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Minireview

Colliding and interacting microbiomes and microbial communities - consequences for human health

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Living 'things' coexist with microorganisms, known as the microbiota/microbiome that provides essential physiological functions to its host. Despite this reliance, the microbiome is malleable and can be altered by several factors including birth-mode, age, antibiotics, nutrition, and disease. In this minireview, we consider how other microbiomes and microbial communities impact the host microbiome and the host through the concept of microbiome collisions (initial exposures) and interactions. Interactions include changes in host microbiome composition and functionality and/or host responses. Understanding the impact of other microbiomes and microbial communities on the microbiome and host are important considering the decline in human microbiota diversity in the developed world – paralleled by the surge of non-communicable, inflammatory-based diseases. Thus, surrounding ourselves with rich and diverse beneficial microbiomes and microbial communities to collide and interact with should help to diminish the loss in microbial diversity and protect from certain diseases. In the same vein, our microbiomes not only influence our health but potentially the health of those close to us. We also consider strategies for enhanced host microbiome collisions and interactions through the surrounding environment that ensure increased microbiome diversity and functionality contributing to enhanced symbiotic return to the host in terms of health benefit.

Introduction

Living 'things' coexist with microorganisms that live on and within their macro-eukaryotic hosts composed of bacteria, archaea, and lower and higher eukaryotes (protists and fungi, respectively), referred to as the microbiota (Berg *et al*., 2020). The microbiome describes the microbiota and its 'theatre of activity', embracing the collective nucleic acids (including viruses and bacteriophages), microbial structural elements and microbial metabolites associated with the microbiota (Berg *et al*., 2020). However, the terms are often used interchangeably. In humans and other animals, these microorganisms exist on the skin/surfaces and within certain organs of the body (e.g. airways, gut; Fig. 1A). Similarly, in plants, the microbiota occur on the surfaces where they are referred to as epiphytes and within plant tissues where they are known as endophytes (Flandroy *et al*., 2018; Fig. 1B).

Most studies to date have focused on the role of the microbiome in human health, particularly the bacterial component. Humans have evolved with these microorganisms which essentially shaped the immunoregulatory mechanisms to tolerate commensals and eradicate pathogens (Rook, 2013), while also aiding the immune system in its functions. Indeed, across all body sites, immune education and colonization resistance are common microbial functions while each niche-specific microbiome also may provide niche-specific functions. Microbiomes are characterized by vast inter-individual variation, and the gut microbiota of generally healthy individuals are marked by a richness and diversity of species/strain composition that can withstand and recover from perturbations, such as antibiotic exposure (Rinninella *et al*., 2019).

However, industrialization and the lifestyles associated with it have moulded a decline in the diversity of our microbiota. Diminished contact with the natural world, unhealthy dietary patterns, antibiotics and heightened sanitation in our indoor environments are some of the factors which have contributed to this decline. But this can begin as early as birth when gut microbiota seeding can be compromised by increasing maternal age, lack of breastfeeding, antibiotic exposure and aseptic environments with consequences for microbiota succession and

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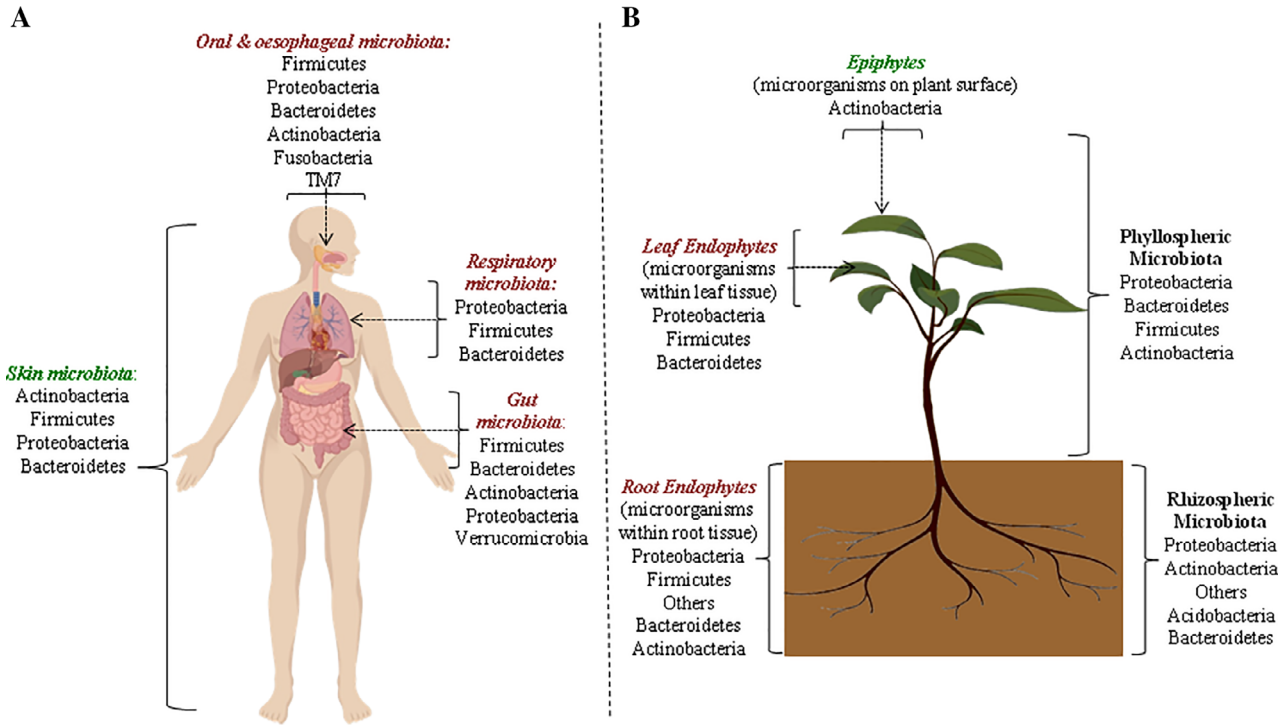

