Review article

Soil biota, antimicrobial resistance and planetary health

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ARTICLE INFO	ABSTRACT
	The concept of planetary health acknowledges the links between ecosystems, biodiversity and human health and well-being. Soil, the critical component of the interconnected ecosystem, is the most biodiverse habitat on Earth, and soil microbiomes play a major role in human health and well-being through ecosystem services such as nutrient cycling, pollutant remediation and synthesis of bioactive compounds such as antimicrobials. Soil is also a natural source of antimicrobial resistance, which is often termed intrinsic resistance. However, increasing use and misuse of antimicrobials in humans and animals in recent decades has increased both the diversity and prevalence of antimicrobial resistance in soils, particularly in areas affected by human and animal wastes, such as organic manures and reclaimed wastewater, and also by air transmission. Antimicrobials and antimicrobial resistance are two sides of the sword, while antimicrobials are essential in health care; globally, antimicrobial resistance is jeopardizing the effectiveness of antimicrobial drugs, thus threatening human health. Soil is a crucial pathway through which humans are exposed to antimicrobial resistance determinants, including those harbored by human pathogens. In this review, we use the nexus of antimicrobials and antimicrobial resistance as a focus to discuss the role of soil in planetary health and illustrate the impacts of soil microbiomes on human health and well-being. This review examines the sources and dynamics of antimicrobial resistance in soils and uses the perspective of planetary health to track the movement of antimicrobial-resistance genes between environmental compartments, including soil, water, food and air.

1. Introduction

Planetary health is a new field examining the links between human health and the natural environment (Clark, 2015; Seltenrich, 2018; Al-Delaimy, 2018). 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 the long-term health of human populations (Cole and Bickersteth, 2018). Planetary health specifically addresses the interconnectivity of processes and phenomena, some of which may not seem connected when viewed conventionally. For example, rising atmospheric CO_2 concentrations may lead to zinc malnutrition, as they limit nutrient uptake by crop plants (Nakandalage et al., 2016).

Planetary health requires interdisciplinary studies to address complex and cross-cutting issues (Seltenrich, 2018). 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 (Gillings and Hagan-Lawson, 2014). Planetary health
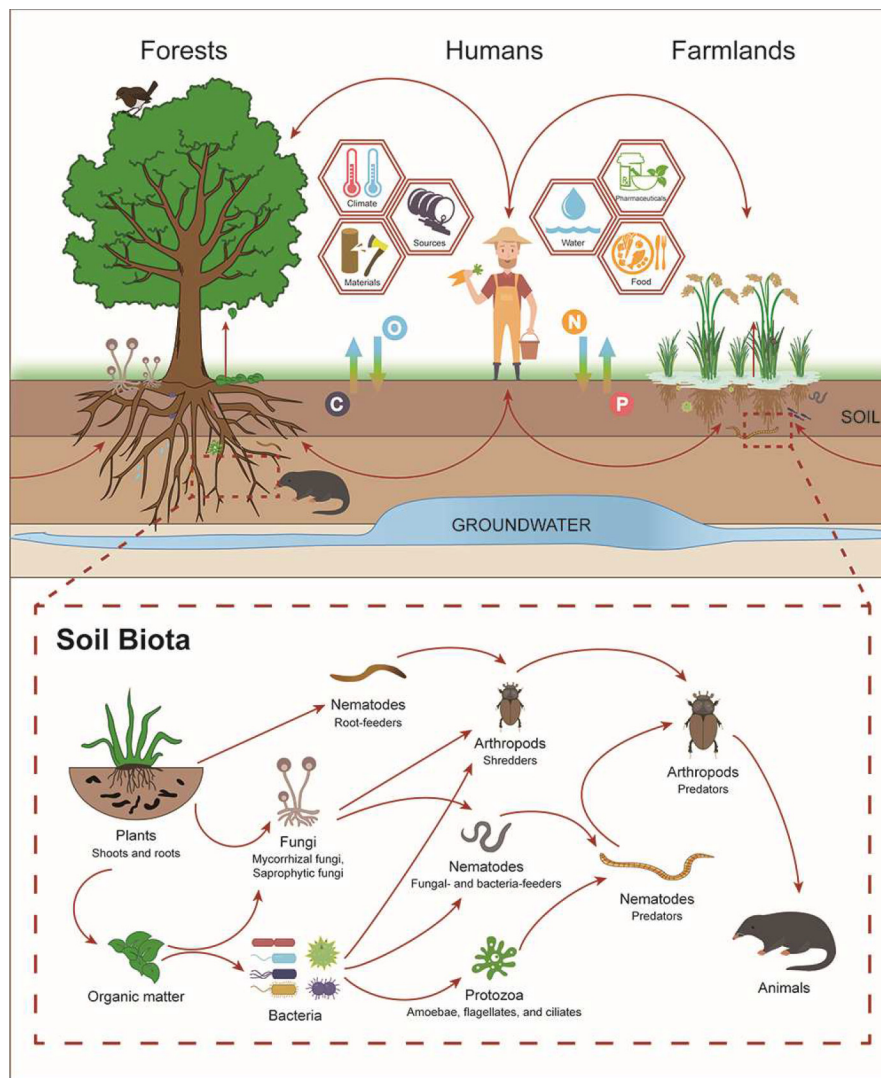
Fig. 1. The role of soil biota in supporting the planetary health system. Soil biota constitutes a complex food web, through which soil offers an array of ecosystem services to human, thus safeguarding planetary health.

