, A.; Shamovsky, Y.; Epshtein, V.; Tam, K.; Vasilyev, N.; Hao, Z.; Quarta, G.; Pani, B.; Li, L.; Vallin, C.; et al. Analysing the fitness cost of antibiotic resistance to identify targets for combination antimicrobials. *Nat. Microbiol.* **2021**, *6*, 1410–1423. doi: 10.1038/s41564-021-00973-1.
48. Maddamsetti, R.; Yao, Y.; Wang, T.; Gao, J.; Huang, V.T.; Hamrick, G.S.; Son, H.I.; You, L. Duplicated antibiotic resistance genes reveal ongoing selection and horizontal gene transfer in bacteria. *Nat. Commun.* **2024**, *15*, 1449. doi: 10.1038/s41467-024-45638-9.
49. Leeansyah, E.; Boulouis, C.; Kwa, A.L.H.; Sandberg, J.K. Emerging role for MAIT cells in control of antimicrobial resistance. *Trends Microbiol.* **2021**, *29*, 504–516. doi: 10.1016/j.tim.2020.11.008.
50. Woelfel, S.; Silva, M.S.; Stecher, B. Intestinal colonization resistance in the context of environmental, host, and microbial determinants. *Cell Host Microbe* **2024**, *32*, 820–836. doi: 10.1016/j.chom.2024.05.002.
51. Lund, D.; Parras-Moltó, M.; Inda-Díaz, J.S.; Ebmeyer, S.; Larsson, D.G.J.; Johnning, A.; Kristiansson, E. Genetic compatibility and ecological connectivity drive the dissemination of antibiotic resistance genes. *Nat. Commun.* **2025**, *16*, 2595. doi: 10.1038/s41467-025-57825-3.
52. Perry, E.K.; Meirelles, L.A.; Newman, D.K. From the soil to the clinic: the impact of microbial secondary metabolites on antibiotic tolerance and resistance. *Nat. Rev. Microbiol.* **2022**, *20*, 129–142. doi: 10.1038/s41579-021-00620-w.
53. He, L.X.; He, L.Y.; Tang, Y.J.; Qiao, L.K.; Xu, M.C.; Zhou, Z.Y.; Bai, H.; Zhang, M.; Ying, G.G. Deciphering spread of quinolone resistance in mariculture ponds: cross-species and cross-environment transmission of resistome. *J. Hazard Mater.* **2025**, *487*, 137198. doi: 10.1016/j.jhazmat.2025.137198.
54. Wang, X.; Wang, M.; Zhang, W.; Li, H.; Tiedje, J.M.; Zhou, J.; Topp, E.; Luo, Y.; Chen, Z. Treatment of antibiotic-manufacturing wastewater enriches for *Aeromonas veronii*, a zoonotic antibiotic-resistant emerging pathogen. *ISME J.* **2025**, *19*, wraf077. doi: 10.1093/ismejo/wraf077.
55. Knight, M.E.; Farkas, K.; Kiss, A.; Jones, D.L. National-scale insights into AMR transmission along the wastewater-environment continuum. *Water Res.* **2025**, *282*, 123603. doi: 10.1016/j.watres.2025.123603.
56. Carvalho, I.T.; Santos, L. Antibiotics in the aquatic environments: a review of the European scenario. *Environ. Int.* **2016**, *94*, 736–757. doi: 10.1016/j.envint.2016.06.025.
57. Lyu, J.; Yang, L.; Zhang, L.; Ye, B.; Wang, L. Antibiotics in soil and water in China-a systematic review and source analysis. *Environ. Pollut.* **2020**, *266*, 115147. doi: 10.1016/j.envpol.2020.115147.
58. Danko, D.; Bezdan, D.; Afshin, E.E.; Ahsanuddin, S.; Bhattacharya, C.; Butler, D.J.; Chng, K.R.; Donnellan, D.; Hecht, J.; Jackson, K.; et al. A global metagenomic map of urban microbiomes and antimicrobial resistance. *Cell* **2021**, *184*, 3376–3393. doi: 10.1016/j.cell.2021.05.002.
