Antimicrobial resistance (AMR) is unquestionably one of the most severe, international public health crises that mankind faces now and in the next decades, with the latest data indicating global deaths quintupling over the past five years to claim nearly 5 million lives [1], which seems substantially underestimated the projected health impact (10 million deaths) and economic burden (US$100 trillion) of AMR by 2050 [2]. To counteract the burgeoning AMR crisis, the One Health initiative has called for international collective effort in improving human, animal and environmental health through integrated management of this interfacial triad. Among which, the environmental dimension is often underrepresented, especially soil compartment as the origin, reservoir and transmission route for propagating antibiotic resistance genes (ARGs) in microbiota that exacerbate AMR [3]. Despite a clear correlation between higher antimicrobial exposure to enhanced resistance can be established in the clinical setting, a direct causal dose–response relationship in the natural environment remains indistinct otherwise. It unveils a potential missing link that has been overlooked between the human-animal-environment interfaces while assessing the roles of antimicrobials in triggering resistance, which is bioavailability. This commentary intends to draw on the unique perspective of this often-secluded element, bioavailability, for environmental surveillance to monitor the partition and fate of bioavailable antimicrobials as well as to identify the threshold concentration that contributes to the development of resistance. Taking into account the bioavailability factor might be paramount in striking a balance between the necessity of antibiotic applications for safeguarding human health, preventing the growth of AMR and environmental protection.

Environmental monitoring endeavors thus far emphasize only on total measured environmental concentrations (MECs) of antimicrobials, while the bioavailable fraction is often neglected. Similar to clarification in pharmacology that refers bioavailability as the portion of administered medication being absorbed by the human body, environmental bioavailability is defined as such: molecules that exist in the form of freely dissolved concentrations and rapidly desorbing fractions in pore waters of soils or sediments with an emphasis on the ability of these chemicals to interact or move across the cell membrane making it readily available for biotic uptake or to be transformed by living organisms [4]. To date, bioavailability analyses, regardless of chemical methods or biological methods, are centered around hydrophobic organic contaminants (HOCs) and trace elements. Chemical methods encompass adsorbent-based extraction techniques such as solid phase microextraction (SPME) and cyclodextrins, organic solvent extraction techniques, and passive sampling approach such as diffusive gradients in thin-films (DGT), are designated for quantification of environmental concentration [5,6], whilst biological methods pivot on biological process-driven ecotoxicology measurements including altered dehydrogenase activity, biomass or growth inhibition. Meanwhile, studies on the bioavailability of hydrophilic hazardous organic pollutants akin to antimicrobials in the environment are scarce. Indeed, one could argue that the half-lives of antimicrobials are generally short making them less threatening due to their rapid biodegradation rate. However, when the hydrophilic antimicrobials undergo an extremely slow desorption process into the aqueous phase prior to biodegradation, it can be considered as persistent due to limited bioavailability [7]. By considering the bioavailable fractions of antimicrobials, we will be able to pinpoint the precise correlation of realistic environmental concentrations that impose ecotoxicological effects and for the determination of causative toxicant without biased justification nor false positive outcomes [8]. Apart from that, these readily-available portions of antimicrobials in soil or sediment are believed to play a decisive role as selection pressure in inducing the dissemination of antibiotic resistome for horizontal gene transfer, thus promoting the proliferation of AMR (Fig. 1). All of this, could subsequently provide accurate scientific proof for regulators to formulate pertinent regulations and monitoring guidelines that minimize antimicrobial selection pressure, thus alleviating the spread of resistance.

Among the limited bioavailability studies in recent years, researches that specifically delved into the interplay between bioavailable antimicrobials, environmental factors and the expression of AMR across varied environmental settings have been dedicated to explicating the uptake and transfer pathway in these media. Studies on the partition mechanisms of antimicrobials in soil or sediment are believed to play a decisive role as selection pressure in inducing the dissemination of antibiotic resistome for horizontal gene transfer, thus promoting the proliferation of AMR (Fig. 1). All of this, could subsequently provide accurate scientific proof for regulators to formulate pertinent regulations and monitoring guidelines that minimize antimicrobial selection pressure, thus alleviating the spread of resistance.