studies thus facilitate the engagement of all stakeholders in the stewardship of a common future.

Soil is a critical component of the planetary health system (Fig. 1). It plays a fundamental role in human health and well-being, primarily because most food is derived from soil – plants represent the major pathway for the delivery of essential nutrients, such as nitrogen, phosphorus and trace elements, to humans (Beavington, 2000; Steffan et al., 2018). The flourishing of early civilizations in the "fertile crescent" demonstrates the contribution of soil to human development (Roquero De Laburu, 2000). The functions of soil from biological, chemical and physical perspectives consequently have direct impacts on human health and well-being (Fig. 1).

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 consuming contaminated crop and animal products (Li et al., 2014). For example, soil contaminated by arsenic due to industrial activity and irrigation with contaminated groundwater has led to elevated arsenic levels in rice (Abedin et al., 2002; Gillispie et al., 2015), which is now recognized as a major source of human exposure to arsenic. Indeed, an estimated 60% of arsenic ingestion in China is from rice, and this presents a significantly increased risk of cancer for the general population (Li et al., 2011a).

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 a billion bacterial cells, of ten thousand species (Fierer, 2017). Soil microbiota play multiple roles in providing ecosystem services relevant to human health, including food production, nutrient cycling and bioremediation (Ikoyi et al., 2018). Direct roles in plant nutrition, such as those that occur 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 (Prescott, 2013), which may partly account for the increased prevalence of allergies and perturbations to immune responses in cities, where there is less contact with soils and other natural ecosystems.

Ecosystem services provided by soil biota are also under threat from human activity (Sharma et al., 2009; Barrios, 2007; Wardle et al., 2004). Soil is a rich source of bioactive compounds that can be explored as pharmaceuticals (Bahram et al., 2018). Soil, however, is also a reservoir of antimicrobial resistance and can act as a source of resistance determinants that can spread to human pathogens (Forsberg et al., 2014; Wright, 2010; Forsberg et al., 2012). Antimicrobial resistance is recognized as one of the biggest threats to global public health and food

security, which has received increasing attention over the past years (Laxminarayan et al., 2013). There are hundreds of thousands human deaths each year worldwide attributable to antimicrobial-resistant infections, and scientists predicted this number will reach 10 million in 2050 when the antimicrobial-resistant infection will become a bigger killer than cancer (O'neill, 2014). The antimicrobial resistome has the significant relevance to human health since it is immanent, highly mobile, and has the capability of causing failures in the antibiotic treatment for infectious diseases in human. There is a variety of routes of antimicrobial resistome transmission from soil to human including direct contact, food chain, and water/air environment as a transfer stop, consequently posing a threat to public health (Ashbolt et al., 2013; Li et al., 2018a; Larsson et al., 2018; Ochoa-Hueso, 2017). For example, antimicrobial resistance in soils can be absorbed by plants and subsequently migrate into the food chain (Chen et al., 2019). Meanwhile, soil resistome also could spread to water bodies by naturally surface runoff and could be aerosolized into the air, facilitating further transport of antimicrobial resistome with soil origins to human (Zhu et al., 2017).

In this paper, we 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. Here, our aims are to examine the sources and dynamics of antimicrobial resistance in the soil ecosystem and use the perspective of planetary health to track the movement of antimicrobial-resistance genes between environmental compartments, including soil, animal, water, food and air. Finally, we advance the recommendations for future research.