59. Xiang, Q.; Chen, Q.L.; Zhu, D.; An, X.L.; Yang, X.R.; Su, J.Q.; Qiao, M.; Zhu, Y.G. Spatial and temporal distribution of antibiotic resistomes in a peri-urban area is associated significantly with anthropogenic activities. *Environ. Pollut.* **2018**, *235*, 525–533. doi: 10.1016/j.envpol.2017.12.119.
60. Wang, Y.; Xu, X.; Jia, S.; Qu, M.; Pei, Y.; Qiu, S.; Zhang, J.; Liu, Y.; Ma, S.; Lyu, N.; et al. A global atlas and drivers of antimicrobial resistance in Salmonella during 1900-2023. *Nat. Commun.* **2025**, *16*, 4611. doi: 10.1038/s41467-025-59758-3.
61. Zhang, Z.; Zhang, Q.; Wang, T.; Xu, N.; Lu, T.; Hong, W.; Penuelas, J.; Gillings, M.; Wang, M.; Gao, W.; et al. Assessment of global health risk of antibiotic resistance genes. *Nat. Commun.* **2022**, *13*, 1553. doi: 10.1038/s41467-022-29283-8.
62. Wang, Y.F.; Liu, Y.J.; Fu, Y.M.; Xu, J.Y.; Zhang, T.L.; Cui, H.L.; Qiao, M.; Rillig, M.C.; Zhu, Y.G.; Zhu, D. Microplastic diversity increases the abundance of antibiotic resistance genes in soil. *Nat. Commun.* **2024**, *15*, 9788. doi: 10.1038/s41467-024-54237-7.
63. Tang, X.; Yuan, X.; Lu, W.; Wen, X.; Wu, Y.; Chen, T. Microplastics in livestock manure and compost: environmental distribution, degradation behavior, and their impact on antibiotic resistance gene dissemination, *Chem. Eng. J.* **2025**, *513*, 162881, doi: 10.1016/j.cej.2025.162881

 doi:10.20944/preprints202506.2442.v2

64. Li, K.; Rahman, S.U.; Rehman, A.; Li, H.; Hui, N.; Khalid, M. Shaping rhizocompartments and phyllosphere microbiomes and antibiotic resistance genes: The influence of different fertilizer regimes and biochar application. *J. Hazard Mater*. **2025**, *487*, 137148. doi: 10.1016/j.jhazmat.2025.137148.
65. Zhang, H.; Zhang, X.; Sun, H.; Ling, H.; Xie, R.; Fang, L.; Guo, M.; Wu, X. Polyvinyl chloride microplastic triggers bidirectional transmission of antibiotic resistance genes in soil-earthworm systems. *Environ. Int*. **2025**, *198*, 109414. doi: 10.1016/j.envint.2025.109414.
66. Dorninger, C.; Menéndez, L.P.; Caniglia, G. Social-ecological niche construction for sustainability: understanding destructive processes and exploring regenerative potentials. *Philos. Trans. R. Soc. Lond. B Biol. Sci*. **2024**, *379*, 20220431. doi: 10.1098/rstb.2022.0431.
67. Wong, F.; Zheng, E.J.; Valeri, J.A.; Donghia, N.M.; Anahtar, M.N.; Omori, S.; Li, A.; Cubillos-Ruiz, A.; Krishnan, A.; Jin, W.; et al. Discovery of a structural class of antibiotics with explainable deep learning. *Nature* **2024**, *626*, 177–185. doi: 10.1038/s41586-023-06887-8.
68. Laland, K.; Odling-Smee, J.; Endler, J. Niche construction, sources of selection and trait coevolution. *Interface Focus* **2017**, *7*, 20160147. doi: 10.1098/rsfs.2016.0147.
69. Morgan, M.A.; Long, J.S.; Logan, M.W.; Benton, F. Pareto in prison. *Behav. Sci. Law* **2025**, *43*, 299–313. doi: 10.1002/bsl.2716.
70. Olson, B.A.; Mazzuchi, T.A.; Sarkani, S.; Forsberg, K. Problem management process, filling the gap in the systems engineering processes between the risk and opportunity processes. *Systems Eng* **2012**, *15*, 275–286.