Fig. 1. Phyla of the human microbiota and of the plant phyllosphere and rhizospehere.
A. Representative phyla of the human microbiota across different body locations.
B. Microbiota associated with plant phyllosphere (above ground plant organs) and rhizosphere (region of soil in vicinity of and influenced by plant roots) (Sivakumar *et al*., 2020; Trivedi *et al*., 2020). Created with Biorender.com.

immune education. In the fight against the SARS-CoV-2 pandemic, regular hand-sanitizer use, hand-washing and heightened sanitation in public places has now become essential but leads one to speculate about the long-term effects for the microbiota.

Several diseases affecting humans living a westernized lifestyle, notably non-communicable diseases (NCDs) and conditions, have been associated with changes in specific gut microbial levels and loss of overall gut microbial diversity. Inflammation is a common 'pathogenetic' link between many of these NCDs and the loss of microbial diversity (Flandroy *et al*., 2018). However, according to the 'microbial old friends' hypothesis exposure to microbe-rich environments with beneficial microbes from our evolutionary past promotes our microbiota diversity thus reducing risk of inflammatory diseases (Tasnim *et al*., 2017). Such old friends (e.g. Spirochaetaceae, *Prevotella* and *Desulfovibrio*) were recently detected in the Neanderthal gut microbiome (Rampelli *et al*., 2021).

In this minireview, we discuss opportunities for host microbiome collisions and interactions with other microbiomes and the microbial communities of food and soil (Fig. 2). Collisions (initial exposures) may lead to interactions such as altered host microbiome composition and functionality (in extreme cases, infection), and/or may elicit host responses such as immunomodulation via antigen presentation. Alternatively, collisions and interactions with non-human taxa may reduce the risk of interactions with human pathogens that colonize, invade and infect us, a hypothesis proposed by Kirjavainen and colleagues (2019). Understanding these collisions and interactions is important for many reasons but especially given the decline in the diversity of our microbiota. Thus, surrounding ourselves with rich and diverse microbiomes and microbial communities to collide and interact with may help to diminish the loss in microbial diversity and provide protection against certain diseases. Initiatives have already commenced to increase our exposure to diverse microbiomes and microbial communities in our surrounding environment including urban rewilding, Microbiome-Inspired Green Infrastructure (MIGI) and the Healthy Urban Microbiome Initiative (HUMI), which we discuss here. But we begin by providing evidence of the bacterial components of our microbiomes colliding and interacting with other microbiomes and the microbial communities of food and soil. We discuss the consequences of these collisions and interactions for the host microbiome and host health. Indeed, results are beginning to indicate that we may influence the health of those

Fig. 2. Colliding and interacting microbiomes. In the image, the microbiomes of living 'things' are depicted as microbial 'galaxies' with potential to collide and interact with each other with consequences for the host microbiome and host health.

close to us through our microbiomes given the presence of shared operational taxonomic units (OTUs) between individuals from the same household (Finnicum *et al*., 2019). With this in mind, we discuss strategies to ensure increased symbiotic return to the host in terms of health through microbiome collisions and interactions.

Colliding and interacting microbiomes and microbial communities

Microbiome collisions and interactions with food microbial communities

The microbial communities of food collide and often interact with our gut microbiome and much research has focused on this aspect of fermented foods and probiotic-containing fermented foods and how they contribute to human health. The most commonly used food probiotics belong to the lactic acid bacteria (LAB) group and LAB are the predominant microorganisms used in the production of fermented foods. Fermented dairy products contain up to 10^9 LAB per ml or per gram (Rezac *et al*., 2018) and it is estimated that we take in 10^8 to 10^{12} colony forming units (CFU) of LAB per day through the ingestion of fermented foods and probiotics (Derrien and van Hylckama Vlieg, 2015). Probiotic strains have been detected in faeces a few days after ingestion but seldom after 1 week (Costa *et al*., 2014; Bogovič Matijašić *et al*., 2016). Despite this, these microorganisms are transient residents ('tourists') of the gut microbiome but are capable of impacting its composition and functionality, or indeed, eliciting a host response. Derrien and van Hylckama Vlieg (2015) state that ingested bacteria can impact the resident microbiota by at least three different means: (1) trophic interactions (e.g. carbohydrate metabolism) that alter metabolic outputs; (2) direct alterations in fitness (e.g. due to bacteriocin production); and (3) indirect alterations in fitness (e.g. host response that modifies microbiota composition and/or functionality).

