
Linking soil biota to planetary health: Resistance to antimicrobials

ZHAO, YI., ZHU, D., GILLINGS, M., PENUELAS, J., SIK OK, Y., CAPON, A., BANWART, S. 2019.

Abstract

The concept of planetary health emphasizes the links between ecosystem properties and human health and well-being. Soil is a critical component of the Earth's biosphere and represents the most biodiverse habitat on the planet. Soil microbiomes play an important role in human health and well-being via multiple functions, such as nutrient cycling, decomposition of organic matter, pollutant remediation and synthesis of bioactive compounds (such as antimicrobials) for human health. The soil microbiome can also influence the ecology of human microbiota, thus influencing physiology and the immune system. We used the nexus of antimicrobials and antimicrobial resistance as a focus to discuss the role of soil in planetary health for illustrating the impacts of soil microbiomes on human health and well-being. Soil microbes can produce antimicrobials, so soil is a natural source of antimicrobial resistance, often termed intrinsic resistance. The increasing use and misuse of antimicrobials in humans and animals in the few decades, however, have increased both the diversity and abundance of antimicrobial resistance in soils, particularly in environments affected by human and animal wastes, such as organic manures and reclaimed wastewater. Soil thus represents a hotspot through which humans are exposed to antimicrobial resistance determinants, including those harbored by human pathogens. This paper examines the sources and dynamics of antimicrobial resistance in soils and uses the perspective of planetary health to track the movement of resistance genes between environmental compartments, including soil, water

and food.

Keywords: planetary health; human health; soil microbiome; soil fauna; antimicrobials; One Health; resistome

Introduction

Planetary health is a new discipline examining the links between human health and the natural environment (Ref). Planetary health acknowledges that human health and well-being are inextricably linked to planetary systems, and the integrity of the natural environment needs to be protected to ensure long-term human health. Planetary health specifically addresses the interconnectivity of processes and phenomena, some of which may not seem connected when viewed conventionally. For example, rising atmospheric CO₂ concentrations may lead to zinc malnutrition by their effects on nutrient uptake by crop plants (ref).

Planetary health requires interdisciplinary studies to address complex and cross-cutting issues. The emergence of new systems knowledge will help to anticipate and manage the unpredictability of Earth systems into the future. Studies of planetary health will help to unite disparate fields, from the arts to the sciences, in the same manner that Anthropocene studies provide an umbrella for interdisciplinarity [1] (Gillings and Hagan-Lawson 2014). Planetary health studies thus facilitate the engagement of all stakeholders in the stewardship of a common future.

Soil is a critical component of this entire planetary-health system. It plays

a fundamental role in human health and well-being, primarily because most food is derived from soil. The flourishing of early civilizations in the “fertile crescent” demonstrates the contribution of soil to human development. Soil-plant systems represent the major pathway for the delivery of essential nutrients, such as nitrogen, phosphorus and trace elements. The functions of soil from biological, chemical and physical perspectives consequently have direct impacts on human health and well-being.

The provision of these soil services to humans is currently being degraded by human activity. For example, human activity can increase soil concentrations of pollutants to levels high enough to pose long-term health risks to humans via the food chain. For example, soil contaminated by arsenic due to industrial activity and irrigation with arsenic-contaminated groundwater has led to elevated arsenic levels in rice (ref), which is now recognized as a major source of human exposure to arsenic (ref). An estimated 60% of arsenic ingestion in China is from rice, which represents a significantly increased risk of cancer for the general population[2] (Li et al., 2011).

The chemical composition of soil can have direct impacts on human health, but the soil microbiota is also critically important in safeguarding human health. Soil is arguably the most biodiverse habitat on Earth. A gram of soil can contain an estimated one billion bacterial cells, representing up to 10 000 species (ref). Soil microbiota play multiple roles in providing ecosystem services relevant to human health, including food production, nutrient cycling and bioremediation. Direct roles in plant nutrition via mutualisms, and the ability to mobilize key nutrients, are well known, but other more indirect effects

on human health are only just beginning to be explored. For example, exposure to the soil microbiome can alleviate human allergies (ref), which may partly account for the increased prevalence of allergies and perturbations to immune responses in cities, where contact with soils and other natural ecosystems is lower (ref).