71. Goldberg, K.; Lobov, A.; Antonello, P.; Shmueli, M.D.; Yakir, I.; Weizman, T.; Ulman, A.; Sheban, D.; Laser, E.; Kramer, M.P.; et al. Cell-autonomous innate immunity by proteasome-derived defence peptides. *Nature* **2025**, *639*, 1032–1041. doi: 10.1038/s41586-025-08615-w.
72. Takahashi, K.M.; Nakasato, J.A.; de Jesus, G.S.; Micheletti, A.C.; Pott, A.; Yoshida, N.C.; Paulo. P.L. Antimicrobial activity of Pantanal macrophytes against multidrug resistant bacteria shows potential for improving nature-based solutions. *Plant Stress* **2024**, *11*, 100304. doi: 10.1016/j.stress.2023.100304.
73. Feigin, S.V.; Wiebers, D.O.; Lueddeke, G.; Morand, S.; Lee, K.; Knight, A.; Brainin, M.; Feigin, V.L.; Whitfort, A.; Marcum, J.; et al. Proposed solutions to anthropogenic climate change: A systematic literature review and a new way forward. *Heliyon* **2023**, *9*, e20544. doi: 10.1016/j.heliyon.2023.e20544.
74. Ren, W.; Liang, P.; Ma, Y.; Sun, Q.; Pu, Q.; Dong, L.; Luo, G.; Mazhar, M.; Liu, J.; Wang, R.; Yang, S. Research progress of traditional Chinese medicine against COVID-19. *Biomed. Pharmacother*. **2021**, *137*, 111310. doi: 10.1016/j.biopha.2021.111310.
75. Alshehri, K.; Gao, Z.; Harbottle, M.; Sapsford, D.; Cleall, P. Life cycle assessment and cost-benefit analysis of nature-based solutions for contaminated land remediation: a mini-review. *Heliyon* **2023**, *9*, e20632. doi: 10.1016/j.heliyon.2023.e20632.
76. Mercado, G.; Wild, T.; Hernandez-Garcia, J.; Baptista, M.D.; van Lierop, M.; Bina, O.; Inch, A.; Ode Sang, Å.; Buijs, A.; Dobbs, C.; et al. Supporting nature-based solutions via nature-based thinking across European and Latin American cities. *Ambio* **2024**, *53*, 79–94. doi: 10.1007/s13280-023-01920-6.
77. Randrup T.B.; Buijs A.; Konijnendijk, C.C.; Wild T. Moving beyond the nature-based solutions discourse: introducing nature-based thinking. *Urban Ecosyst*. **2020**, *23*, 919–926. doi: 10.1007/s11252-020-00964-w
78. Sparrow, A.; Smith-Torino, M.; Shamamba, S.M.; Chirakarhula, B.; Lwaboshi, M.A.; Benn, C.S.; Chumakov, K. A risk management approach to global pandemics of infectious disease and anti-microbial resistance. *Trop. Med. Infect. Dis*. **2024**, *9*, 280. doi: 10.3390/tropicalmed9110280.
79. Liu, J.; Gefen, O.; Ronin, I.; Bar-Meir, M.; Balaban, N.Q. Effect of tolerance on the evolution of antibiotic resistance under drug combinations. *Science* **2020**, *367*, 200–204. doi: 10.1126/science.aay3041.
80. Odling-Smee, J.; Erwin, D.H.; Palkovacs, E.P.; Feldman, M.W.; Laland, K.N. Niche construction theory: a practical guide for ecologists. *Q. Rev. Biol*. **2013**, *88*, 4–28. doi: 10.1086/669266.
81. Chen, P.; Yu, X.; Zhang, J. Photocatalysis enhanced constructed wetlands effectively remove antibiotic resistance genes from domestic wastewater. *Chemosphere* **2023**, *325*, 138330. doi: 10.1016/j.chemosphere.2023.138330.
82. Zhang, Y.N.; Zhang, T.; Liu, H.; Qu, J.; Li, C.; Chen, J.; Peijnenburg, W.J.G.M. Simulated sunlight-induced inactivation of tetracycline resistant bacteria and effects of dissolved organic matter. *Water Res*. **2020**, *185*, 116241. doi: 10.1016/j.watres.2020.116241.