A qualitative systematic review of 108 studies to determine the effects of yoghurt and fermented milk products consumption (with or without probiotics) on a range of health issues revealed consistent associations between fermented milk consumption and reduced risk of colorectal cancer, breast cancer and type 2 diabetes, improved weight maintenance and improved gastrointestinal (GI), cardiovascular and bone health (Savaiano and Hutkins, 2021). Several plausible mechanisms for these health outcomes have been proposed including the production of bioactive compounds and B vitamins during the fermentation process (Savaiano and Hutkins, 2021). But interactions between these microorganisms and the gut microbiome may also contribute to the health benefits associated with fermented milk products.

For example, consumption of commercial yoghurt supplemented with *Bifidobacterium animalis* subsp. *lactis* (BB-12) and *Lactobacillus acidophilus* (LA-5) significantly increased faecal counts of these strains compared to the placebo treatment (Savard *et al*., 2011). Viable counts of faecal lactobacilli were also significantly higher while those of enterococci were significantly lower for the probiotic-yoghurt group. Thus, consumption of the probiotic-containing yoghurt resulted in microbial collisions and interactions that increased beneficial bacteria in the gut over and above the tourists while lowering the pathogenic load. While 7 weeks of consumption of a consortium of probiotic strains in fermented milk did not result in significant changes to bacterial species composition in monozygotic twins, RNA-Seq analysis of faecal samples revealed that consumption of the probiotic fermented milk product significantly up-regulated the expression of genes involved in carbohydrate metabolism, amino acid metabolism, and metabolism of cofactors and vitamins (McNulty *et al*., 2011). These responses generally subsided within 4 weeks after consumption had ceased. Consumption of a fermented milk product supplemented with *B. animalis* by subjects with irritable bowel syndrome increased the abundance of two butyrate producers, most likely due to the increased availability of acetate or lactate that is utilized by the butyrate producers, while it decreased the abundance of the pathobiont *Bilophila wadsworthia*, and these changes paralleled overall improvements in IBS severity in volunteers (i.e. abdominal distension, acceleration of orocaecal and colonic transit times) (Veiga *et al*., 2014).

The studies presented thus far describe collisions and interactions between products supplemented with probiotic strains which have been selected on their ability to survive GI transit and the harsh conditions which that entails. Despite this, foodborne microorganisms have been shown to survive transit through the GI tract. This was shown by David and colleagues (2014) when assessing the impact of diet on the gut microbiome. Foodborne bacteria identified via 16S rRNA gene sequencing were identified in faecal samples of volunteers, in particular bacteria of commonly consumed fermented foods including cheese and cured meats. Likewise, foodborne fungi were identified in volunteer faecal samples. RNA-Seq data revealed that not only did foodborne microbes survive GI transit but they may have been metabolically active. Lang and colleagues (2014) characterized microbial abundance and taxonomy of three different dietary patterns to elucidate the microbes that we eat which included: (i) the average American diet focusing on convenience foods; (ii) the U.S. Department of Agriculture (USDA) recommended diet promoting whole grains, lean meat, dairy, fruits and vegetables; and (iii) the vegan diet (no animal products). The highest number of microbes (based on plate counts) was identified in the USDA meal plan at 1.3×10^9 CFU per day, followed by the vegan diet at 6×10^6 CFU per day, and then the average American diet at 1.4×10^6 CFU per day. In terms of microbial taxonomic composition, individual meals clustered irrespective of dietary patterns, for example, meals rich in LAB were found in all three dietary patterns. Consuming a single apple coincides with the intake of 100 million bacterial cells (Wassermann *et al*., 2019). In the same study, bacterial signatures with health-affecting potential were enhanced in conventionally managed apples compared with those that were organically produced (Wassermann *et al*., 2019). These studies highlight the need to focus more research into the collisions and interactions that take place between foodborne microorganisms (and not just supplemented probiotic strains) and our gut microbiome. For example, we need to consider the risks and consequences of horizontal gene flow between ingested bacteria and our gut microbes. This is particularly relevant in light of the antibiotic resistance crisis. Kirbis and Krizman (2015) found that 40% of food samples of animal origin contained bacteria with resistance to one or more antibiotics, while horizontal gene transfer of antibiotic resistance genes from exogenous bacteria to gut residents has been confirmed using *in vitro* gut models (Card *et al*., 2017; Lambrecht *et al*., 2019). Another consideration is the impact of dead bacterial cells on the gut microbiome. We now know that dead probiotic bacteria, their metabolites and cellular components can impart beneficial properties on the host including immunomodulation, protection against pathogens and maintenance of intestinal barrier integrity (discussed in detail by Piqué *et al*., 2019). But little if anything is known about the impact of ingested dead and damaged food microbes on the gut microbiome, the load of which is presumably high in processed foods. Moreover, consumption of processed foods may increase our intake of spores, given their ability to survive food processing conditions (Carlin, 2011). Often the ingredients used in processed foods bring the spores with them and can exceed 10^2–10^3 spores per gram of ingredient (Carlin, 2011). The sporobiota represents a significant portion of the human gut microbiome (Tetz and Tetz, 2017). However, given the prevalence of undesirable characteristics of spore-forming bacteria, such as resistance to antibiotics and detrimental triggering of host immunity (Tetz and Tetz, 2017) this microbial aspect of processed foods should be considered in terms of the gut microbiome and human health.

To add to this, a study in rats revealed that the gut microbiome response to transient foodborne microbes was dependent on the base gut microbiota structure

(Zhang *et al*., 2016). Interestingly, a similar fermented milk product had been used in the study by McNulty and colleagues (2011) and re-analysis of the human gut microbiota data revealed similar patterns. Thus, food microbial communities could offer a way for precision microbiomics through nutrition (Mills *et al*., 2019a).