**Commentary**

**Environmental bioavailability: a potentially overlooked element in triggering antimicrobial resistance**

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air-organism systems, not only provide substantial scientific data for elucidating environmental bioavailability in distinctive matrices, but are also critical in examining the risks of escalating AMR on microbiome induced by bioavailable fraction. In fact, distribution coefficient ($K_d$) evidently determined the diffusion of antimicrobials from bulk soil into soil pore water, then the actual bioavailability was governed by dissociation constants ($pK_a$). A previous study manifested an interesting finding in which antimicrobial speciation, specifically zwitterionic species, exhibited higher tendency and faster rate than neutral species to move across the negatively-charged cell membrane and trigger AMR resistance [9]. Within an unsaturated soil environment, coarse-textured soils expedite the diffusion of soil-sorbed antimicrobials into soil pore water, thus increasing the bioavailable fraction that exerts stronger selective pressure on organisms [10]. The competition between organic acid ligands with greater strengths and naturally-occurring metal cations would increase the dissociation of antimicrobial-metal complexes in an environmental medium, leading to the increment of freely available antimicrobials for biological uptake, hence also enhance antimicrobial bioavailability to propagate AMR resistance. Such environmental processes resulted in the distinguishable bioavailable patterns of multi-class antimicrobials in soils, in which bioavailable sulfonamides are akin to total MECs, whereas the bioavailabilities for lincosamides, tetracyclines, macrolides and diaminopyrimidines were at least one order of magnitude lower than total MECs (sub-part per billion level) detected in bulk soil samples [11]. Notwithstanding, the ultra-trace bioavailable concentration is of utmost significance, as previous literatures substantiate the exposure to non-lethal environmental level of ciprofloxacin at 100 part per quadrillion, which is 230-fold below the minimal inhibitory concentration (MIC), can select for resistant bacteria and trigger the evolution of resistance [12]. Simply put, assessing total MECs might profoundly underestimate the induction ability of antimicrobials to disseminate resistance.

In the hopes of mitigating the global crisis of AMR, China’s National Action Plan (NAP) echoes World Health Organization’s (WHO’s) call for global action plan to embrace the One Health concept in extenuating environmental hazards including soil contaminants such as antimicrobials [13]. To evaluate the prevalence of bacteria resistance under NAP, both China Antimicrobial Resistance Surveillance System (CARS) and China Antimicrobial Surveillance Network (CHINET) surveilled 0.2 million bacteria strains sampled from countrywide hospitals for over a decade and ascertained a multifaceted prevalence trend, with decreasing Pseudomonas aeruginosa.

Fig. 1. A diagram illustrating the roles of bioavailability science within the One Health initiative framework, highlighting the (1) environmental processes that bring forth the emergence of resistance, (2) environmental fractions in soils/sediments, with an emphasis on the bioavailable concentration that triggers antibiotic resistance, (3) scientific inquiries concerning the roles of environmental bioavailability in One Health research, and (4) the types of resistance acquisition possibly induced by bioavailable antimicrobials.
inosa, increasing Acinetobacter species and relatively consistent resistance profile of Escherichia coli [14]. Despite lacking likewise surveillance system for environmental compartments, such prevalence pattern in the clinical setting stressed the analogous significance of discovering the ubiquity of environmental resistomes, particularly those in relevance to selection pressure from bioavailable antimicrobials. All is not lost though, as the largest consumer of antimicrobials in the world, China has recently kick-started a nationwide campaign to reduce antimicrobial consumption by 57% over the course of 4 years, as prove of China’s pledge to combat AMR [15]. Hopefully, with China’s resolution, together with the collective efforts of other countries globally, especially nations with high antibiotic consumption, we will be able to see more countries take up a leading role in researching intensively into bioavailable antimicrobials acting as attested selection pressure to induce the acquisition and/or proliferation of AMR.

Nevertheless, the determination of bioavailability still poses a great challenge, as a number of uncertainties have yet to be resolved. One of the main setbacks bioavailability science faces, is the lack of consensus and standardized protocol amongst laboratories conducting bioavailability analysis. Also, a myriad of factors comprising environmental parameters (soil type, pH, organic matter content, etc.) and the physicochemical properties of antimicrobials (ionic strength, solubility, etc.) that can affect the partitioning, equilibration and adsorption of antimicrobials between environmental media (water-soil-sediment-air) and inter-human-animal-environment interfaces bring forth two pivotal scientific questions that need to be answered: unclear bioavailable status (dose) across the One Health interfacial triad, and uncertain rate of transfer for bioavailable antimicrobials from one medium to another that actually confer AMR (response). It is in times of isolation such as now that we need to band together: (I) to establish a uniform analytical protocol integrating both chemical and biological methods for accurate quantification of dose (antimicrobial concentration)-response (AMR acquisition encompassing mutation, gene transfer and selection of pre-existing resistant bacteria) relationship; (II) to identify benchmark bioavailable concentrations, a.k.a. environmental minimum induction concentration (eMIC) that may trigger resistance or impose detrimental impact on human-animal-ecosystem health under the One Health ideology; (III) to share a vision of a global surveillance system on bioavailability science and to agree on making research data publicly accessible for all scientists to achieve the formulation of universal standards. By virtue of attaining worldwide environmental bioavailability data that scrutinizes the discrepancy and/or interrelationship of bioavailable antimicrobials between the human-animal-environmental interfaces for driving global environmental monitoring campaign progress, the One Health approach, in return, can devise data-driven international policies for guiding scientists in the implementation of mitigation measures to ensure antimicrobial levels are always inferior to distinctive eMIC for safeguarding the intrinsic tripartite health, hence establishing an interdependence relationship between the realms of bioavailability science and One Health Initiative. With structured guideline for proper prescription and systematic bioavailability-based environmental surveillance, we can help to avert the worsening crisis of AMR and contribute to the preservation of planetary health.

Conflict of interest

The authors declare that they have no conflict of interest.

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