 doi:10.20944/preprints202506.2442.v2

83. Liu, J.; Wang, Z.; Zhao, C.; Lu, B.; Zhao, Y. Phytohormone gibberellins treatment enhances multiple antibiotics removal efficiency of different bacteria-microalgae-fungi symbionts. *Bioresoure Technol*. **2024**, *394*, 130182. doi: 10.1016/j.biortech.2023.130182.
84. Zhou, T.; An, Q.; Zhang, L.; Wen, C.; Yan, C. Phytoremediation for antibiotics removal from aqueous solutions: a meta-analysis. *Environ. Res.* **2024**, *240*, 117516. doi: 10.1016/j.envres.2023.117516.
85. Goh, Y.X.; Anupoju, S.M.B.; Nguyen, A.; Zhang, H.; Ponder, M.; Krometis, L.A.; Pruden, A.; Liao, J. Evidence of horizontal gene transfer and environmental selection impacting antibiotic resistance evolution in soil-dwelling Listeria. *Nat. Commun*. **2024**, *15*, 10034. doi: 10.1038/s41467-024-54459-9.
86. Yi, X.; Liang, J.L.; Su, J.Q.; Jia, P.; Lu, J.L.; Zheng, J.; Wang, Z.; Feng, S.W.; Luo, Z.H.; Ai, H.X.; et al. Globally distributed mining-impacted environments are underexplored hotspots of multidrug resistance genes. *ISME J.* **2022**, *16*, 2099-2113. doi: 10.1038/s41396-022-01258-z.
87. Delgado-Baquerizo, M.; Hu, H.W.; Maestre, F.T.; Guerra, C.A.; Eisenhauer, N.; Eldridge, D.J.; Zhu, Y.G.; Chen, Q.L.; Trivedi, P.; Du, S.; et al. The global distribution and environmental drivers of the soil antibiotic resistome. *Microbiome* **2022**, *10*, 219. doi: 10.1186/s40168-022-01405-w.
88. Zhou, Z.C.; Shuai, X.Y.; Lin, Z.J.; Zheng, J.; Chen, H. Comprehensive profiling and risk assessment of antibiotic resistance genes in a drinking water watershed by integrated analysis of air-water-soil. *J. Environ. Manage.* **2023**, *347*, 119092. doi: 10.1016/j.jenvman.2023.119092.
89. Zhu, G.; Wang, X.; Yang, T.; Su, J.; Qin, Y.; Wang, S.; Gillings, M.; Wang, C.; Ju, F.; Lan, B.; et al. Air pollution could drive global dissemination of antibiotic resistance genes. *ISME J.* **2021**, *15*, 270–281. doi: 10.1038/s41396-020-00780-2.
90. Rao, C.; Liu, X.; Xue, L.; Xiang, D.; Xian, B.; Chu, F.; Fang, F.; Tang, W.; Bao, S.; Fang, T. Determining the spatiotemporal variation, sources, and ecological processes of antibiotic resistance genes in a typical lake of the middle reaches of the Yangtze River. *Sci. Total Environ.* **2024**, *907*, 167779. doi: 10.1016/j.scitotenv.2023.167779.
91. Mao, X.; Yin, X.; Yang, Y.; Gao, F.; Li, S.; Shi, X.; Deng, Y.; Li, L.; Leung, K.M.Y.; Zhang, T. Longitudinal metagenomic analysis on antibiotic resistome, mobilome, and microbiome of river ecosystems in a sub-tropical metropolitan city. *Water Res.* **2025**, *274*, 123102. doi: 10.1016/j.watres.2025.123102.
92. Dželalija, M.; Kvesić-Ivanković, M.; Jozić, S.; Ordulj, M.; Kalinić, H.; Pavlinović, A.; Šamanić, I.; Maravić, A. Marine resistome of a temperate zone: distribution, diversity, and driving factors across the trophic gradient. *Water Res.* **2023**, *246*, 120688. doi: 10.1016/j.watres.2023.120688.
