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Biosafety and Health

Perspective

Evaluating human exposure to antibiotic resistance genes

Zhenchao Zhou [a], Hong Chen [a,b,*]

[a] College of Environmental and Resource Sciences, Zhejiang University, Hangzhou 310058, China
[b] International Cooperation Base of Environmental Pollution and Ecological Health, Science and Technology Agency of Zhejiang, Zhejiang University, Hangzhou 310058, China

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ABSTRACT

Antibiotic resistance is an escalating global concern, leading to millions of annual fatalities. Antibiotic resistance genes (ARGs) present in bacteria equip them to withstand the effects of antibiotics. Intra- and interspecific ARGs transmission through horizontal gene transfer further exacerbates resistance dissemination. The presence of ARGs in the environment heightens the probability of human exposure via direct inhalation, ingestion, or contact with polluted air, food, or water, posing substantial biosafety and health hazards. Consequently, ARGs represent a critical focal point in public health and environmental safety and are classified as emerging contaminants. This perspective underscores the necessity to assess ARG exposure within the One Health framework and to accord greater attention to the mitigation strategies and tactics associated with ARGs.
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1. Introduction

Antibiotic resistance occurs when bacteria evolve and develop mechanisms to resist antibiotics, rendering them ineffective in treating infections. Central to this growing concern are antibiotic resistance genes (ARGs), which are genetic elements that confer antibiotic resistance. In bacteria, the presence of these genes enables them to withstand antibiotic action, leading to prolonged illnesses, treatment failures, and increased healthcare costs. The transmission of ARGs between different bacterial species through horizontal gene transfer further exacerbates resistance spread, making ARGs emerging contaminants. These genes can be found in human and animal populations, as well as in nature such as in air, soil, and water [1]. The presence of ARGs in the environment increases the likelihood of human exposure through direct inhalation, ingestion, or contact with contaminated air, food, or water, posing significant biosafety and health risks [2]. This makes ARGs critical in public health and environmental safety. However, evaluating ARGs exposure is a challenging task, and data in this area are limited. Therefore, we aim to prospect ARGs exposure and explore its implications for human health.

2. One health calculating antibiotic resistance exposure

The One Health concept acknowledges the interconnected and interdependent nature of human, animal, and environmental health [3]. It emphasizes the importance of considering the health of all these components as a unified whole. Understanding human exposure to ARGs through the One Health perspective is crucial for devising effective mitigation strategies (Fig. 1).

ARGs can be aerosolized and transported in both indoor and outdoor environments, potentially leading to inhalation exposure [4]. Our research also demonstrated that $PM_{2.5}$ air pollution was associated with a rise in antibiotic resistance [5]. Indoor air can become contaminated with ARGs from various sources, including human activities (e.g., antibiotic use, shedding of resistant bacteria), pets, sewage, and aerosols generated during specific processes (e.g., wastewater treatment). Similarly, outdoor air may also contain ARGs derived from various sources, such as agricultural runoff, sewage, animal waste, and other environmental reservoirs.

Contaminated water and food consumption can introduce antibiotic-resistant bacteria and their genes into the human gastrointestinal system [6]. Research on ARGs in domestic and recreational water indicated that these environments can serve as potential ARGs reservoirs and sources [7]. People who come into contact with domestic and recreational water may be exposed to ARGs through ingestion, aerosol inhalation, or direct contact with contaminated water. Livestock, pets, and wildlife may carry resistant bacteria and ARGs, which can spread to humans through direct contact or consumption, leading to challenges in treating human infections [8,9]. Additionally, ARGs occur in indoor and outdoor dust, raising concerns about their potential role as a reservoir and vehicle for antibiotic resistance transmission [10]. People can be exposed to ARGs in dust through inhalation of particles, ingestion of dust-contaminated food or hand-to-mouth contact, and direct contact with dust-contaminated surfaces.

