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Review

The impact of human activities and lifestyles on the interlinked microbiota and health of humans and of ecosystems

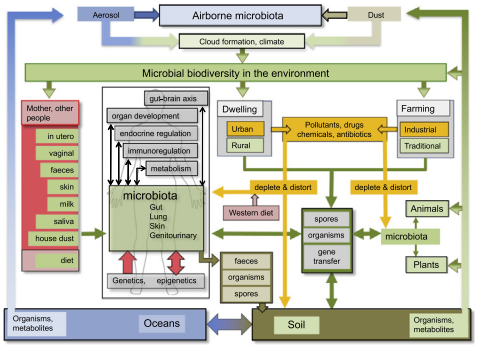
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HIGHLIGHTS

- Microbiotas of humans, animals and plants influence the hosts' physiology and health.
- Microbe biodiversity is linked to health and to transgenerational benefit to progeny.
- Humans, animals, plants and the environment continuously exchange microbiota.
- Microbiotas can be damaged by antibiotics, agri/industrial chemicals, and lifestyle.
- The *lifestyle-microbiota-human health* nexus must influence societal decision making.

GRAPHICAL ABSTRACT



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ABSTRACT

Plants, animals and humans, are colonized by microorganisms (microbiota) and transiently exposed to countless others. The microbiota affects the development and function of essentially all organ systems, and contributes to adaptation and evolution, while protecting against pathogenic microorganisms and toxins. Genetics and lifestyle factors, including diet, antibiotics and other drugs, and exposure to the natural environment, affect the composition of the microbiota, which influences host health through modulation of interrelated physiological systems. These include immune system development and regulation, metabolic and endocrine pathways, brain function

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and epigenetic modification of the genome. Importantly, parental microbiotas have transgenerational impacts on the health of progeny.

Humans, animals and plants share similar relationships with microbes. Research paradigms from humans and other mammals, amphibians, insects, planktonic crustaceans and plants demonstrate the influence of environmental microbial ecosystems on the microbiota and health of organisms, and indicate links between environmental and internal microbial diversity and good health. Therefore, overlapping compositions, and interconnected roles of microbes in human, animal and plant health should be considered within the broader context of terrestrial and aquatic microbial ecosystems that are challenged by the human lifestyle and by agricultural and industrial activities.

Here, we propose research priorities and organizational, educational and administrative measures that will help to identify safe microbe-associated health-promoting modalities and practices. In the spirit of an expanding version of "One health" that includes environmental health and its relation to human cultures and habits (EcoHealth), we urge that the *lifestyle-microbiota-human health nexus* be taken into account in societal decision making.

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1. Introduction

Animals and plants harbor very diverse and abundant microbial communities that provide specific functions and traits. These communities are called microbiota when referring to the ecological community of microorganisms within a defined environment, or microbiome when referring to the collective genomes of all microorganisms from a given environmental niche. A recent workshop (Workshop Session, 2016b) discussed correlations between disturbed gut microbiota (dysbiosis) and chronic pathologies (non-communicable diseases – NCDs) including allergies (Fujimura and Lynch, 2015; Hua et al., 2016), autoimmunity (Chen et al., 2016), gastrointestinal disorders (Cenit et al., 2015), obesity, diabetes (Cani et al., 2014; de Goffau et al., 2013; Knip and Siljander, 2016), and other metabolic and cardiovascular disorders (Tang and Hazen, 2014), cancer (Poutahidis et al., 2015), and central nervous system dysfunctions such as learning and memory impairment,

anxiety, stress, depression (Dinan and Cryan, 2013) and autism (Vuong and Hsiao, 2017). A link with the microbiota has also been suggested for neurodegenerative disorders like Alzheimer's disease (Fox et al., 2013).

Research in this area has focused mostly on the interactions with host health of the intestinal microbiota. This is viewed as a paradigm for exploring the whole body microbiota, including that of skin (Fyhrquist et al., 2014), respiratory (Yu et al., 2015), and reproductive systems and upper gastrointestinal tract. It is recognized that inflammation, whether chronic or acute, is a common pathogenetic link between the disturbed gut microbiota and the NCDs mentioned above. For example, this is true for asthma, linked to the impact of the microbiota on the respiratory tract (Rook et al., 2004), and for arthritis (Scher et al., 2013), and for inflammation in the pancreas leading to Type 1 diabetes (Knip and Siljander, 2016). This suggests that the immune system has a central role in the axis connecting the gut microbiota to tissue damage located distant from the gut (Rao et al., 2007; Round and Mazmanian, 2009), but most, perhaps all physiological systems are involved, as discussed below.

It should be noted that defining a general "health-promoting" versus "disease-predisposing" gut microbiota is difficult, since it may depend on various factors such as age, geographical situation, diet, and genetics. Moreover, the resulting metabolome might be more important than the underlying community structure (Maurice et al., 2013; O'Keefe et al., 2015). More needs to be learnt about the normal variability of the human intestinal microbiota and the factors that determine it. At present, a disturbed microbiota can only be defined by comparison with an average "normal" microbiota in a given population (Falony et al., 2016; Raes, 2016), and perhaps only at the level of the individual (Zeevi et al., 2015).

The *Environmental and internal microbiome* session of the workshop mentioned above aimed at opening a window on the microbiota in a OneHealth/EcoHealth perspective, leaning on their potential ecosystem services for human and environment health and on their potential disturbance by various factors (Fig. 1). The objective of this review (which expands the original workshop with additional authors and material) is to explore these issues in the broader context of the microbiotas of animals, plants, soil and the natural environment, with particular emphasis on the parallels between the compositions and functions of these different microbiotas, and the crucial links between these natural compartments. We also discuss the ways in which human activities are distorting these microbiotas and creating risks to human, animal and plant health. Finally, we suggest research priorities, and propose administrative and educational measures that can help to stop this damage to our microbial environment.