2. 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 to adapt to environmental changes (Audrain et al., 2015). Microbial secondary metabolites comprise two major families: non-ribosomal peptides and polyketides. These two families account for most antibiotics, antifungals and other antimicrobial compounds that have been characterized from culturable bacteria (Lorena et al., 2014; Guzman et al., 2012). During the 1940s–60s, many antibiotics were initially isolated by screening streptomycetes from soils for antimicrobial activity, including streptomycin, which was discovered by 1952 Nobel Prize Winner Selman Waksman and his colleagues. More recently, the advent of molecular and genomic technologies has led to a resurgence of interest in mining antibiotics from the soil microbiome, with high-throughput genomic tools now being used in the search for bioactive compounds (Tong et al., 2017; Hautbergue et al., 2018).

3. Soil: A major reservoir of the environmental resistome

3.1. The intrinsic resistome

Genes that can confer resistance to antibiotics are referred to as antibiotic-resistance genes (ARGs), regardless of their originally ascribed function (Perron et al., 2013). A subset of these genes has rapidly and vastly increased in abundance, largely driven by selection imposed by the application of clinical concentrations of antibiotics. As a result of the increased transmission and abundance of these genes in humans, food producing animals and domestic animals, clinically relevant ARGs are now considered to be emerging environmental contaminants (Wright, 2010; Devarajan et al., 2015).

Like antibiotics, ARGs occur naturally (D'Costa et al., 2011). Since penicillin was first isolated in 1928 (Chain et al., 1940), diverse antibiotics was discovered and introduced in the 1940s. Soil harbors diverse microbes that produce antibiotics, and is therefore a vast natural reservoir of the corresponding ARGs. These naturally occurring soil ARGs are collectively known as the intrinsic resistome, and they vastly outnumber the resistance genes that have become clinically relevant.

The intrinsic resistome is also diverse. The molecular mechanisms that underlie the intrinsic resistome often involve inherent characteristics that are either structural (e.g., affecting the outer membrane) or functional (e.g., affecting efflux pumps) (Blair et al., 2015). Moreover, like ARGs themselves, this mechanistic diversity arose independently of human activity – for example, 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) (Galán et al., 2013). ARGs with diverse resistance mechanisms have also been identified in remote Antarctic soils with little human impact (Goethem et al., 2018).

3.2. Humans enrich the soil resistome

The advent of antibiotics in the 20th century revolutionized medicine, and easy access to antibiotics has saved millions of lives and enabled high-density animal production; however, it has also led to misuse and overuse. According to the Centers for Disease Control and Prevention in the USA, up to half of antibiotics used in humans are unnecessary or inappropriate (States, 2017). A large amount of antibiotics are used in livestock production for disease treatment, or more frequently, as a growth promoter – in China 96 million kg were used in 2007, whereas in the USA over 384 million kg were used in 1999.

Sustained selection pressure on bacteria by antibiotic use has led to increased prevalence of ARGs in a wide variety of clinical pathogens and commensal bacteria. Bacteria become resistant to antibiotics by diverse mechanisms, including mutational modification of genes for antibiotic target molecules, or acquisition of ARGs via lateral gene transfer. These mechanisms have been the subject of recent reviews (Peterson and Kaur, 2018; Lambert, 2005; Qiao et al., 2018; Sultan et al., 2018).

New antibiotic-resistant bacteria are then shed from humans and animals into the environment and have become recognized as an important environmental contaminant (Wright, 2010; Forsberg et al., 2012). In particular, there has been an enrichment of a specific subset of clinically relevant ARGs in the environment (Peterson and Kaur, 2018). 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. Instead, resistant microorganisms increasingly acquire their resistance from human activity.

Human activity also exposes soils to pollutants, such as antibiotics, heavy metals or disinfectants, that are themselves selective agents (Fig. 2). Subinhibitory concentrations of antibiotics raise the background rates of mutation, recombination and lateral gene transfer among microbial populations. 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 (Hotopp et al., 2007; Durao et al., 2018; Knopp and Andersson, 2018). 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 ARGs, and thus co-selection then becomes a driving force for promoting and fixing resistance determinants in soil microbial populations (Zhao et al., 2019; Pal et al., 2015; Khan et al., 2016).