Given that the collisions and interactions that occur between food microbial communities and the gut microbiome have the potential to benefit human health, a group of scientists recently discussed if there should be a recommended daily intake of microbes (Marco *et al*., 2020). However, despite the evidence that consumption of safe, live microbes in the diet may improve and support health, further work is required to address the gaps in the current research, which is discussed in depth by Marco and colleagues (2020).

Microbiome collisions and interactions with soil microbial communities

Soil is one of the most significant components of the natural environment providing essential environmental, social and economic functions, yet it is largely non-renewable (Blum, 2005). It also harbours more species in number and quantity than all other above-ground biota combined (Blum, 2005), and soil bacteria are considered the most abundant and diverse group of organisms on Earth (Bardgett and van der Putton, 2014). The number of microbial cells in soil is approximately 10^7–10^9 per gram with an estimated 4×10^3 to 5×10^4 species per gram (Raynaud and Nunan, 2014).

Studies in animals neatly show how soil microbes can collide and interact with the gut microbiome with consequences for health. Using a mouse model, Zhou and colleagues (2018) investigated the effect and extent to which soil in our environment can influence gut microbiota composition. Results revealed that exposure to soil was a key factor influencing the mouse gut microbiota and its effect was deemed comparable to diet. Interestingly, while sterile soil altered the composition and structure of the gut microbiota, the unsterile soil altered the same and increased diversity and richness as well, hence close contact with soil and its microbes can benefit the gut microbiota. This effect of soil is presumably elicited through the ingestion of soil microbes which come into contact with food as mice often store their foodstuff in soil. Furthermore, mice participate in coprophagia and thus may swallow soil directly. More recently, realistic exposures to trace-level dust from a high biodiversity soil altered the gut microbiota of mice in comparison to exposure to dust from a low biodiversity soil or no soil (Liddicoat *et al*., 2020). In the high biodiversity-treatment mice, higher levels of the soil-derived, anaerobic, butyrate-producing bacterium *Kineothrix alysoides* were noted, which correlated with reduced anxiety-like behaviour in the most anxious mice. Likewise, another soil bacterium, *Mycobacterium vaccae*, has been shown to modulate immune responses in both rodents and humans (Groschel *et al*., 2014), to protect against stress-induced behavioural impairments in rats (Reber *et al*., 2016; Frank *et al*., 2018), and protect rats from surgery-elicited neuroinflammation and cognitive dysfunction (Fonken *et al*., 2018).

Nowadays, more than half of the world's population lives in highly dense cities (Ritchie and Roser, 2020), a situation suggested to be analogous to animal captivity in terms of microbiome effects. In the urban environment, natural soil is largely replaced with concrete or asphalt (Von Hertzen and Haahtela, 2006), thus opportunities for microbiome collisions and interactions with soil microbial communities have been dramatically reduced compared to our ancestors who lived in close contact with the soil (Blum *et al*., 2019). In fact, urbanization has been shown to result in the loss of specific microbiome traits in the human gut such as fibre degraders and causes low inter-individual variation owing to the lack of extensive contact with the natural environment (Ayeni *et al*., 2018). In contrast to this, certain gut inhabitants of the Hadza hunter-gatherers have been identified in the surrounding environment (Fragiadakis *et al*., 2019). By examining the microbial biogeography of homes across a gradient of urbanization in South America (jungle village of open huts versus rural village with external latrine versus typical townhouses versus city houses), Ruiz-Calderon and colleagues (2016) reported proportionally higher environmental bacteria, including soil bacteria, in jungle and rural village houses compared with the urban houses, the latter of which were increasingly humanized in terms of microbial communities despite lower occupant density.

It has been hypothesised that our disconnection from the soil as a consequence of urbanization may be one of the contributing factors in the ongoing asthma and atopy epidemics in western societies (Von Hertzen and Haahtela, 2006). For example, the abundance and diversity of the skin commensal *Acinetobacter*, from the Proteobacteria phylum, among school children from the Republic of Karelia in Russia was significantly higher than their counterparts in the bounding region of Finland (Ruokolainen *et al*., 2017). However, allergy prevalence (asthma, hay fever, atopic eczema, self-reported rhinitis and atopic sensitization) was 3- to 10-fold more common in Finland. It was thus concluded that the high abundance and diversity of *Acinetobacter* in Russia contributed to allergy protection (Ruokolainen *et al*., 2017). Haahtela and colleagues (2015) suggest that the more

urbanized Finns have made an earlier disconnection from soil microorganisms than their Russian counterparts.