93. Yu, W.; Xu, Y.; Wang, Y.; Sui, Q.; Xin, Y.; Wang, H.; Zhang, J.; Zhong, H.; Wei, Y. An extensive assessment of seasonal rainfall on intracellular and extracellular antibiotic resistance genes in Urban River systems. *J. Hazard Mater*. **2023**, *455*, 131561. doi: 10.1016/j.jhazmat.2023.131561.
94. Shi, J.; Thakur, M.P. Climate extremes disrupt fungal-bacterial interactions. *Nat. Microbiol.* **2023**, *8*, 2226–2229. doi: 10.1038/s41564-023-01531-7.
95. Sokol, N.W.; Slessarev, E.; Marschmann, G.L.; Nicolas, A.; Blazewicz, S.J.; Brodie, E.L.; Firestone, M.K.; Foley, M.M.; Hestrin, R.; Hungate, B.A.; et al. Life and death in the soil microbiome: how ecological processes influence biogeochemistry. *Nat. Rev. Microbiol.* **2022**, *20*, 415–430. doi: 10.1038/s41579-022-00695-z.
96. Jansson, J.K.; Hofmockel, K.S. Soil microbiomes and climate change. *Nat. Rev. Microbiol.* **2020**, *18*, 35–46. doi: 10.1038/s41579-019-0265-7.
97. Guo, M.; Wu, Y.; Huang, H.; Li, S.; Zhao, L.; Cao, J.; Wang, C. Revealing the critical role of rare bacterial communities in shaping antibiotic resistance genes in saline soils through metagenomic analysis. *J. Hazard Mater.* **2025**, *491*, 137848. doi: 10.1016/j.jhazmat.2025.137848.
98. Zhao, M.; Zhou, X.; Li, Z.; Xu, G.; Li, S.; Feng, R.; Xia, D. The dynamics and removal efficiency of antibiotic resistance genes by UV-LED treatment: an integrated research on single- or dual-wavelength irradiation. *Ecotox. Environ. Safe* **2023**, *263*, 115212. doi: 10.1016/j.ecoenv.2023.115212.
99. Huang, S.; Wang, Q.; Fan, Z.; Xu, M.; Ji, R.; Jin, X.; Gu, C. Dry-to-wet fluctuation of moisture contents enhanced the mineralization of chloramphenicol antibiotic. *Water Res.* **2023**, *240*, 120103. doi: 10.1016/j.watres.2023.120103.

 doi:10.20944/preprints202506.2442.v2

100. Simonsen, A.K. Environmental stress leads to genome streamlining in a widely distributed species of soil bacteria. *ISME J.* **2022**, *16*, 423–434. doi: 10.1038/s41396-021-01082-x.
101. Liu, J.; Xue, S.; Jiang, C.; Zhang, Z.; Lin, Y. Effect of dissolved organic matter on sulfachloropyridazine photolysis in liquid water and ice. *Water Res*. **2023**, *246*, 120714. doi: 10.1016/j.watres.2023.120714.
102. Qian, G.; Shao, J.; Hu, P.; Tang, W.; Xiao, Y.; Hao, T. From micro to macro: the role of seawater in maintaining structural integrity and bioactivity of granules in treating antibiotic-laden mariculture wastewater. *Water Res*. **2023**, *246*, 120702. doi: 10.1016/j.watres.2023.120702.
103. Ruan, C.; Ramoneda, J.; Kan, A.; Rudge, T.J.; Wang, G.; Johnson, D.R. Phage predation accelerates the spread of plasmid-encoded antibiotic resistance. *Nat. Commun.* **2024**, *15*, 5397. doi: 10.1038/s41467-024-49840-7.
104. Xia, R.; Yin, X.; Balcazar, J.L.; Huang, D.; Liao, J.; Wang, D.; Alvarez, P.J.J.; Yu, P. Bacterium-phage symbiosis facilitates the enrichment of bacterial pathogens and antibiotic-resistant bacteria in the plastisphere. *Environ. Sci. Technol.* **2025**, *59*, 2948–2960. doi: 10.1021/acs.est.4c08265.