Rapid expansions in the diversity and abundance of ARGs in soil have been documented (Bengtsson-Palme et al., 2018; Zhu et al., 2017). While historical data are rare, there is no evidence of ARGs on plasmids in the pre-antibiotic era (Hughes and Datta, 1983) and that resistance genes have increased in abundance in archived soils over time (Knapp et al., 2010). Wastewater-treatment plants are believed to be the principal anthropogenic sources of resistance genes into soil (Rizzo et al., 2013). Resistance determinants from clinical settings, pharmaceutical industries, private households and other origins enter
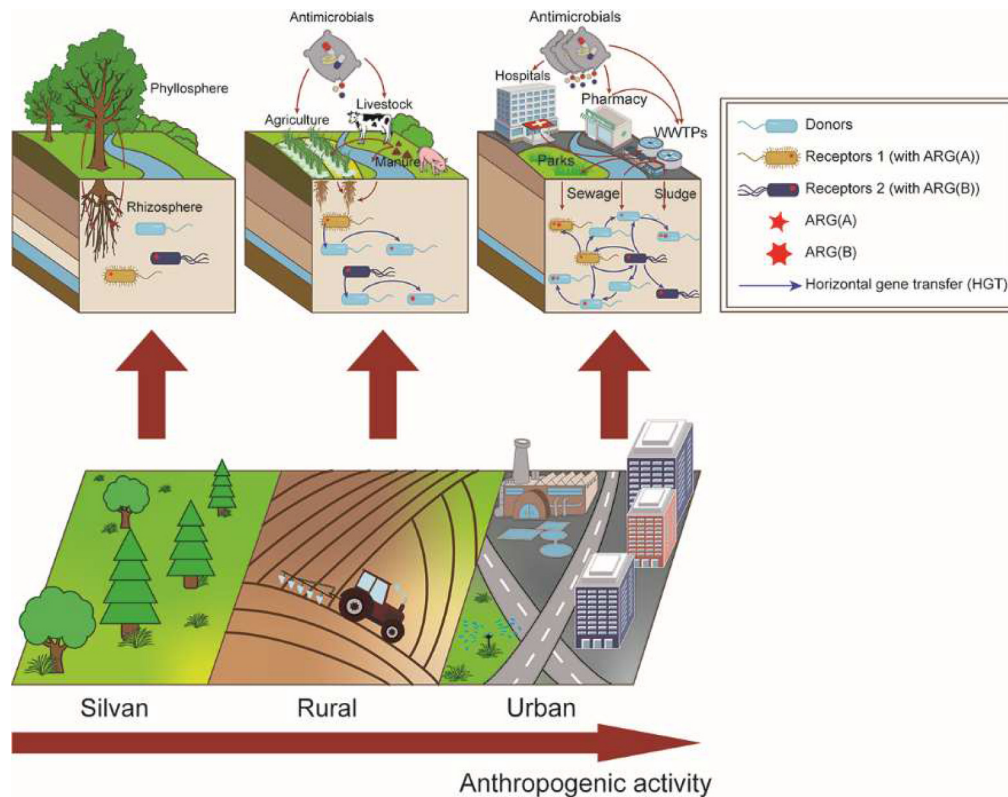
Fig. 2. The effects of anthropogenic activity on antimicrobial resistance in the soil ecosystem. Urbanization intensifies the dispersal of resistance genes in the soil environment and beyond, therefore threatening planetary health.

treatment plants, where they are often poorly removed before the released effluent carries these determinants into environmental compartments. For example, 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 then become enriched in sewage sludge and effluents (An et al., 2018). These resistance elements can contaminate urban soils and agricultural land via irrigation with reclaimed water or application of sewage sludge (Qiao et al., 2018; Wang et al., 2014a; Wang et al., 2014b; Su et al., 2017). Resistance genes in urban park soils can be enriched more than 8000-fold after irrigation with reclaimed water (Wang et al., 2014a). 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 (Chen et al., 2016).

Animal manure is also widely used as a soil amendment for cost-effective crop production (Insam et al., 2015; Zeng et al., 2017). The intensive use of in-feed antibiotics and metals as growth promotors massively enriches ARGs in the animal gut (Zhao et al., 2018) and associated environments (Zhu et al., 2013). These genes are then released to soils and enriched during manure application (Zhu et al., 2013; Zhang et al., 2017; Xie et al., 2018). Comprehensive evidence suggests that manure use promotes the enrichment and dissemination of resistance in soils and the general environment.