2. Microbiota and health

2.1. Lessons learnt from studies on humans and animals

Germ free mouse models have demonstrated that microbiota can play a role in the prevention or causation of several of the pathologies mentioned above (Noval Rivas et al., 2013; Turnbaugh et al., 2006; Wu et al., 2010) and (workshop presentations by Clarke, 2016; Dao, 2016; Plovier, 2016; Poutahidis, 2016). Similarly, introducing certain bacterial species or cocktails into the gut microbiota of mouse models can improve their health or make sensitive strains more resistant to disease than controls (Bravo et al., 2011; Forsythe et al., 2007; Poutahidis et al., 2013b). Thirdly, when germ free mice are colonized with the

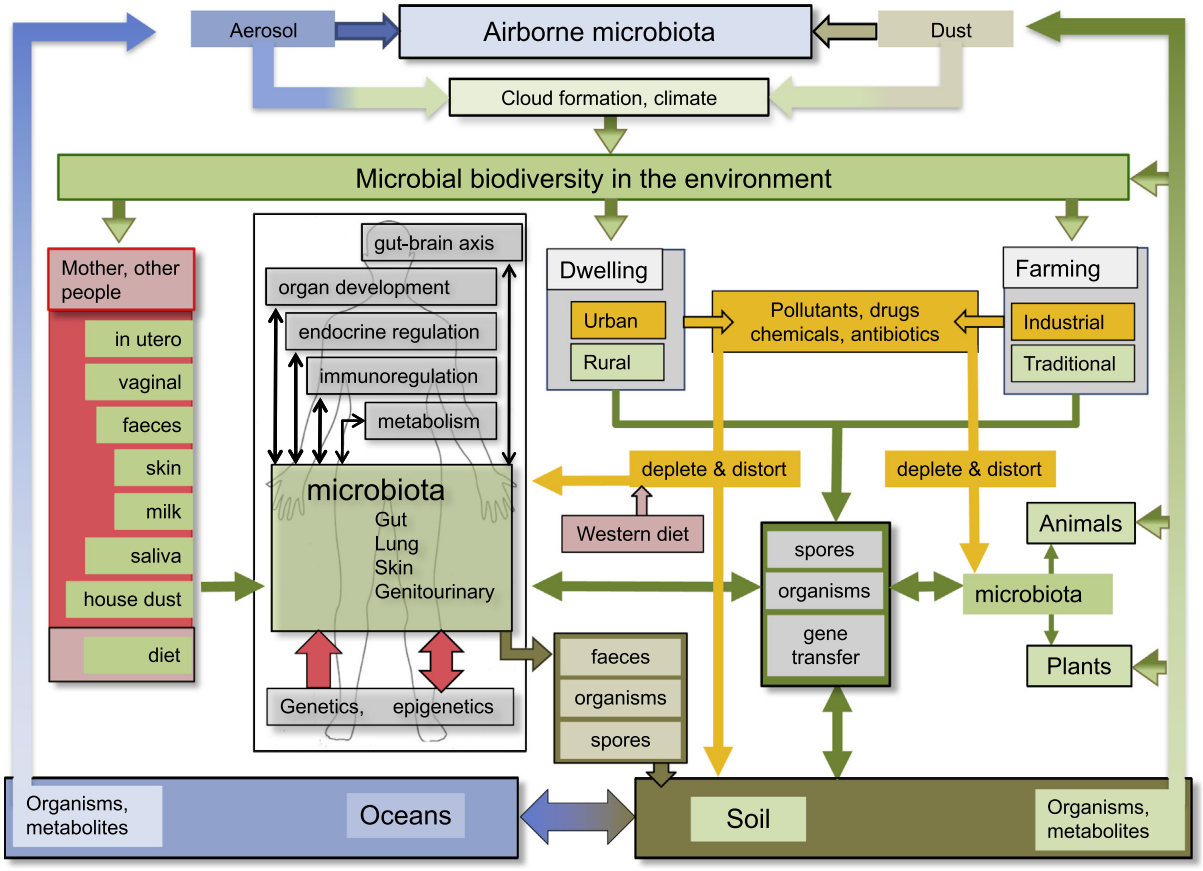


Fig. 1. A summary of the main issues. The microbial world influences human wellbeing directly via effects on human development, physiology and health, and indirectly via effects on food quality, climate and the environment. Human activities are depleting and distorting the overlapping microbiota in all these domains. This has a substantial effect on the genetic and community composition of the microbiota. The consequences for human health are likely to be severe. Already we are seeing increases in non-communicable inflammatory diseases and metabolic disorders that are at least partly attributable to distortions of human or environmental microbiota.

dysbiotic microbiota of diseased individuals of different species, including humans, they recapitulate features of the donor disease (Collins, 2016; Ridaura et al., 2013; Zheng et al., 2016) and (workshop presentations by Clarke, 2016; Dao, 2016; Plovier, 2016; Poutahidis, 2016).

However, data from experiments on animals cannot easily be translated to humans (Kelly et al., 2016; Nguyen et al., 2015). Some microbial strains or cocktails were shown to have different effects in different animal species. The parameters that control the microbiota of each individual are complex and not fully understood. Under different laboratory and animal housing conditions, the replication of supposedly similar experiments do not always give the same results (Franklin and Ericsson, 2017).

Importantly, several specific bacterial strains of the species *Akkermansia muciniphila* (Dao et al., 2016; Derrien et al., 2017; Everard et al., 2013), *Bacteroides uniformis* (Gauffin Cano et al., 2012), *Lactobacillus reuteri* (Poutahidis et al., 2013a), *L. rhamnosus*, and *L. johnsonii*, among others, have been associated with positive health effects in animals and to a lesser extent in humans (Agustina et al., 2013; Agustina et al., 2012) (also discussed in workshop presentations by Clarke, 2016; Dao, 2016; Plovier, 2016; Poutahidis, 2016). Therapeutic potential of manipulating the microbiota is discussed in a later section.

2.2. Mechanisms of health benefits

The precise mechanisms that enable a beneficial gut microbiota to prevent NCDs remain to be fully characterized, although some important aspects of this phenomenon have been elucidated, and common patterns of action start to be understood.

2.2.1. Regulation of immune and endocrine systems

Several metabolites and structural components of a healthy microbiota behave as biologically active molecules that interact with physiological pathways of the host (workshop presentations by Clarke, 2016; Dao, 2016; Plovier, 2016; Poutahidis, 2016), to regulate organ development (including the brain) (Cryan and Dinan, 2012; McFall-Ngai et al., 2013), metabolism (Canfora et al., 2015), and immunoregulation (Tan et al., 2016; Zeng and Chi, 2015). These active bacterial molecules include short-chain fatty acids (SCFA) and metabolites of tyrosine or tryptophan that play important roles as modulators of both immune and neuroendocrine systems. They have been shown to upregulate regulatory T lymphocytes, downregulate pro-inflammatory cytokine production, and induce hormonal secretion (serotonin, oxytocin, indole derivatives - exerting anti-inflammatory effect on the CNS - T4 hormone, testosterone) in relation to anti-inflammatory effects (Erdman and Poutahidis, 2016; Poutahidis et al., 2013a, 2014; Varian et al., 2016; Yano et al., 2015). Overall, those microbial products activate interrelated immune, endocrine and central nervous system pathways that counteract NCDs (Carabotti et al., 2015; Marsland, 2016; Moloney et al., 2014). Importantly, keeping a healthy immune, metabolic and neuroendocrine profile may be important for preventing cancer. Indeed, it is strongly suggested that interactions between immune system function, hormones, and psychosomatic factors could determine whether pre-neoplastic lesions progress towards cancer (Erdman and Poutahidis, 2015; Poutahidis and Erdman, 2016). Moreover, sex steroids are conjugated in the liver, and then secreted into the gut with the bile. The gut microbiota then deconjugates these steroids, which allows them to be re-absorbed (conjugated forms are mostly lost in the feces). But the microbiota also modifies the sex steroids so that the profile of metabolites that is reabsorbed depends on the nature of the microbiota. Among other potential effects, it is suggested that this variable metabolite profile modulates cancer risk in post-menopausal women (Adlercreutz et al., 1976; Fuhrman et al., 2014).