Despite our industrialized way of life, collisions and interactions with plant microbiomes through diet may provide indirect opportunities for exposure to soil microbes through the ingestion of plant endophytes – certain members of the herbivore gut microbiota are in fact common plant microbes (Martínez-Romero *et al*., 2021). However, less is known about the role of vegetables as actual microbe providers in humans (Martínez-Romero *et al*., 2021). Furthermore, both the rhizosphere (below ground microbial habitat of plant root systems) and the phyllosphere (above ground microbial habitat provided by plants) are associated with tens of thousands of microbial species (Rook, 2013). In general, wild populations of plant species have more diverse endophytic microbial communities than their agricultural counterparts (Hassani *et al*., 2018). Unsurprisingly perhaps, soil fauna and microbial biodiversity loss have been reported in many rural areas owing to intensive agricultural practices, low plant biodiversity and agrochemicals (Tsiafouli *et al*., 2015; Blum *et al*., 2019). Indeed, the earth is currently suffering from an 'unprecedented crisis of soil deterioration …' (Timmis and Ramos, 2021). However, organic farming has generally been shown to reduce the negative impacts of conventional farming on soil microbial communities. Lupatini and colleagues (2017) reported that organically managed soils had greater microbial taxonomic and phylogenetic richness, diversity, and heterogeneity compared with soils from conventional farming systems, while soil health treatments altered microbial composition but not diversity or heterogeneity. Soils supporting a higher diversity of crops in rotation also have higher microbial richness and diversity scores (Venter *et al*., 2016). A meta-analysis of 56 mainly peer-reviewed studies reported that organic systems had 32% to 84% greater microbial abundance and activities compared with conventional systems (Lori *et al*., 2017). Organic fertilization has been shown to increase soil microbial biomass by stimulating microbial growth through the provision of organic substrates (Hartmann *et al*., 2006; Esperschütz *et al*., 2007). The increased microbial activity along with the presence of specific bacterial genera of organically managed soils has been linked to their pathogen-suppressing properties (Hiddink *et al*., 2005; Gu *et al*., 2013). The data thus clearly indicate that increased consumption of organically grown, unprocessed foods should increase our collisions and interactions with soil microbial communities to help us reap the benefits of the soil through our microbiomes.

Microbiome collisions and interactions with other microbiomes

We are increasingly exposed to other human microbiomes in our homes and cities where the air that we breathe and the surfaces we touch serve as vectors for transfer of microbes from human to human, particularly skin-associated microbes. Indeed, humans have been estimated to shed 10^7 microorganisms per person per hour in an occupied indoor space (Qian *et al*., 2012; Hospodsky *et al*., 2015), many of which are closely associated with human skin microbiota (Qian *et al*., 2012). Unsurprisingly perhaps, high-throughput sequencing studies investigating the microbial composition of urban amenities that attract high numbers of humans indicate that human-dominated environments are enriched for human-associated microbes. For example, Afshinnekoo and colleagues (2015) tracked the metagenome of surfaces in highly accessed locations across New York City including the entire New York City subway system using marker-gene sampling. Subway surface bacteria were enriched for human-skin associated microbes. A low but positive correlation ($R^2 = 0.2$) was found between number of commuters and numbers of taxa found at a site. Similar trends were reported for station and train surface microorganisms of Mexico City's subway (Hernández *et al*., 2020), Moscow subway surfaces (Klimenko *et al*., 2020), and aerosol samples from multiple subway lines in Hong Kong (Leung *et al*., 2014). However, whether the bacterial numbers in these microbial communities are dense enough to collide and interact with our microbiomes is questionable. A study by Kang and colleagues (2018) indicates that collisions do occur. Here, shotgun sequencing was used to investigate the human skin microbiome (palm of hand) after contact with handrails within the Hong Kong Mass Transit Railway involving eight urban lines. *Propionibacterium acnes* (now called *Cutibacterium acnes*) was identified as the dominant species following contact. Indeed, of the 10 most populated species, 8 were common human and skin commensals. This study suggests that urban environments are vectors for colliding human microbiomes, at the very least. Further research will be necessary to determine if such collisions result in meaningful interactions that alter microbiome composition and functionality.

With regards to the indoors, it has been estimated that humans in the industrialized world spend up to 90% of their lives indoors (Kelley and Gilbert, 2013). As for human-occupied urban spaces, humans themselves are significant contributors to indoor microbial assemblages. A meta-analysis of 16 surveys of indoor environments around the globe using 16S rRNA gene data sets revealed outdoor air and skin as consistent sources of indoor microorganisms, and the percentage of human-derived sequences in samples ranged from 11% to 32% (Adams *et al*., 2015). Unsurprisingly perhaps, household members, especially couples, have been shown to share skin microbiota taxa (Song *et al*., 2013; Lax *et al*., 2014; Ross *et al*., 2017). Interestingly, in the study by Song and colleagues (2013) dogs appear to serve as vectors for

human-human microbiome collisions as dog ownership increased the shared skin microbiota between cohabiting adults. Another study reported that shared skin microorganisms in cohabiting individuals ranged from 7% to 94% (Leung *et al*., 2018). Increased similarities in the skin microbiomes of unrelated and non-romantically involved U.S. Air Force cadet pairs living together for the first time has also been reported, although the similarity was lost after a vacation period of several weeks (Sharma *et al*., 2019). By mapping microbial dynamics through the environment of a newly operational hospital for a period of a year, Lax and colleagues (2017) showed that the hospital environment became dominated by human skin-associated bacteria following the introduction of staff and patients. Furthermore, admitted patients initially acquired the taxa that had already been in the room prior to their admittance but over several days the patient's microbial signature influenced that of the room with patient skin and room surfaces becoming more similar as the stay progressed. This clearly demonstrates the occurrence of microbiome collisions across time but whether these collisions lead to interactions is as yet unknown.