Air pollution is also potentially introducing ARGs to soils through wet and dry deposition (Li et al., 2018b). A global survey reported the ARG spread in air crossing 19 international cities and highlights the threat of urban airborne transmission of ARGs and the importance of studying $PM_{2.5}$-borne ARGs (Li et al., 2018b). A recent study investigated the airborne ARGs in highly polluted air in Beijing and reported that up to 30% of positive detection of ARGs in polluted air was attributed to multidrug resistant *NDM-1* gene, with carrier *Bacillus halotolerans* disseminate more diverse ARGs (Zhang et al., 2019). These airborne resistance determinants and other pollutants that potentially

selecting ARGs in air could be transported cross physical barriers and settled even to soils in remote regions, exacerbating the soil selection and dissemination of ARGs. In return, soil pollutants and microbes may also be aerosolized into the air and further aggravate ARG spread in air.

Moreover, the soil bacteria commonly vary from one location to another, and they respond to the environment differently. This leads to effects of human activities on ARGs existing difference in different regions. A recent study has showed that soil types had a significant effect on the dispersal of ARGs after the application of sludge composts (Zhang et al., 2018). In addition to direct transport from anthropogenic sources, the wide range of antibiotic-resistant microbes in soil are also enriched by the selection process under stress from exogenous contaminants such as antibiotic residues, toxic metals, and biocides, which enter the soil from urban wastewater, agriculture and industry (Pal et al., 2015). Specifically, resistant microbes have a selective advantage under such conditions and can become dominant members of the soil microbial population. Their ARGs can spread to susceptible bacteria via lateral gene transfer, creating a cycle of positive feedback for propagating resistance in the soil microbiota. Soil thus 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.

4. Resistance in the gut microbiomes of soil fauna

Soil fauna are an essential component of soil ecosystems – indeed, they represent 23% of known animals (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 (Rusek, 1998; De Deyn et al., 2003). Microorganisms routinely colonize animals, where they significantly affect host nutrition, development and immunity (Adair et al., 2018; Thaiss et al., 2016). Recent studies have reported that soil

fauna have abundant bacterial communities in their guts and that these communities differ significantly from the soil communities surrounding the host (Maureen et al., 2016; Pass et al., 2015; Zhu et al., 2018a). This suggests the existence of a hidden soil microbiome residing within the digestive tracts of soil fauna.

Soil fauna are constantly exposed to large numbers of microorganisms within the soil matrix and thus are likely to have developed strategies for controlling microbial growth and colonization by pathogens. One such strategy could involve harnessing the production of antimicrobial agents by gut microbiota, which would then enhance the immunity of the host. This strategy might also provide a rich resource for the discovery of new antimicrobials (Broza et al., 2001; Dromph and Vestergaard, 2002). A previous study isolated many bacteria from collembolan guts that showed inhibitory effects on other microorganisms – including a bacterium that could inhibit the activity of all bacterial and fungal pathogens tested (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 (Li et al., 2011b; Liu et al., 2004). 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 other closely related insect groups. This surprising 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 (Roelofs et al., 2013; Suring et al., 2016; Suring et al., 2017).

Human activities alter the abundance and diversity of ARGs in the soil environment (Wright, 2010; Chen et al., 2018). The resident fauna preferentially graze on this material when manure is applied to soil, and thus through that manure, the soil fauna and their gut microbiota are likely to be exposed to both ARGs and antibiotics. 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 (Zhu et al., 2018b), suggesting that collembolans are particularly important in the accumulation and dissemination of ARGs in soil ecosystems. The accumulation of ARGs in the gut microbiome of soil fauna (e.g. collembolan) could have an important, but underappreciated, role in the dispersal of ARGs and their transfer through the food chain (Fig. 3).

Fauna in soil ecosystems are commonly exposed to multiple stressors. Disturbances caused by human activities add to these stressors and can have a major influence 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 (Zhu et al., 2018c), indicating that the effects of pollutants on ARG diversity and abundance are complex. Exploration of the relative influences of different pollutants on the distribution of ARGs in soil and the gut microbiota of soil fauna should be prioritized in future research, especially for emerging pollutants.

5. Perspectives on managing soil biota for planetary health

Soil and soil fauna microbiomes are the source of bioactive compounds, including antibiotics, which have the diverse and abundant intrinsic resistome. Human activities (e.g. misuse of antibiotics) are increasing these resistome and promoting the dispersal of them at the global scale. The increasing abundance of ARGs in the soil ecosystem has clear and direct implications for planetary health.

Management of 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 ARGs. These relationships existed long before antibiotic use became widespread in human and animal medicine. Soil organisms are thus preadapted 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. It is therefore not surprising that these organisms can respond rapidly to perturbations driven by human pollution. The abundance of specific organisms, genes and phenotypes can be influenced by pollution with clinical antibiotics or bacterial cells that carry clinically relevant ARGs, 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. This issue is further exacerbated by the potential co-selection of ARGs by other chemical contaminants, such as metals and pharmaceutical compounds.