Maintenance of an intact gut barrier function may also be crucial for reducing disease risk. Optimal gut barrier function depends on several components such as secretory IgA and selective paracellular permeability. A recent study focused on inducers of gut mucosal IgA production, and its levels in relation to the transition from breast feeding to more diverse diets (Planer et al., 2016). Disruption of the gut barrier leading to increased intestinal permeability facilitates the translocation of immunogenic (bacterial) components beyond the gut. This is linked to various NCDs and has been specifically suggested to trigger systemic inflammation and favor distal cancer development (Erdman and Poutahidis, 2015).

Heat-killed forms of some microbes retain their ability to induce positive effects on our physiology through interaction with the immune system and anti-inflammatory effects (Reber et al., 2016; Ruiz et al., 2014; Varian et al., 2017). Therefore, structural bacterial components with health-promoting effects (called postbiotics) could hold promise as they can be present in regimens containing non-viable bacterial cells (Adams, 2010; Plovier et al., 2017).

This phenomenon is not restricted to the gastro-intestinal tract. Interestingly, living bacteria or bacterial components that we breathe in the environment/green spaces and inhale into our upper respiratory tract have been shown to have anti-inflammatory effects similar to those of living beneficial gut microbes (Schuijs et al., 2015). The lipopolysaccharides (LPS) from Gram-negative bacterial membranes may have anti-inflammatory effects on lung epithelium by reducing the production of inflammatory cytokines involved in allergy. This occurs after repeated low dose exposure, via the mechanisms of "endotoxin tolerance". These LPS components also have similar effects on the intestinal epithelium. But interestingly, the molecular structure of LPS varies between bacterial strains and this variation can modify the immunomodulatory effect. This can explain a higher incidence of auto-immune diseases in different countries/regions, due to prevalent exposure to different bacterial strains and their variant LPS (Vatanen et al., 2016). Other bacterial components or metabolites modulate the immune system via the arylhydrocarbon receptor (Zelante et al., 2014), respiratory neuroendocrine cells (Branchfield et al., 2016), toll-like receptors and other cellular sensory systems (Moore, 2015).

2.2.2. Educating immune system memory

The previous paragraphs concentrate on the immunoregulatory signals derived from microbial exposures. However, as far as the immune system is concerned, exposure to a wide diversity of microorganisms does more than merely set up immunoregulatory circuits. The immune system at birth resembles a computer with hardware and software, but almost no data. The necessary data are provided mostly by microorganisms that increase the repertoire of memory T lymphocytes. But because all life forms ultimately share many structures and genes, these memory cells, even when driven by harmless environmental species, can include cells that recognize pathogens. For example, HIV-1-specific $CD4^+$ T cells are abundant in the blood of seronegative donors. These cells have the typical properties of memory T cells, and were shown to cross-react with other organisms from the environment (Su et al., 2013). Thus, in addition to priming immunoregulatory circuits, exposure to microbial biodiversity provides crucial data that builds up the antigenic repertoire of the immune system. This repertoire is clearly relevant to eventual attack responses against pathogens, but also contributes to the development of a repertoire of tolerated bacteria, foods and environmental molecules. Lack of priming through external antigens could compromise this part of development and contribute to auto-immune and allergic diseases.

Ensuring long term contributions of the various microbiota (gut, skin, month, vaginal, respiratory tract) to good health may require more than transient enrichment with specific microbes, metabolites or components. Good health may require continuous cross-talk between the host and the microbiota in a symbiotic relationship (Everard et al., 2013), which needs to be characterized better. This includes a better understanding of the ecology of the microbiota in our whole body.

2.2.3. Metabolism of chemicals, including toxic environmental pollutants

Gut microorganisms have been known for decades to be involved in the biotransformation of xenobiotics. Approximately 1500 biocatalytic reactions on environmental pollutants have been listed. In a recent review analyzing various studies using isolated bacteria, or fecal/caecal suspensions from humans or animals, it was noted that human or rat feces could detoxify PAHs (polycyclic aromatic hydrocarbons), nitro- and nitrated PAHs, some pesticides, PCBs (polychlorobyphenyls), and azo-dyes (Claus et al., 2016). These compounds are known to have carcinogenic, and/or mutagenic properties, and exposure to some of them (like PCBs) has also been associated with impairment of the immune system, metabolic disruption, delayed neurodevelopment and adverse reproductive outcomes. Bioactivation of some toxic compounds (in particular some benzene derivatives) by intestinal microbiota was also observed. In conclusion, the gut microbiota is potentially a major player in the toxicity of environmental pollutants (Claus et al., 2016).

2.2.4. Microbial biodiversity

The bulk of research data already suggest that a microbiota with a high level of biodiversity is generally linked to good health, especially for preventing NCDs (Cotillard et al., 2013; Ege et al., 2011; Haahtela et al., 2015; Le Chatelier et al., 2013). This is consistent with the so-called "biodiversity hypothesis" or "old friends" hypothesis (Rook et al., 2004; von Hertzen et al., 2011), and (workshop presentations by Dao, 2016; Furman, 2016; Ruokolainen, 2016). Some of the microbes met by man in early times evolved symbiotically or commensally with us and are considered as useful rather than pathogenic (Guarner et al., 2006; Rook, 2013; von Hertzen et al., 2011). By contrast, considerable environmental disturbance, such as the Neolithic agricultural revolution, may have favored the emergence of microbial strains that are more likely to predispose to or cause disease. It has been demonstrated that the fecal microbiota of children living as humans at the birth of agriculture is significantly different from the microbiota of European children with modern food and lifestyle (De Filippo et al., 2010). Still more significant perturbations of the relationship between humans and nature happened in the last centuries with urbanization, development of very large communities, intensive agricultural systems, excavating industries and other landscape disturbing works like large dams, and fast travel. This drives microbial evolution favorable for the appearance of pathogenic strains (Workshop Session, 2016c) and has also considerably changed the exposure of human beings to "ancient" microbiota (Daszak et al., 2001; Harper and Armelagos, 2010; Karesh et al., 2012). Whether the reduced microbial exposures linked to modern life conditions contribute to increased susceptibility to inflammatory diseases is a hypothesis that is currently being explored, and is discussed further below.