In the cited studies by Sharma and colleagues (2019) and Song and colleagues (2013), cohabitation did not significantly influence gut microbiota composition. However, cohabitation was found to result in similar gut microbiota alpha diversity and lower Bray–Curtis distances in a study by Finnicum and colleagues (2019). Interestingly, in the same study, two species-level OTUs were found to be significantly associated between cohabiting twin pairs and spouse pairs but not within non-cohabiting monozygotic twin pairs, and one of these OTUs is significantly associated with inflammatory and cardiometabolic disease burden. In fact, the clinical relevance of this was evidential in both the inflammatory and cardiometabolic burden scores of the individuals, perhaps an example of an undesirable interaction following microbiome collision. Shared diet is suggested to be responsible for the similarities between the cohabiting gut microbiomes. It is well accepted that diet and dietary components shape the gut microbiota (Mills *et al*., 2019b). But collisions and interactions with food microbial communities should not be ruled out as a contributing factor, or indeed, collisions and interactions between the microbiomes of the cohabiting individuals. In fact, Dill-McFarland and colleagues (2019) state that we must consider the many microbiotas with which individuals interact after their study revealed that spouses had more similar gut microbiota and more bacterial taxa in common than siblings, irrespective of diet. The closer the relationship between couples, the more similar the gut microbiota profiles. The authors suggest direct microbial transfer or reinforcement of healthy microbiota behaviours as responsible for their observations.

Homes occupied by dogs have higher relative abundances of dog-associated bacterial taxa and more diverse bacterial communities (Dunn *et al*., 2013; Dannemiller *et al*., 2016). Song and colleagues (2013) reported shared skin/fur microbes between humans and their dogs but whether these are just transient members following contact or have a real niche on the human body is unknown. Misic and colleagues (2015) also reported microbiota sharing between cohabiting humans and pets (cats and dogs). Exposure to dogs in early life has been associated with decreased risk of atopic dermatitis (Li *et al*., 2020), and exposure to a dog before and during pregnancy has been shown to decrease the risk of food allergy in the first year of life, which the authors suggest may be due to the beneficial effects of the dog's microbes (Smejda *et al*., 2020). The beneficial effect arising from dogs in the home may be a consequence of immune modulation following exposure to a more diverse microbiota. Indeed, exposure to microbes capable of activating and modulating innate and adaptive immune responses has been identified as an essential factor in the protective effects of the farm environment in terms of asthma in children (von Mutius and Vercelli, 2010). Yet by modelling the differences in house dust microbial composition between farm and non-farm homes, Kirjavainen and colleagues (2019) have shown that non-farm indoor dust bacterial/archaeal communities similar to that of the farming environment are protective in non-farm homes. The researchers hypothesized that a key feature of this protective microbial community was the high abundance of environmental bacteria (including those derived from animals) relative to human bacteria, thus, the protective effect could be arising from altered microbiota composition and the subsequent absence of microbiome interactions with human-derived bacteria that may be more likely to colonize, invade and infect us and trigger detrimental proinflammatory immune responses. In a study assessing microbiome sharing between children, livestock and household surfaces in Western Kenya, Mosites and colleagues (2017) reported that not only did children from the same household significantly share their gut microbiomes, but certain children shared microbes with cattle faecal samples and chicken cloacal swabs.

Without a doubt, the recent SARS-CoV-2 pandemic has highlighted the importance of understanding indoor microbiology given that sharing of indoor space is a major risk factor in transmission of the virus from person to person (Qian *et al*., 2021). This has led to ventilation-focused recommendations to reduce indoor transmission (Allen and Marr, 2020), and a call for a much better understanding of 'building–occupant–microbiome interactions' to enhance

public health and reduce risk of disease transmission (Li *et al*., 2021).

Strategies to improve microbiome collisions and interactions through the environment around us

The environment, outdoor and indoor, serves as a vector for microbiome collisions and interactions and can be enhanced to ensure that optimal collisions and interactions occur, principally through the diversity of living things that occupy it and by conserving soil health (Ramos and Timmis, 2021). Indeed, living in close contact with nature has been proven to be beneficial to human health (Rook, 2013). A recent systematic review and meta-analysis of cohort studies reported evidence of an inverse association between surrounding greenness and all-cause mortality (Rojas-Rueda *et al*., 2019). Apart from the associated psychological benefits, the natural environment is a source of important microorganisms, often referred to as 'old friends,' that we evolved with, learned to tolerate and thus they became essential in orchestrating our immunoregulation (Rook, 2013). However, urbanization has curtailed our exposure to these old friends, which may also be termed the 'missing microbes,' and indeed, as reported in earlier sections we are largely exposed to human-derived microorganisms in our cities and our homes, which as stated earlier could be more likely to trigger detrimental immune and other responses. In contrast, the source of microbial biodiversity in the natural environment arises from the soil, the plants and any animals present (Rook, 2013). Urban 'rewilding' has been proposed as a strategy to restore microbial biodiversity in urban environments by developing well designed green spaces with native and diverse plant communities and where the flora and fauna are managed (Mills *et al*., 2017; 2019) (Fig. 3). Indeed, plants themselves support microbial biodiversity and they attract and support insects, birds and mammals which themselves promote microbial biodiversity (Mills *et al*., 2019) and are sources for more microbiome collisions and interactions. As an example, a comparison of the airborne bacterial communities in parks (highly vegetated) and parking lots (non-vegetated) in the city of Eugene, OR, USA, revealed significant differences (Mhuireach *et al*., 2016). A number of key taxa were substantially more abundant in parks, such as *Acinetobacter*, a genus associated with allergy protection (see previous section - Microbiome collisions and interactions with soil microbial communities).