Ecosystem services provided by soil biota are also under threat from human activity. Soil is a rich source of bioactive compounds that can be explored as pharmaceuticals. Soil, however, is also a reservoir of antimicrobial resistance and can act as a source of resistance determinants that can spread to human pathogens. In this paper, we will use the connection between antimicrobials and antimicrobial resistance as an example to demonstrate the complex feedbacks that occur when humans perturb environmental processes. These complex feedbacks are discussed in the context of broad ecosystem dynamics within the framework of planetary health.

Soil: A source of bioactive compounds

Soil microorganisms produce a wide array of secondary metabolites, including antibiotics. These compounds may be primarily used in communication and competition with other organisms and in coping with environmental changes [3]. Microbial metabolites comprise two major families: nonribosomal peptides (NRPs) and polyketides (PKs). These two families account for most antibiotics, antifungals and other antimicrobial compounds that have been characterized from culturable bacteria (ref). Many antibiotics were initially isolated by screening streptomycetes from soils, particularly from the 1940s to the 1960s. Perhaps the most famous example is the discovery of

streptomycin by screening soil-derived streptomycetes for antimicrobial activity by Waksman and his colleagues in the 1940s. Waksman was awarded the 1952 Nobel Prize for this work. The recent advent of molecular and genomic technologies has led to a resurgence of mining antibiotics from the soil microbiome. High throughput genomic tools are being used to mine the soil microbiome for bioactive compounds [4].

Soil: A major reservoir of the environmental resistome

Intrinsic resistome

Genes that can confer resistance to antibiotics are referred to as antibiotic-resistance genes (ARGs), even though their original function may not have been to confer resistance [5]. A subset of these genes has rapidly and vastly increased in abundance, largely driven by selection in front of clinical concentrations of antibiotics. The increased transmission and abundance of these genes in humans and their domestic animals indicate that clinically relevant ARGs are now considered to be emerging environmental contaminants [6][7].

Like antibiotics, ARGs are naturally occurring and ancient [8](D'Costa et al., 2011). Soil harbors diverse microbes that produce antibiotics and is therefore also a vast natural reservoir of corresponding resistance genes. These resistance genes are known as the intrinsic resistome and vastly outnumber the resistance genes that have become clinically relevant. The molecular mechanisms that underlie the intrinsic resistome often involve inherent structural (outer membrane) or functional characteristics (efflux

pumps)[9] (Blair et al., 2015). A metagenomic analysis of DNA from 30 000-year-old permafrost identified high diversity in the intrinsic resistome, with genes encoding resistance to multiple drugs (β -lactams, glycopeptides and tetracycline antibiotics) [8](D'Costa et al., 2011). ARGs with diverse resistance mechanisms were identified from remote Antarctic soils with little human impact. These studies demonstrate that the intrinsic resistomes are ancient, as are their mechanisms.

Humans enrich the soil resistome

The advent of antibiotics revolutionized medicine in the 20th century, and antibiotics are one of the greatest advances in medical treatment. Easy access to antibiotics has saved millions of lives and enabled high density animal production but has also led to misuse and overuse. According to the Centers for Disease Control and Prevention, up to half of antibiotics used in humans are unnecessary or inappropriate [10](States, 2017). A large proportion of antibiotic consumption in China (96 million kg, 2007) and the USA (over 384 million kg, 1999) is used in livestock industries for disease treatment, or more frequently, as a growth promoter.

The sustained selection pressure on bacteria by antibiotic use has led to the fixation of resistance genes in a wide variety of clinical pathogens and commensal bacteria. Bacteria become antibiotic resistant by diverse mechanisms, including mutational modification of genes for antibiotic target molecules, or acquisition of resistance genes via lateral gene transfer. These

mechanisms have been the subject of recent reviews[11][12][13].

Newly antibiotic-resistant bacteria are then shed from humans and animals into the environment and have become recognized as an important environmental contaminant[6][14][15]. The widespread use of antibiotics has consequently led to the enrichment of a specific sub-set of clinically relevant antibiotic-resistance genes in the environment. This enrichment has reached the stage where endemic resistant microorganisms in soils no longer represent the majority of resistant organisms in the soil microbial population. Resistant organisms are instead increasingly the result of contamination from anthropogenic activity.