Generally, inhalation exposure occurs when ARGs are present in the air as aerosols or particulates. This can arise in various settings,

* Corresponding author: College of Environmental and Resource Sciences, Zhejiang University, Hangzhou 310058, China.
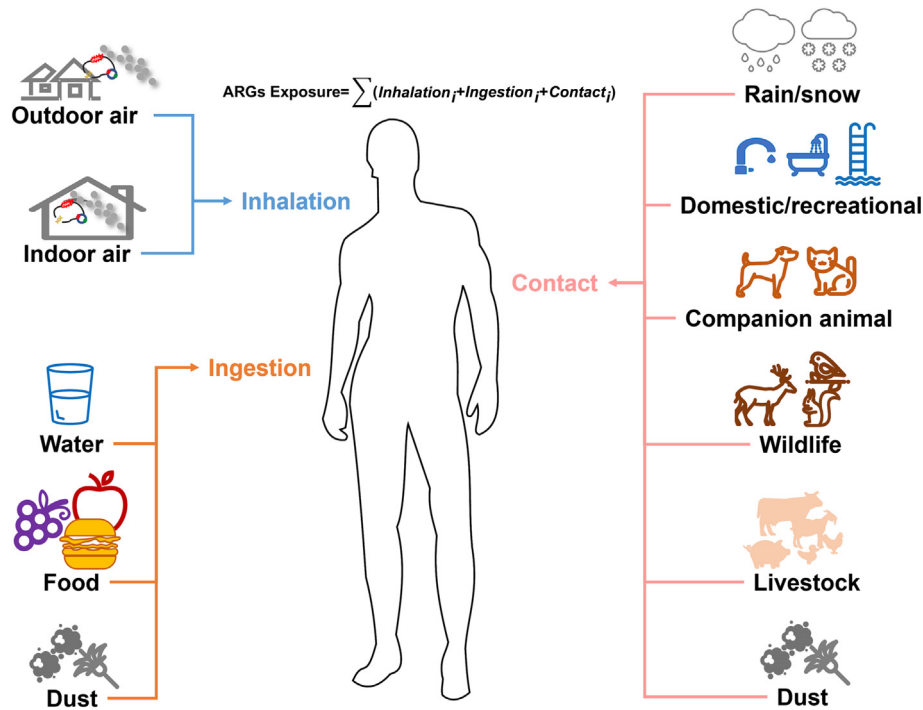E-mail address: chen_hong@zju.edu.cn (H. Chen).

Fig. 1. Pathways of human exposure to antibiotic resistance genes.

including healthcare facilities, agricultural environments, and urban areas. Ingestion exposure occurs when individuals consume food, water, or other materials containing ARGs. Some ingestion exposure sources include contaminated food, drinking water, and the fecal-oral route. Contact exposure occurs when individuals come into direct or indirect contact with surfaces or objects contaminated with antibiotic-resistant bacteria and ARGs. Understanding the different ARGs exposure routes is crucial for developing effective mitigation strategies for antibiotic resistance spread. Moreover, when calculating ARGs intake, its permeability coefficient should be taken into account [11]. ARGs exposure dose and intake can be calculated using the following equations:

$$ARGs\ exposure = \sum(Inhalation_i + Ingestion_i + Contact_i) \tag{1}$$

$$ARGsintake = \sum(\alpha \times Inhalation_i + \beta \times Ingestion_i + \gamma \times Contact_i) \tag{2}$$

where, i is the ARGs exposure pathway, α, β, and γ are the ARGs intake permeability coefficients. After exposure, for instance, ARGs need to penetrate the skin to contact the microbiome, where the permeability coefficient is the rate which ARGs permeate the skin under steady-state conditions [11].

3. Unbalanced ARGs exposure level

The ARGs exposure level can vary significantly across different regions and countries. Regions with higher antibiotic usage rates (both in human medicine and agriculture), tend to exhibit a higher prevalence of antibiotic-resistant bacteria and ARGs [12]. Antibiotic overuse and misuse can expedite resistance development and spread. Healthcare settings, particularly in regions with limited infection control measures, can be hotspots for antibiotic-resistant bacteria and ARGs transmission [13]. Moreover, high-density populations and inadequate sanitation contribute to this problem. In countries where antibiotics are extensively used in agriculture (e.g., for livestock growth promotion and disease prevention), ARGs prevalence can be higher due to the selection pressure imposed on bacteria. Moreover, inadequate or insufficient wastewater treatment can lead to ARGs release from

human and animal waste into the environment, contributing to increased exposure levels [14]. Rapid urbanization and industrial activities can further lead to environmental contamination with ARGs, particularly in regions with inadequate waste management practices. The movement of people, animals, and goods across borders can facilitate the global dissemination of antibiotic-resistant bacteria and ARGs, contributing to unbalanced exposure. Not all regions have the same capacity for research and surveillance on antibiotic resistance. This disparity in data collection and reporting can result in an incomplete picture of ARGs global distribution, so addressing this requires a coordinated global effort.