MIGI builds on urban rewilding and refers to the 'design and management of innovative living urban features that could potentially enhance public health via health-inducing microbial interactions' (Robinson *et al*., 2018). Foraging-friendly green space has been

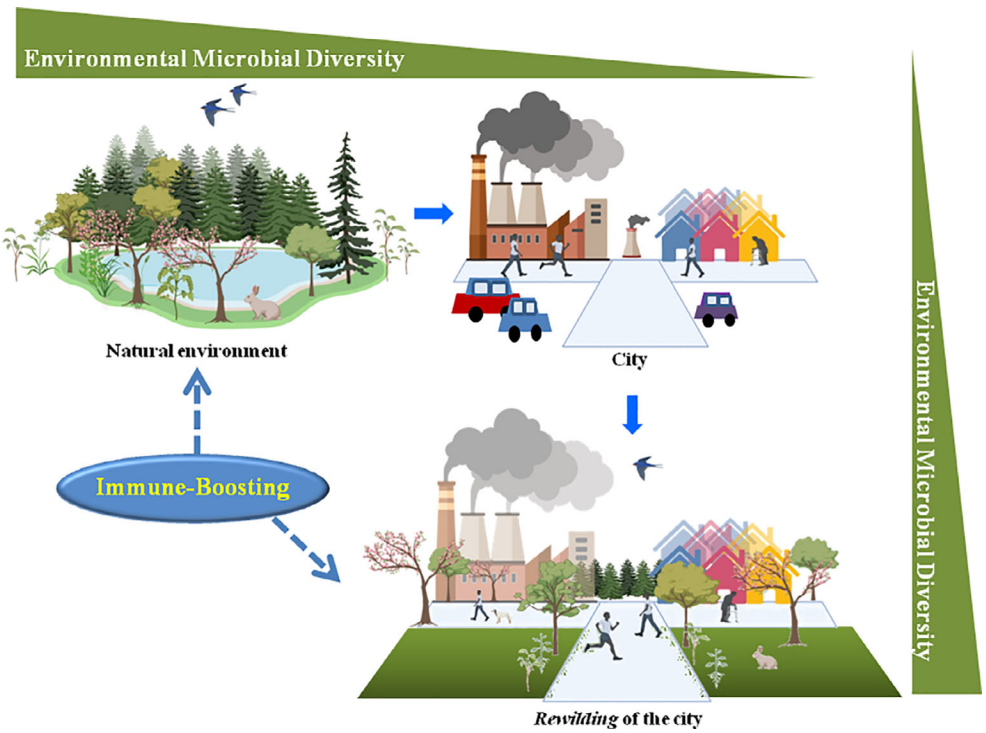

Fig. 3. Impact of rewilding on environmental microbial diversity in the urban environment. Microbial diversity in the urban environment is lower than that in the natural environment. Rewilding of the urban environment offers an opportunity to increase microbial diversity and enhance its immune-boosting potential. Created with Biorender.com.

proposed as an important application of MIGI (Gupta *et al*., 2017) and involves the creation of innovative food-planting schemes that support foraging behaviour and enhance 'human–environment microbial interactions' in urban settings (Robinson *et al*., 2018). Other applications include natural green walls such as hedgerows and trees, inter-ethnic ancestral environments that harbour cultural and ancestral microbiomes, applying MIGI to spaces where children spend time, the merits of which have been discussed in detail by Robinson and colleagues (2018). The HUMI is a science-led, community-focused initiative that aims to understand and recreate biodiverse green spaces with immune-boosting power in cities (www.humi.site). Mills and colleagues (2019) propose that such initiatives could reduce healthcare costs associated with NCDs by up to $USD 350 billion if rewilding reduces such diseases by just 5%. Guo and colleagues (2018) reported that revegetation of degraded lands altered the taxonomic and functional diversity of the soil microbial communities where the taxonomic diversity positively correlated with plant diversity. Interestingly, *Acinetobacter* was more abundant in revegetated sites. In terms of functional diversity, revegetation increased microbial genes involved in carbohydrate and energy metabolism and xenobiotic biodegradation and metabolism, indicating higher levels of soil nutrient cycling.

With regard to indoor microbiology, plants have also been considered important contributors with potential to increase its biodiversity (Berg *et al*., 2014). Indeed, Mahnert and colleagues (2015) showed that the spider plant *Chlorophytum comosum* altered microbial abundance and diversity within a pre-cleaned chamber (2.27 m^3). Specifically, microbial abundance on surrounding walls and floor surfaces increased within 6 months of plant isolation in the cleaned indoor environment. Bacterial diversity increased while fungal diversity decreased, the latter of which could be due to the decrease in relative humidity. Dannemiller (2019) states that we have at least three critical research priorities to address: (i) we need to define healthy indoor microbial communities; (ii) we need to better understand how our choices (e.g. building design and conditions, occupant behaviour) influence such; and (iii) identify the best assessment methods. This could include an assessment of inflammatory responses to different microbial communities of the indoor environment along with knowledge of, if and how they impact microbiome composition and functionality.

Concluding remarks

In this minireview, we consider how human microbiomes behave in the presence of other microbiomes and bacterial communities through the concept of collisions (initial exposures) and interactions, the latter of which refers to changes in host microbiome composition and functionality and/or host responses as a consequence. We ingest large numbers of microorganisms through our food every day, and the microbiota on living 'things' and the microorganisms in soil gather in the air and on surfaces, creating new consortia of microorganisms that may collide and interact with our microbiomes. We also share components of our microbiomes with those close to us.