3. The composition of the human microbiota, and impacts on health: genetics vs lifestyle and lifecycle

While data exist on other human microbiota, in particular those of the skin and respiratory tract, most studies have concentrated on the gut. The adult human gut microbiota is dominated by the phyla *Firmicutes* and *Bacteroidetes* (~90% of total population), followed by members of the *Proteobacteria* and *Actinobacteria*, which are much less abundant (<1–5%). The phylum *Bacteroidetes* contains the well-known genera *Bacteroides* and *Prevotella*. *Firmicutes* constitute the largest bacterial phylum, which contains >200 genera, including clostridial clusters and *Ruminococcus*. *Proteobacteria* are facultative anaerobic bacteria that include the well-known *Enterobacteriaceae* family and may represent only ~0.1% of the total population. The phylum *Actinobacteria* includes the genus *Bifidobacterium* and their abundance varies greatly (from 90 to 2%) depending on age and diet (Gerritsen et al., 2011). In some populations *Actinobacteria* are increased in obese individuals (Castro-Penalonga et al., 2017). In an attempt to classify human subjects according to their microbiota, the concept of enterotypes was developed consisting of three different groups according to the dominant genera: *Bacteroides*, *Prevotella*, and *Ruminococcus*, though it is not clear whether it is more realistic to think in terms of discrete enterotypes or of continuous spectra of microbial composition (Cani and Everard, 2016; Knights et al., 2014).

3.1. Genetics and the human microbiota composition

The relative contributions of genetics, environment, and lifestyle factors, to the composition of our gut microbiota is far from fully understood (Spor et al., 2011). Although diet has an obvious effect (Blanton et al., 2016; David et al., 2014; De Filippo et al., 2010; Ridaura et al., 2013), host genetics and interpersonal variation also have a profound impact (Dabrowska and Witkiewicz, 2016; Goodrich et al., 2016; Goodrich et al., 2014; Lahti et al., 2014; Olivares et al., 2015; Org et al., 2015). Thus genetics, diet, environment and the microbiota interact. The individual's gut microbiota is partly determined by genetics and seems to influence the effectiveness of dietary intervention to lose weight (Nadal et al., 2009). Work is in progress to unravel the respective roles of genetics, birth mode and early feeding in the development of gut/immune system/microbiota relationships.

3.2. Diet and the composition of human microbiota

Many studies have shown that dietary habits modulate the composition of the gut microbiota but effects vary depending on the type of dietary change, and whether long- or short-term dietary patterns are considered (Benítez-Páez et al., 2016; Portune et al., 2016). For example, the relative ratio between these so-called "enterotypes" has been shown to be broadly affected by long-term dietary habits but not by short-term intervention (Wu et al., 2011). However, there are many examples showing that different dietary habits and patterns (e.g. vegetable rich diets, in particular containing fiber, vs. diets rich in animal products, mainly meat) as well as short-term dietary interventions, lead to significant compositional and functional differences in the gut microbiota (Falony et al., 2016; presentation by Raes, 2016). The different bacterial populations colonizing the human gut are not susceptible to changes in the diet to the same degree. Depending on the age of the host and the nature of its initial microbiota composition, some groups of bacteria seem to remain unaffected by dietary change (presumably those that can use a wide array of nutritional resources and are flexible enough to adapt and thrive irrespective of host dietary constituents). Consumption of ultraprocessed foods (e.g. preserved meats, refined grains, hydrogenated oils) encouraged by the media and advertising, is linked with dietary patterns, particularly the Western-style diet, that are associated with lower microbial diversity and increased chronic disease risks (Broussard and Devkota, 2016; Mozaffarian, 2016).

3.3. Microbiota and antibiotics

In addition to food, any absorbed substances, including pharmaceutical products such as metformin used to treat type 2 diabetes, have an obvious impact on gut microbiota (Forslund et al., 2015). Studies on human cohorts show the influence of treatments with laxatives, hormones and immunosuppressive compounds on the composition of the gut microbiota (Falony et al., 2016), and above all a major influence of antibiotics (Jernberg et al., 2010; Korpela et al., 2016).

Antibiotics not only reach pathogenic bacteria but also impact our beneficial microbiota, leading to perturbation of its composition and biodiversity, and often to an increase in Proteobacteria because of the high content of antimicrobial resistance genes in this phylum. The disruption of our microbiota caused by antibiotics favors the development of NCDs characteristic of dysbiosis (Francino, 2015; Gensollen et al., 2016). The risk of obesity, atopic disease, asthma, Crohn's disease, type 2 diabetes, auto-immune diseases (like type 1 diabetes) have been shown, in human epidemiological studies, to be positively correlated

with antibiotic use, particularly if absorbed during early life (reviewed in Gensollen et al., 2016; Trasande et al., 2013). The microbiota of infants who were not treated by antibiotics but whose mothers received antibiotics before delivery showed the same alterations as infants treated by antibiotics, with consequences in later life (Tanaka et al., 2009). An important aspect of this problem is the fact that doctors are often forced by anxious parents to provide antibiotics for which there is no justification. This situation is exacerbated in countries where antibiotics are available to the public without a prescription. This misuse is harmful to the children, and antibiotic resistance is reaching a crisis point (Van Puyvelde et al., 2017).

The organisms depleted by antibiotics include microbes that protect us against infectious pathogens or parasites. As a consequence of the substantial loss of gut microbiota biodiversity caused by antibiotics, susceptibility to opportunistic pathogenic infections can increase. This is confirmed in antibiotic-associated diarrheas due to nosocomial pathogens, like *Staphylococcus aureus* and *Clostridium difficile* inducing potentially lethal colitis. Risk of sepsis has also been related in premature infants to the length of treatment with broad spectrum antibiotics and the consequent altered gut microbiota (Madan et al., 2012).

This reveals another aspect of the harmful effect of antibiotics. Those defensive microbes that are eliminated by antibiotics could be considered as useful alternatives to antibiotics (see section below: Microbiota and current medical intervention) in a period of disease emergence or re-emergence (see session on zoonotic diseases of the workshop) and when resistance to the classical antibiotics is increasing.