105. Yi, X.; Liang, J.L.; Wen, P.; Jia, P.; Feng, S.W.; Liu, S.Y.; Zhuang, Y.Y.; Guo, Y.Q.; Lu, J.L.; Zhong, S.J.; et al. Giant viruses as reservoirs of antibiotic resistance genes. *Nat. Commun*. **2024**, *15*, 7536. doi: 10.1038/s41467-024-51936-z.
106. Kim, K.; Weiss, A.; Ma, H.R.; Son, H.I.; Zhou, Z.; You, L. Antibiotic-mediated microbial community restructuring is dictated by variability in antibiotic-induced lysis rates and population interactions. *Nat. Commun*. **2025**, *16*, 2299. doi: 10.1038/s41467-025-57508-z.
107. Yu, J.S.L.; Correia-Melo, C.; Zorrilla, F.; Herrera-Dominguez, L.; Wu, M.Y.; Hartl, J.; Campbell, K.; Blasche, S.; Kreidl, M.; Egger, A.S.; et al. Microbial communities form rich extracellular metabolomes that foster metabolic interactions and promote drug tolerance. *Nat. Microbiol*. **2022**, *7*, 542–555. doi: 10.1038/s41564-022-01072-5.
108. Yu, Y.; Zhang, Q.; Zhang, Z.; Zhou, S.; Jin, M.; Zhu, D.; Yang, X.; Qian, H.; Lu, T. Plants select antibiotic resistome in rhizosphere in early stage. *Sci. Total Environ*. **2023**, *858*, 159847. doi: 10.1016/j.scitotenv.2022.159847.
109. Forster, S.C.; Liu, J.; Kumar, N.; Gulliver, E.L.; Gould, J.A.; Escobar-Zepeda, A.; Mkandawire, T.; Pike, L.J.; Shao, Y.; Stares, M.D.; et al. Strain-level characterization of broad host range mobile genetic elements transferring antibiotic resistance from the human microbiome. *Nat. Commun*. **2022**, *13*, 1445. doi: 10.1038/s41467-022-29096-9.
110. Lamberte, L.E.; van Schaik, W. Antibiotic resistance in the commensal human gut microbiota. *Curr. Opin. Microbiol*. **2022**, *68*, 102150. doi: 10.1016/j.mib.2022.102150.
111. Wang, F.; Sun, R.; Hu, H.; Duan, G.; Meng, L.; Qiao, M. The overlap of soil and vegetable microbes drives the transfer of antibiotic resistance genes from manure-amended soil to vegetables. *Sci. Total Environ.* **2022**, *828*, 154463. doi: 10.1016/j.scitotenv.2022.154463.
112. McInnes, R.S.; McCallum, G.E.; Lamberte, L.E.; van Schaik, W. Horizontal transfer of antibiotic resistance genes in the human gut microbiome. *Curr. Opin. Microbiol*. **2020**, *53*, 35–43. doi: 10.1016/j.mib.2020.02.002.
113. Yaffe, E.; Dethlefsen, L.; Patankar, A.V.; Gui, C.; Holmes, S.; Relman, D.A. Brief antibiotic use drives human gut bacteria towards low-cost resistance. *Nature* **2025**, *641*, 182–191. doi: 10.1038/s41586-025-08781-x.
114. Zhao, C.; Wang, Y.; Mulchandani, R.; Van Boeckel, T.P. Global surveillance of antimicrobial resistance in food animals using priority drugs maps. *Nat. Commun.* **2024**, *15*, 763. doi: 10.1038/s41467-024-45111-7. Erratum in: *Nat. Commun*. **2024**, *15*, 933. doi: 10.1038/s41467-024-45494-7.
115. Proctor, D.M.; Sansom, S.E.; Deming, C.; Conlan, S.; Blaustein, R.A.; Atkins, T.K.; NISC Comparative Sequencing Program; Dangana, T.; Fukuda, C.; Thotapalli, L.; et al. Clonal *Candida auris* and ESKAPE pathogens on the skin of residents of nursing homes. *Nature* **2025**, *639*, 1016–1023. doi: 10.1038/s41586-025-08608-9.