Indeed, our diet and the environment around us serve as vectors for microbiome collisions and interactions and offer opportunities to improve such through (i) the acquisition of functionally beneficial microbial members, (ii) antigen presentation that can shape microbiome composition and functionality, or (iii) perhaps by lowering the ratio of potentially infective human bacteria to non-infective environmentally derived bacteria. The natural environment with its soil and vast biodiversity of plant and animal species boasts a rich microbial environment that may foster optimal collisions and interactions with our microbiomes. Indeed, many of the microorganisms associated with the natural environment appear to have positive impacts on mammalian health. In contrast, urban and indoor environments occupied predominantly by one species, humans, suffer from a microbial poverty in terms of diversity but are abundant in human-derived microorganisms. The consequence of this reduced microbial diversity, and possibly increased exposure to human bacteria, is a surge in immune-related diseases in developed nations which have largely disconnected from the natural environment. Further to this, it is as yet unknown how the increased sanitation procedures necessary to curb the spread of SAR-CoV-2 will impact indoor and urban environmental microbiology and the human microbiome as a whole.

Exposure to 'old friends' or missing microbes is potentially critical to the optimal health of the holobiont and future research will undoubtedly uncover a wealth of such microorganisms which could be artificially enriched in the environment or in our diets to ensure health-inducing interactions with the microbiota. Aside from probiotic-containing foods for which the research is ample in terms of health-inducing properties, microbe-based products that enrich the environment around us are becoming available on the market place (e.g. Enviro-Biotics™, described as a *Bacillus* ferment that purifies the air and cleans surfaces generating a healthy microbiome; https://www.betterindoors.com/products/enviro-biotics/).

Microbial-based cleaning products which contain microbes as the active ingredients are gaining popularity as alternatives to chemical-based cleaning products for both domestic and commercial settings (Arvanitakis

et al., 2018). The active microorganisms may metabolize/degrade undesirable compounds but also outcompete undesirable microorganisms on surfaces (Spök *et al*., 2018; Horve *et al*., 2020). Future research in this field may even see the development of age/condition-specific environmental probiotics which could be used as aids in neonatal units in hospitals, for example, thus ensuring that newborns are given every opportunity to acquire an optimal microbiota or to help promote the lost microbial diversity observed in the elderly microbiota, especially in individuals in long-stay care facilities.

With regard to the outdoors, initiatives such as urban rewilding, MIGI and HUMI aim to increase our exposure to green biodiversity and hence enhance environmental-based, human-microbial interactions in urban settings. Indeed, environmental microorganisms can now be seen as providing an essential ecosystem service with a role in regulating mammalian immunity. However, the health of soil itself is imperative to the success of these initiatives and several recommendations have been proposed towards its prophylaxis and therapy where microbes and microbial biotechnology have a central role to play (Timmis and Ramos, 2021).

In terms of diet, evidence is pointing to the need for a recommended daily intake of safe, live microorganisms, analogous to that of dietary fibre, given the wealth of science supporting the role of such microorganisms in sustaining and improving health (Marco *et al*., 2020). However, more research is necessary to understand the microbial load and specific taxa within the food we consume and the impacts on our health through the gut microbiome.

The evidence presented here takes in the bacterial component given the wealth of data on this aspect of the microbiome. But growing research is linking other microbiome components including the phageome (Mills *et al*., 2020) and the mycobiome (Chin *et al*., 2020) to human health and disease. Indeed, 12 months after faecal microbiota transplantation, recipient phageomes resemble that of donor phageomes revealing the long-term impact of bacteriophages on gut microbial dynamics (Draper *et al*., 2018). Thus, moving forward, we will have to consider all microorganisms to which our microbiomes are exposed. We will need to decipher the exact nature of collisions and interactions (how the host microbiome specifically reacts in terms of its composition and functionality and the host itself in terms of immunological and neural responses) along with the vectors which mediate such. Information of this nature will strengthen the evidence that our microbiomes may be influencing the health not only of us but of those close to us. It is also imperative to assess if particular microbiome structures (e.g. antibiotic-denuded microbiomes) are more susceptible or resistant to interactions, and the consequences of such for our health. Another important consideration for colliding and interacting microbiomes and microbial communities is the exchange of genetic information, particularly when such genetic information poses a health risk to the host as in the case of antimicrobial resistance, a topic mentioned in the section 'Microbiome collisions and interactions with food microbial communities'. A recent systematic review of the literature highlighted the risk for travel-related acquisition of antimicrobial resistant microbes, the majority of which were enteric (Bokhary *et al*., 2021). Antimicrobial resistant enteric bacteria, as colonizers or pathogens, can transfer resistance genes to other bacteria in the gut (Launay *et al*., 2006). Thus, international travel is now recognized as a vector for global antimicrobial resistance transmission (Bokhary *et al*., 2021).

In time, we envisage that in depth knowledge of colliding and interacting microbiomes and microbial communities may prove invaluable in assessing our impact on the health of other humans but also other species on the planet – by assessing how our microbiomes may be influencing the microbiomes of other living 'things' and consequently their health. Knowledge of this nature should ensure a cycle of symbiotic return to each host in terms of health benefit.

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