Those defensive microbes act through mechanisms that it will be important to understand if we want to exploit them to modulate our microbiota and use them as alternatives to antibiotics. They can act through direct interaction with the pathogen/parasite (by production of compounds that are toxic to the pathogen, or killing or parasitising the pathogen, or by competing for host resources) or through host-mediated effects (eliciting an efficient immune response of the host towards the pathogen, or enhancing the host tolerance towards the pathogen) (Ford et al., 2016; Ford and King, 2016). Those different mechanisms of action imply different patterns of adaptation and co-evolution between host, defensive microbe and pathogen.

Antibiotics also have the disadvantage that they enrich our gut microbiota in antibiotic resistance genes (ARGs). The gut has been shown to be a very favorable site for horizontal gene transfer, including between different bacterial species (Liu et al., 2012; Smillie et al., 2011). This transfer may include ARGs and has been shown to be stimulated by low concentrations of antibiotics (Whittle et al., 2002). Infants may inherit ARGs from their mother even before birth (Francino, 2015). The abundance of ARGs in our intestine is directly correlated with the time that the relevant antibiotics have been on the market and approved for human and animal use (Francino, 2015).

Spread of the antibiotic resistance genes often used to select transgenic plants is of particular concern, and has been documented (Turrini et al., 2015). These genes could be transferred from GM plants to bacteria in the rhizosphere or in the intestine. Both environments are hot spots for horizontal gene transfer (Liu et al., 2012; Smillie et al., 2011; Turrini et al., 2015). WHO has drawn attention to this problem (WHO, 1993), and asked for transition towards other existing marker technologies (reviewed in Breyer et al., 2014; Turrini et al., 2015), and emphasized this subsequently in a joint report with the Food and Agriculture Organization (FAO/WHO, 2000). After repeated discussions and some internal disagreements, the European Food Safety Authority recommended that only genes coding for resistance against antibiotics supposedly not used any more in human and veterinary medicine in the European Union should be allowed when making GM seeds and plants in the EU (European Food Safety Authority, 2009). The European Commission finally stated that "*the applicant shall aim to develop GMOs without the use of antibiotic resistance marker genes*" since "*it is now possible to develop GMOs without the use of antibiotic resistance marker genes*" (European Commission, 2013). Horizontal gene transfers, in particular between different phyla, are often considered as rare events, but few if any studies have analyzed the potential cumulative impacts of such events, and a recent report has drawn attention to the potential importance of the spread of such resistance genes in the environment (Midtvedt, 2014).

Currently the ecological functions and services that are involved in the regulation of resistance to antibiotics are poorly understood ((Workshop Session, 2016a), and see further sections of this review: "Microbiota, adaptation and evolution: examples in animal species", and "Influence of chemical substances on the microbiota: still a lot to explore").

In addition to protecting us against pathogenic microorganisms, our gut microbiota can metabolize environmental chemical pollutants, as outlined above. By disrupting the equilibrium of bacteria in our guts, antibiotics may alter the ability of our microbiota to metabolize environmental chemicals.

3.4. Contact with the natural environment and its effects on the microbiota

Residential proximity to the natural environment has striking effects on overall health (Maas et al., 2006; Mitchell and Popham, 2008). In the past, it was assumed that these benefits were attributable mostly to relaxation, exposure to sun, and exercise, but while these factors do undoubtedly enhance health, it is now clear that exposure to microbial biodiversity from the natural environment is also important (reviewed in Rook, 2013).

Living in proximity to the natural environment affects the composition of the skin microbiota (Hanski et al., 2012; Ruokolainen et al., 2017; Ruokolainen et al., 2015), and increases exposure to microbial biodiversity via the airways (Moore, 2015; Rook, 2013; Schuijs et al., 2015). Unfortunately, no complete and conclusive studies yet compare the gut microbiota of people living close and far away from green areas in big cities but work is in progress (Mhuireach et al., 2016). However, studies in several countries show a large difference in gut microbiota composition between people living in urban and in rural areas (workshop presentation by Raes, 2016; Winglee et al., 2017). Interestingly, physical exercise, which is more prevalent in green environments, has been added to the list of factors reported to modify the gut microbiota (Cook et al., 2016). Moreover, characterizing the human fecal microbiota of long-gone people on archeological sites revealed microbial communities similar to those of present–day residents of remote rural areas (Tito et al., 2012).

The microbiota of buildings containing plants is richer in diversity of microbes than that of buildings deprived of plants (Mahnert et al., 2015). The impact on our internal microbiota and health however remains to be studied (Berg et al., 2014b, c). The microbiota of a building is also influenced by the construction materials used and can influence our internal microbiota and thus health (many studies in USA; very few in the EU) (Hoisington et al., 2015; Levin et al., 2015; NESCent Working Group on the Evolutionary Biology of the Built Environment et al., 2015). Moreover, modern biocide-treated building materials, concrete and plastic, when damp and degrading, can become colonized with unusual strains of bacteria and fungi producing secondary metabolites that are toxic to humans. Traditional buildings that used untreated timber, dung, mud and thatch contained strains from the natural environment similar to those with which humans co-evolved (Sahlberg et al., 2010).

3.5. Epigenetic effects of the microbiota

Interestingly, diet, but also other factors, affect more than just the health of the individual concerned. Recent evidence suggests that diet may also influence the health of the progeny. A well substantiated transgenerational hypothesis is emerging. Epigenetic effects of the microbiota on the host genome have been described, and might explain some transgenerational inheritance of the impacts of the microbiota

(Alenghat, 2015; Cortese et al., 2016; Majnik and Lane, 2015; Neu, 2016). There seems to be a *critical window* during early mammalian development, including the in utero period, during which environmental factors can cause epigenetic modulation of the genome. The relevant factors include the maternal diet and antibiotic use (Cox et al., 2014; Heard and Martienssen, 2014; Rando and Simmons, 2015; Supic et al., 2013; Vickers, 2014), possibly acting through the intermediary of the microbiota (Kumar et al., 2014; Paul et al., 2015). This can have long-lasting consequences on health, or predispose to NCDs. Thus the data suggest that westernized dietary habits of the mother during pregnancy shape disease susceptibility profiles of her descendants via epigenetic mechanisms (de Assis et al., 2012).

Recent studies on an animal model provide direct evidence that the gut microbiota is indeed a key mediator of diet-induced transgenerational disease predisposition (workshop presentation by Poutahidis, 2016). In mice, diet-induced maternal gut dysbiosis not only transcends the local boundaries of GI tract, but may undermine the health of the progeny as well (Poutahidis et al., 2015). In that study, mice with a Western-type diet and obesity-related gut microbiota had descendants over two generations which, although fed normal diets, developed lung and liver cancers, and lymphomas at particularly high rates, coexisting with an increased systemic inflammatory tone. But these adverse health effects in descendant mice, including high cancer incidence, were prevented by daily consumption of the probiotic bacterium *Lactobacillus reuteri* (Poutahidis et al., 2015).