Anthropogenic activity also exposes soils to pollutants, such as antibiotics, heavy metals or disinfectants, that are themselves selective agents. Sub-inhibitory concentrations of antibiotics raise the background rates of mutation, recombination, and lateral gene transfer. These effects indicate that previously susceptible soil microbes can more readily acquire antibiotic resistance via mutation or lateral gene transfer from co-polluting resistant bacteria[17][18]. Lateral gene transfer can continue to propagate these genes through the soil microbiota via conjugation, transformation and transduction, mediated by mobile genetic elements. Genes for resistance to disinfectants and heavy metals are often on the same mobile elements as antibiotic-resistance genes, so co-selection then becomes a driving force for promoting and fixing resistance determinants in soil microbial populations[19][20][21].

Rapid expansions in the diversity and abundance of antibiotic-resistance

genes in soil have been documented. Historical data are rare, but we do know that resistance genes were not on plasmids in the “pre-antibiotic’ era[22] (Hughes and Datta, 1983) and that resistance genes have increased in abundance in archived soils over time [23]. Wastewater-treatment plants are believed to be principal anthropogenic sources of the spread of resistance genes into soil [24](Rizzo et al., 2013). Resistance determinants from clinical settings, private households, pharmaceutical industries and other origins enter treatment plants, where they are often poorly removed before the released effluent carries these determinants into environmental compartments. Over 200 resistance genes were detected in a series of Chinese wastewater-treatment plants, with a considerable proportion of these genes persisting during treatment to be enriched in sewage sludge and effluents[25] (An et al., 2018). These resistance elements can contaminate urban soils and agricultural land via irrigation with reclaimed water or application of sewage sludge[26][27][28][29]. Resistance genes in urban park soils can be enriched more than 8000-fold after irrigation with reclaimed water[30](Wang et al., 2014). A recent study found that the application of sewage sludge facilitated a shift in the microbiome of arable land and enriched resistance genes more than 3000-fold[31] (Chen et al., 2016).

Animal manure is also widely used as a soil amendment for cost-effective crop production. The intensive use of in-feed antibiotics and metals as growth promoters massively enriches resistance genes in the animal gut [32](Zhao et al., 2018) and associated environments [33](Zhu et al., 2013). These genes are released to soils and enriched during manure application[28] [34][35].

Comprehensive evidence suggests that manure use promotes the enrichment

and dissemination of resistance in soils and the general environment.

In addition to direct transport from anthropogenic sources, spectra of soil resistance are also enriched by the selection process under stress from exogenous contaminants. The volume of potential selective agents released into the pedosphere from anthropogenic sources is enormous. These contaminants include antibiotic residues, toxic metals, and biocides. They enter the soil from urban wastewater, clinical settings, application of manure and treated waste, waste disposal and the refining, agricultural and animal industries. Resistant microbes have advantages under such conditions and can become dominant members of the soil microbial population. Their resistance genes can spread to susceptible bacteria via lateral gene transfer, creating a cycle of positive feedback for propagating resistance in the soil microbiota. Soil collectively then serves as a reservoir for both intrinsic and more recently acquired resistance determinants at a time when soil security is becoming ever more important for human and environmental health.

Resistance in the gut microbiomes of soil fauna

Soil fauna are an important component of soil ecosystems. They comprise enormous biodiversity, represent 23% of known animals and form complicated food webs[36][37] (Decaënsa et al., 2006; Lavellea et al., 2006). Soil fauna substantially contribute to planetary health by influencing litter decomposition, nutrient cycling, energy transfer, maintenance of biodiversity and degradation of pollutants[38][39] (Rusek, 1998; De Deyn et al., 2003). Microorganisms

routinely colonize animals, where they significantly affect host nutrition, development and immunity[40][41] (Thaiss et al., 2016; Adair et al., 2018). Recent studies have reported that soil fauna have abundant bacterial communities in their guts and that these communities differ significantly from the soil communities that surround them [42][43][44](Pass et al., 2015; Maureen et al., 2016; Zhu et al., 2018b), indicating a “hidden” soil microbiome residing within the digestive tracts of soil fauna.

Soil fauna are constantly exposed to large numbers of microorganisms so may have developed strategies for controlling microbial growth and colonization by pathogens. Harnessing the production of antimicrobial agents by their gut microbiota may be one strategy. The production of antimicrobial agents would then enhance the immunity of the host and incidentally also provide a rich resource for the discovery of new antimicrobials[45][46] (Broza et al., 2001; Dromph and Vestergaard, 2002). Many bacteria isolated from collembolan guts have inhibitory effects on other microorganisms. One bacterium was isolated that could inhibit the activity of all bacterial and fungal pathogens tested[47] (Agamennone et al., 2018). These observations suggest that gut microbiota from soil fauna are a neglected source of new antimicrobials.