4. Exposure effect of ARGs

Exposure to ARGs can significantly affect both individual health and the broader population and environment. This leads to infections that are challenging or even impossible to treat with standard antibiotic therapies, limiting available treatment options for patients. Infections caused by antibiotic-resistant bacteria, which are difficult to treat, may lead to prolonged illnesses, increased healthcare complications, and higher mortality rates. Treating such infections often requires more extended hospital stays, more expensive medications, and additional medical interventions, thereby leading to increased healthcare costs for individuals and healthcare systems. ARGs exposure can contribute to antibiotic resistance spread within healthcare facilities, communities, and the environment. Resistant bacteria can transfer ARGs to other bacteria through horizontal gene transfer, further amplifying antibiotic resistance problems. Moreover, in animals, ARGs exposure can lead to zoonotic infections, where resistant bacteria and ARGs are transmitted from animals to humans. This poses additional challenges in treating such infections and highlights the importance of adopting the One Health approach in addressing antibiotic resistance. Furthermore, ARGs exposure can lead to the dissemination of antibiotic-resistant bacteria and ARGs into the environment through agricultural runoff, wastewater discharge, and other sources. This, in turn, can contribute to the emergence and persistence of resistance in the environment, impacting ecosystems and potentially affect-

ing human health through contaminated food and water. Overexposure to ARGs can accelerate the development of multidrug-resistant bacteria, rendering some antibiotics ineffective for both common and severe infections. Additionally, ARGs exposure may lead to cross-resistance, where resistance to one antibiotic confers resistance to others with similar mechanisms of action. This further reduces the number of effective treatment options available to combat infections.

5. Prospective strategies and tactics

Addressing biosafety and health concerns related to ARGs requires a multifaceted approach. The widespread distribution of ARGs and their complex interactions within microbial communities make their removal from the environment difficult. Currently, there is no single universally accepted method for completely eradicating ARGs from the environment. Nevertheless, various approaches and technologies are being explored to reduce their prevalence and impact [15,16]. For example, advanced wastewater treatment involves upgrading wastewater treatment plants with advanced technologies, such as ozonation, ultra violet (UV) irradiation, and activated carbon adsorption. These methods can help remove antibiotics and ARGs from wastewater before they are discharged into the environment. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based gene editing technologies, such as CRISPR-Cas systems, show promise in specifically targeting and removing ARGs from bacterial genomes. Nanotechnology is also being investigated, where nanomaterials like nanoparticles can potentially target and neutralize antibiotic-resistant bacteria and ARGs. Furthermore, phage therapy, involving the use of bacteriophages (viruses that infect and kill bacteria), is being researched as a potential tool to target and eliminate antibiotic-resistant bacteria carrying ARGs. Purified phage as an adjunct therapy was used to cure pandrug-resistant *Pseudomonas aeruginosa* spinal abscess [17]. Additionally, accepted soil management practices, such as using organic matter and crop rotation, can promote diverse microbial communities that potentially reduce ARGs abundance in soil. Notably, many of these approaches are still in the experimental or early research stages, and their effectiveness, safety, and potential side effects need further investigation. Continued research is necessary to understand antibiotic resistance mechanisms and to develop new antibiotics, alternative therapies, and diagnostic tools to effectively combat resistant infections.

In conclusion, driven by One Health framework, comprehensive and innovative approaches, combined with ongoing research efforts, are critical in tackling challenges posed by ARGs. By adopting a proactive strategy and implementing effective technologies, we can work towards mitigating ARGs impacts on public health and the environment.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Zhenchao Zhou: Conceptualization, Writing – original draft, Writing – review & editing. **Hong Chen:** Supervision, Writing – review & editing.

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