3.6. The microbiota in early life

Against this background of genetic and epigenetic determinants, the human microbiota seems to be rather flexible during the early life period. Until the age of three years it remains sensitive to various influences that can impact its composition and cause long-term effects on our physiology (Clemente et al., 2012; Dogra et al., 2015; Koenig et al., 2011; Rautava et al., 2012).

Retrospective epidemiological studies in humans indicate that the microbiota acquired during the perinatal period and early infancy has important effects on the developing immune system and on its systemic role in health or disease later in life (Gensollen et al., 2016). Similarly, the early airway microbiota may prime the developing pulmonary immune system, and dysbiosis in its development may set the stage for subsequent lung diseases (Lal et al., 2016). Notably, there are less allergy symptoms in children who grow up in natural environments with rich microbial diversity than in children in urban areas deprived of microbes with which humans evolved (von Mutius and Vercelli, 2010). The ability of exposure to the natural environment to reduce the risk of allergy during childhood has been corroborated in piglets (Lewis et al., 2012). Such a long term effect on the immune system is particularly important given that this system is a major communication link between the external environment and internal mammalian body, including the brain (Rook et al., 2014b). In the holistic integrative approach of OneHealth/EcoHealth which considers human and animal health within the broader context of their environment, one way of communication between the internal body and the external environment is via environmental microbial signaling to the immune system.

Similarly, natural childbirth (vaginal delivery) (Jakobsson et al., 2014; Kristensen and Henriksen, 2016) and breast feeding (Latuga et al., 2014), help to transmit microbes (or factors stimulating the growth of some bacterial strains) from mother to child (Charbonneau et al., 2016; Mueller et al., 2015). All this is consistent with the fact that germ-free animals are sensitive to the various pathologies mentioned above that are mediated by immune system dysfunction. Animal data show that the maternal microbiota has effects on the development of the fetal immune system, perhaps even in utero (Hornef and Penders, 2017; Romano-Keeler and Weitkamp, 2015). The development of the infant small intestine is also dependent on bacterial colonization that contributes greatly to its future normal function (Yu et al., 2016).

3.7. The microbiota in later life

Later in life, however, during the transition to adolescence and adulthood, the link between microbes dominating the microbiota in early infancy and health status is still less clear but knowledge is progressing (Falony et al., 2016).

To explain some apparent inconsistent data on the impacts in later life of the microbiota met in early infancy, some authors suggest that 'old friends' microbes have a crucial effect on the initial development of our immune system in early infancy or even before birth, and that the impact of these effects lasts throughout life. But the training of the immune system may need to be regularly renewed in later life by new exposures to "good" microbes (Rook et al., 2014a). Lack of this regular training may lead to impaired immune tolerance and dysregulation of the immune system that play an essential role in the genesis of non-communicable diseases (Rook et al., 2014a). Even diseases of the central nervous system like Alzheimer's might be linked to a "lack of training" of the immune system by disconnection from the natural environment, including its microbes (Fox et al., 2013).

The gut microbiota in human adults is more resilient than in early life and seems largely defined by its progressive acquisition and stabilization through long term dietary habits and our general living environment (Falony et al., 2016; workshop presentation by Raes, 2016; Wu et al., 2016).

Recent data indicate that even in adult animals gut microbial composition mediates epigenetic programming in multiple host tissues in a diet-dependent manner. In a mouse model, a Western-type diet prevents many microbiota-dependent chromatin changes that occur on a polysaccharide-rich diet. Concomitantly, a Western-type diet limits microbial SCFA production. Supplementation of germ-free mice with SCFA (known to play an important role in immunity) recapitulates chromatin-modification states associated with bacterial colonization (Krautkramer et al., 2016). These observations may help to explain the influence of diet in later life on microbial impacts acquired in early life. For example, in another mouse model, the composition of the gut microbiota was shown to be impacted mainly by early life history and genetics and less influenced by dietary changes, whereas the gut metabolome was mostly shaped by diet with specific non-dietary metabolites of microbial origin (Snijders et al., 2016). Loss of biodiversity in the gut microbiota in the elderly is associated with systemic markers of inflammation, and declining health (Claesson et al., 2012). Thus diet and our general environment and lifestyle can influence our microbiota and health throughout life, as discussed further in other sections.

4. Use of microbiota in clinical intervention

In recent years, microbiota research has attracted a lot of attention worldwide since it holds promise for counteracting pathologies that are an alarming burden in modern industrialized societies and that are also increasing rapidly in developing countries as they adopt western diets and urban lifestyles. More research, and especially clinical trials are needed to ensure the safety and efficacy of novel applications such as food products targeting the gut microbiota as disease prevention or therapy. As a pioneer in curative use of microbes, the technique of fecal microbiota transplantation (FMT) has emerged to counteract health problems due to intestinal dysbiosis (workshop presentation by Stephenne, 2016). This method attempts to replace harmful bacteria in the intestine of a patient with a more balanced "healthy" microbiota. The latter comes from a healthy donor without drug treatment and having a family history free of chronic disease, especially gut-microbiota associated. In Belgium, fecal transplantation is at present considered as a tissue transplantation following the advice of the national Superior Council of Health. The method has been used in many different countries and brings good results against diarrhea caused by overgrowth of multi-resistant *Clostridium difficile* usually resulting from multiple antibiotic treatment, that causes disturbed gut microbiota (Kachrimanidou

et al., 2016). A consensus report was published recently in order to establish guidelines of technical, regulatory, administrative and laboratory requirements for the implementation of fecal transplants for *C. difficile* infection (Cammarota et al., 2017). Convincing data for other therapeutic applications are currently lacking. Attempts to treat ulcerative colitis have only shown a beneficial effect in specific populations (yet to be determined). This technique provokes few side effects, and holds promise. But sound data from clinical trials are needed before considering the treatment of more intestinal diseases linked to dysbiosis, and perhaps even for treatment of psychological pathologies (Dinan and Cryan, 2013). It must be noted that the colonic microbiota, currently used in these transplantations, is not representative of the microbiota in all parts of the intestine. The precise results of the technique seem to be influenced by the biodiversity of the donor microbiota. More standardization is obviously needed to make this technique operational and safe. Cryo-preservation banks of fecal material should be constituted to improve the research in this field. Such banks would enable epidemiological studies and enhance both safety and efficacy. The characteristics of the microbiota in each sample could be linked to clinical results in the recipient. The strategy would also be improved if we could develop our capacity to grow the consortia of beneficial bacteria in laboratory conditions to ensure safety and reproducibility. A careful but not too complex regulation will be necessary to reduce the risks of "auto-medication" (Vandenplas et al., 2015).