However, the potential for more general perturbations to soil ecosystems and thus planetary processes remains unclear. 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 – however, these biogeochemical consequences are not yet known. Moreover, 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 ARGs as they move from human-dominated ecosystems to more natural environments and back again (Food and Agriculture Organization of the United Nations et al., 2008; World Health Organization, 2015). There is a pressing need to quantify the extent of selective agents being added to soil ecosystems by human activity and to examine their consequences for the endemic soil organisms upon which future human health and well-being depends.

Finally, as with other environmental contamination, it is urgent to develop frameworks of risk assessment for antibiotics and ARGs in soils, which should include human exposure pathways and risk quantification. Such frameworks shall be developed with the "One Health" perspective considering the connectivity of the entire ecosystem.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgements

Author contributions

Y.G.Z. conceived the manuscript. Y.G.Z., Y.Z. and D.Z. wrote the manuscript. M. G., J. P., Y.S.O., A.C. and S.B. edited the manuscript.
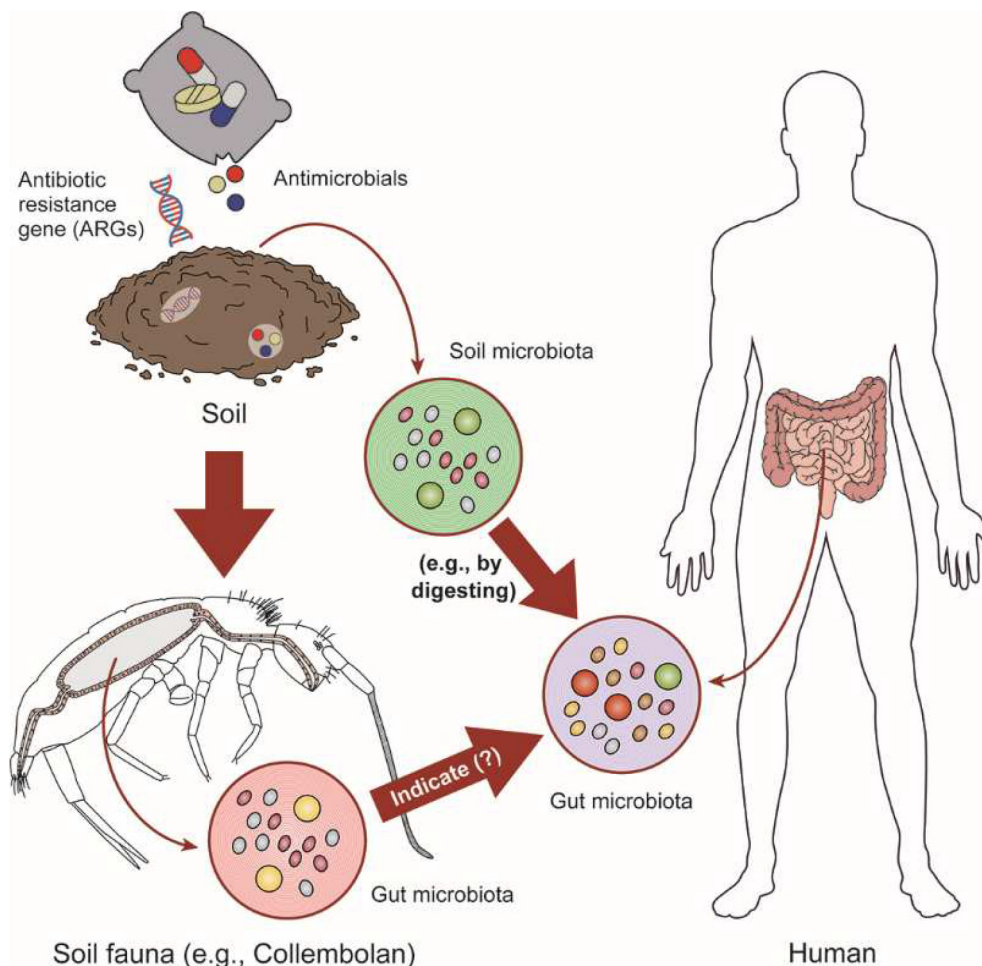
Fig. 3. Antimicrobials and antimicrobial resistance in the gut microbiomes of soil fauna are linked to human microbiome.

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