116. Häsler, R.; Kautz, C.; Rehman, A.; Podschun, R.; Gassling, V.; Brzoska, P.; Sherlock, J.; Gräsner, J.T.; Hoppenstedt, G.; Schubert, S.; et al. The antibiotic resistome and microbiota landscape of refugees from Syria, Iraq and Afghanistan in Germany. *Microbiome* **2018**, *6*, 37. doi: 10.1186/s40168-018-0414-7.

 doi:10.20944/preprints202506.2442.v2

117. Ren, L.; Yang, J.; Xiao, Y.; Guo, L.; Rao, J.; Wu, C.; Wang, X.; Wang, Y.; Zhang, L.; Zhang, L.; et al. Transmission of the human respiratory microbiome and antibiotic resistance genes in healthy populations. *Microbiome* **2025**, *13*, 115. doi: 10.1186/s40168-025-02107-9.
118. Yuan, M.; Huang, Z.; Malakar, P.K.; Pan, Y.; Zhao, Y.; Zhang, Z. Antimicrobial resistomes in food chain microbiomes. *Crit. Rev. Food Sci. Nutr*. **2024**, *64*, 6953-6974. doi: 10.1080/10408398.2023.2177607.
119. Lu, J.; Guo, J. Disinfection spreads antimicrobial resistance. *Science* **2021**, *371*, 474. doi: 10.1126/science.abg4380.
120. Wang, Y.; Dagan, T. The evolution of antibiotic resistance islands occurs within the framework of plasmid lineages. *Nat. Commun*. **2024**, *15*, 4555. doi: 10.1038/s41467-024-48352-8.
121. Jiang, M.; Zheng, J.; Tang, Y.; Liu, H.; Yao, Y.; Zhou, J.; Lin, W.; Ma, Y.; Liu, J.; Zhou J. Retrievable hydrogel networks with confined microalgae for efficient antibiotic degradation and enhanced stress tolerance. *Nat. Commun.* **2025**, *16*, 3160. doi: 10.1038/s41467-025-58415-z.
122. Yang, L.; Vadiveloo, A.; Chen, A.J.; Liu, W.Z.; Chen, D.Z.; Gao, F. Supplementation of exogenous phytohormones for enhancing the removal of sulfamethoxazole and the simultaneous accumulation of lipid by *Chlorella vulgaris*. *Bioresoure Technol.* **2023**, *378*, 129002. doi: 10.1016/j.biortech.2023.129002.
123. Jacoby, R.P.; Koprivova, A.; Kopriva, S. Pinpointing secondary metabolites that shape the composition and function of the plant microbiome. *J. Exp. Bot*. **2021**, *72*, 57–69. doi: 10.1093/jxb/eraa424.
124. Zhao, Z.; Gao, B.; Henawy, A.R.; Rehman, K.U.; Ren, Z.; Jiménez, N.; Zheng, L.; Huang, F.; Yu, Z.; Yu, C.; et al. Mitigating the transfer risk of antibiotic resistance genes from fertilized soil to cherry radish during the application of insect fertilizer. *Environ. Int*. **2025**, *199*, 109510. doi: 10.1016/j.envint.2025.109510.
125. Liu, Y.; Yang, K.; Jia, Y.; Shi, J.; Tong, Z.; Fang, D.; Yang, B.; Su, C.; Li, R.; Xiao, X.; Wang, Z. Gut microbiome alterations in high-fat-diet-fed mice are associated with antibiotic tolerance. *Nat. Microbiol*. **2021**, *6*, 874–884. doi: 10.1038/s41564-021-00912-0.
126. de Dios, R.; Proctor, C.R.; Maslova, E.; Dzalbe, S.; Rudolph, C.J.; McCarthy, R.R. Artificial sweeteners inhibit multidrug-resistant pathogen growth and potentiate antibiotic activity. *EMBO Mol. Med*. **2023**, *15*, e16397. doi: 10.15252/emmm.202216397.
127. Yao, Y.; Yang, P.; Wang, B.; Xu, Q.; Song, F.; Wang, Y.; Zhao, Y.; Guo, L.; Wang, X.; Xu, M. Divergent mitigation mechanisms of soil antibiotic resistance genes by biochar from different agricultural wastes. *Environ. Pollut*. **2025**, *374*, 126247. doi: 10.1016/j.envpol.2025.126247.