5. Biodiversity and the plant and soil microbiota

Regarding the importance of microbial diversity, it is useful to draw parallels with knowledge gained from other microbial systems, including the plant microbiota and its interaction with the soil microbiota (Fig. 2) (workshop presentation by Berg, 2016). We also need to explore their links with human microbiota and health.

5.1. Biodiversity of the plant microbiota

In parallel to what is found in animals, the microbiota of plants depends on species, genotype and the environment, differs in various organs and tissues such as leaves, roots and fruits, and changes with age (Wagner et al., 2016). Interestingly, microbes present inside or on the surface of the seed have a key role in the development of plant microbiota (Barret et al., 2015), which is reminiscent of the role of perinatal microbiota exposures in animals.

5.1.1. Plant microbiota and plant health

The plant microbiota has been known to be one of the key determinants of plant health and productivity for more than a century (Hartmann et al., 2007). Briefly, its impact can be summarized as five key roles: (i) improving nutrient acquisition and growth, (ii) sustaining plant growth under biotic and/or abiotic stress, (iii) inducing resistance against pathogens, (iv) interacting with plant or human pathogens, and (v) interacting with other trophic levels like insects (Massart et al., 2015). Both gut and root bacteria contribute to host metabolism, produce similar bioactive compounds, such as vitamin B12, and compete with pathogens for successful colonization (Bakker et al., 2014). They both affect host gene expression and also adjust their own gene expression profiles according to the host's physiological and circadian rhythm (Leone et al., 2015; Thaiss et al., 2014). Dominant as well as minority bacterial population species in both mammalian gastrointestinal tracts and plant roots have been shown to have important symbiotic roles (Ramirez-Puebla et al., 2013). Interestingly, the microbiota of the plant root interacts with its soil microenvironment (rhizosphere) microorganisms to achieve symbiotic benefits (Berg and Smalla, 2009; Peiffer et al., 2013; Schlatter et al., 2014; Smalla et al., 2001). To what extent this phenomenon translates to the mammalian host-environmental interaction warrants further investigation (Fig. 2).

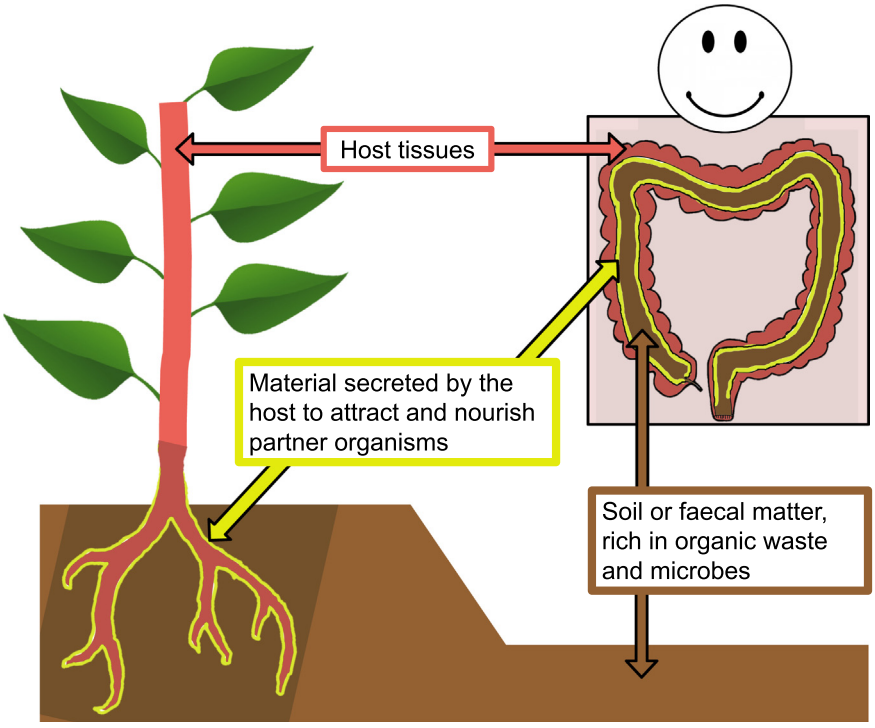


Fig. 2. Animals and plants have similar associations with microbiota. Plants have microbiota both within their tissues (endophytes) and on their surfaces (epiphytes). Some of the organisms associated with the roots (rhizosphere) are attracted and nourished by molecules secreted from the roots, and then take part in 2-way signaling and exchange of nutrients. This situation clearly parallels the organisms associated with the mucus layer in the colon, where the mucus nourishes the microbiota, which in turn provides nutrients and metabolic signals (e.g. short chain fatty acids) to the host.

All these parallels suggest that insights gained from research on plant microbiota may stimulate studies on animal microbiota and vice versa (Berg et al., 2015b; Mendes and Raaijmakers, 2015; Ramirez-Puebla et al., 2013).

5.1.2. Plant microbiota and human health

Moreover, it has been suggested that humans gain health benefits from internalizing plant microbiota either through food or through breathing (Berg et al., 2015a, 2014a, c; Moore, 2015), though this area is currently severely under-investigated.

5.2. Biodiversity of the soil microbiota

Soils harbor very abundant and dynamic microbiotas that are influenced by the physico-chemical properties of the soil, the climate, other trophic levels (plants, macrofauna), depositions (through air dust or water) and human management.

It has been suggested that plant diversity contributes to plant community resistance against pathogens by fostering beneficial bacterial communities in soils (Latz et al., 2012). This indirect soil feedback mechanism may contribute to the positive relationship between plant diversity and productivity. Microbial biodiversity ensures an equilibrium between various strains and their balanced complementary functions (workshop presentation by Berg, 2016; Berg et al., 2013). In this context, the excess proliferation of opportunistic pathogens might be prevented (Latz et al., 2016). Disease in plants is often associated with an unbalanced composition of the microbiota colonizing not only its organs and tissues but its soil environment as well (Berg et al., 2015b; Latz et al., 2016). This parallels the connections of animal and human disease with host and environmental microbiotas. Along these lines, biocontrol practices using bacterial inoculants to promote plant growth and health are equivalent to the use of probiotics for animal or human health. Biocontrol of plants through plant-probiotics, which is neither standardized nor easy to achieve, is currently under intense investigation (van der Heijden et al., 2016). Similarly, there are novel approaches based on molecules able to improve the direct or indirect effects of microbiota against plant pathogens. Some of these molecules could be considered as plant prebiotics (Massart et al., 2015).