Soil fauna may also produce their own antimicrobial agents. For example, multiple antimicrobial peptides have been isolated from earthworm tissues [2][48](Liu et al., 2004; Li et al., 2011). Genes for antibiotic production may have been transferred from bacteria to their hosts in some cases. Gene

pathways for the synthesis of β -lactam antibiotics have been found in the genome of soil-dwelling collembolans but are much rarer in sister taxa that live in leaf litter or on the soil surface and are completely absent in closely related insect groups. This unusual finding has been confirmed by genomic, transcriptomic and phylogenetic analyses and strongly suggests lateral gene transfer from a microbial donor in a deep-rooted collembolan ancestor [49][50][51](Roelofs et al., 2013) (Suring et al., 2016) (Suring et al., 2017).

Anthropogenic activities alter the abundance and diversity of resistance genes in the soil environment. The resident fauna preferentially graze on this material when manure is applied to soil. Manure often contains many antibiotics and resistance genes derived from intensively managed livestock systems, so soil fauna and their gut microbiota will be exposed to resistance genes and the antibiotics that select for the uptake of these genes. In a study of dietary exposure to antibiotics, the number and abundance of ARGs significantly increased in the collembolan gut microbiome after antibiotic exposure for 14 days[52] (Zhu et al., 2018a), suggesting that collembolans are a focus for the accumulation and dissemination of ARGs. Indeed, soil collembola can accelerate the spread of ARGs in soil ecosystems (Zhu et al., 2018d). The accumulation of ARGs in the gut microbiome of soil fauna could have an important, but underappreciated, role in the dispersal of ARGs and their transfer through the food chain.

Fauna in soil ecosystems are commonly exposed to multiple stressors. Different human disturbances add to these stressors, having significant

effects on the distribution of ARGs in the gut microbiomes of soil fauna. Exposure to silver nanoparticles can significantly reduce the number and abundance of ARGs in the soil collembolan gut microbiome [53](Zhu et al., 2018c), indicating that the effects of pollutants on ARG diversity and abundance are complex. Exploring the relative influence of different pollutants on the distribution of ARGs in soil and the gut microbiota of gut microbiomes of soil fauna should be a priority, especially for emerging pollutants.

Perspectives on managing soil biota for planetary health

Managing soil biota, both the microbiota and larger organisms, is vitally important for safeguarding planetary health. The issues facing such management are multifaceted and involve complex ecologies, interactions and evolutionary forces.

Both the soil microbiome and soil fauna have ancient and complex interactions with endemic antibiotics and resistance genes. These relationships existed long before human clinical practices became widespread. Soil organisms are thus pre-adapted to respond rapidly to anthropogenic pollution with antibiotics and other selective agents. They already have the genes, the mobile elements and the biochemical pathways for dealing with such compounds, and these abilities have been improved by millions of years of evolution. These organisms can consequently respond rapidly to perturbations driven by human pollution, which is not surprising. The abundance of specific organisms, genes and phenotypes can be influenced

by pollution with clinical antibiotics or bacterial cells that carry clinically relevant antibiotic-resistance genes, which in turn affects the ARG content of the soil microbiome and the microbiota residing within soil fauna.

The increasing abundance of ARGs in soil has clear and direct implications for human health and clinical practice due to the link between soils and food production and the consequent direct route for novel resistance determinants to transfer from soil to food to human commensal and pathogenic bacteria. The dynamics, frequencies and foci of such events, however, are still being actively investigated.

The potential for more general perturbations to soil ecosystems and thus planetary processes, though, is not clear. Changes to the relative abundances of soil taxa, both microbial and faunal, are likely to have flow-on effects to the larger scale processes mediated by these organisms. The consequences for biogeochemistry are not yet known, and the intimate relationships between soil health and soil fauna may be altered to the detriment of soil ecosystems more generally. A One Health perspective is needed, taking into account the dynamics of antibiotics and resistance genes as they move between human-dominated ecosystems to more natural environments and back again. We even more urgently need to quantify the amount of selective agents being added to soil ecosystems by human activity and to examine their consequences for the endemic soil organisms upon which human health and welfare depends.

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