5.2.1. Soil microbiota and human health; mycobacteria

It has been suggested that soil biodiversity is important for human health (Wall et al., 2015). As was pointed out in the section on the mechanisms of health benefits from microbiota, one crucial role is providing antigenic diversity that expands the repertoire of memory T lymphocytes. The mycobacteria are of particular interest in this context. Most studies of the microbiota fail entirely to report mycobacteria, despite the fact that all soil and many water supplies are enormously rich in members of this genus (Pontiroli et al., 2013). Moreover, we have known for decades that in rural environments most individuals show skin-test reactivity to reagents prepared from mycobacteria living in their geographical area (Fine et al., 2001). Thus, immunologically relevant exposure definitely occurs. This is not surprising, since it has also been known for decades that when mycobacteria are ingested they rapidly associate with gut epithelial cells, and translocate to Peyer's patches (Sangari et al., 1999). Recently, the failure of "omics" approaches to report the mycobacteria has been demonstrated by a study that used drastic methods to break down the tough mycobacterial cell wall. This approach revealed the presence of mycobacteria in the oropharynx of all donors investigated (Macovei et al., 2015). Therefore, mycobacteria will provide a substantial data input to the dendritic cells in the small bowel that sample gut contents (Schulz and Pabst, 2013). The mycobacteria paradigm is important in that regard. It is now clear that vaccination with Bacillus Calmette Guerin (BCG; a mycobacterium) provides health benefits that go far beyond some protection against tuberculosis (Kleinnijenhuis et al., 2015; Netea and van Crevel, 2014). BCG vaccination causes an increase in survival that is independent of tuberculosis. It is therefore possible that BCG vaccination is in some way compensating for mycobacterial exposures that would have been inevitable in human populations living close to the soil.

Interestingly, the mycobacteria paradigm may overlap with the edible plant endophytes hypothesis. Indeed, mycobacteria can be internalized by plants, and up to 10^4/g *M. avium* organisms were demonstrated inside plant tissues (Kaevska et al., 2014). This mycobacterial species is a well-known pathogen of animals and immunocompromised humans (Sangari et al., 1999). The importance of human immune system exposure to low doses of bacteria contained in edible plants, where adaptation to the plant environment might reduce virulence for humans, should be further investigated (workshop poster by Massart et al., 2016).

5.2.2. Soil microbiota and human health; spores

The modern built environment and air-conditioned buildings must also reduce our exposure to bacterial spores, and this issue is often neglected. Spores are remarkably resistant, and can remain viable for thousands, possibly millions of years (Nicholson, 2002). They are relevant in two contexts. First, about 1/3 of the organisms in the gut microbiota are spore-forming, and spores are readily demonstrable in human feces (Hong et al., 2009a). Human feces contain up to 10^4 spores/g while soil contains approximately 10^6 spores/g (Hong et al., 2009b). Wherever humans have lived, the natural environment is inevitably seeded with the spores of human gut-adapted bacterial strains. A recent study revealed that the spore-forming strains within the human microbiota are more diverse than non-spore-forming bacteria and show a higher species turnover or a greater shift in relative abundance over the course of a year (Browne et al., 2016). Therefore, it is possible that when a gut organism becomes extinct as a result of dietary inadequacy or antibiotic misuse (Sonnenburg et al., 2016), it can be "reinstalled" via spores from the environment.

Other spore-forming organisms from the environment might also be important despite not being definite components of the human microbiota. Spores in soil have tended to be studied by environmental microbiologists and ecologists, and the soil has been regarded as the natural habitat of the spore-forming organisms such as *Bacillus* spp., despite awareness of the fact that many of them can germinate and replicate in the intestinal tracts of insects and other animals (Nicholson, 2002). *Bacillus subtilis* strains were obtained from biopsies of human ileum and from fecal samples (Hong et al., 2009a). This organism is an important stimulus for development of the gut-associated lymphoid tissue (GALT) in rabbits and sporulation of live bacilli within the GALT was considered critical to this process (Rhee et al., 2004). At the very least, after germinating in the small bowel these organisms will provide data to the immune system in the ileum where dendritic cells sample gut contents, and where recently ingested organisms can constitute a significant proportion of the microbes present (Schulz and Pabst, 2013).

Interestingly, although Gram-negative organisms cannot produce spores, many of them have similar survival strategies (potent production of osmolytes, dormancy, phase variation etc.) that facilitate their persistence in the environment (Cernava et al., 2016). Thus it is possible, though not yet proven, that the environment, in addition to providing "reinstallation" of lost spore-forming organisms, can also act as a source of relevant Gram-negative components of the human microbiota.

5.3. Microbiota in agricultural systems and food production

Vegetables grown using agro-ecological approaches such as organic agriculture, carry a much larger microbial biodiversity (endophytes and epiphytes) than vegetables grown using current conventional agriculture (Fliessbach et al., 2007; Schmid et al., 2011). Whereas some experts fear this can also be a source of rotting and plant disease, others argue that a balanced natural microbial biodiversity prevents the proliferation of strains causing deleterious effects. Pathogen epidemics are indeed less frequent in wild areas with rich plant biodiversity and a richer

microbial biodiversity (Latz et al., 2012). Fermented food, being richer in terms of microbial biodiversity and useful microbe content, is an attractive "functional food" (Selhub et al., 2014). The hybridized strains of vegetables and crops tested so far, including lettuce, are drastically reduced in microbial biodiversity compared to their parent lines (Cardinale et al., 2015; Peiffer et al., 2013). This is probably not the result of the hybridization process itself. Rather it is the breeding and selection process that has a detrimental effect on the microbiota. The domestication of plants and animals (and humans) includes the domestication of the associated microbiota (Cardinale et al., 2015; Pérez-Jaramillo et al., 2016). One example of this man-made co-evolution is the fate of glucosinolates in Brassicaceae, which, due to their bitter taste, were drastically reduced by breeding. These compounds protect plants against pathogens (e.g. *Verticillium* in oilseed rape) and their metabolites have anti-cancer activities in humans (Ambrosone et al., 2004; Novio et al., 2016). The low glucosinolate content in modern *Brassica* cultivars has enhanced their susceptibility to plant pathogens, and we need to investigate whether this loss of glucosinolate has caused the depletion from human gut microbiota of bacteria with glucosinolate-degrading capacity.

Recent studies showed that moss spores and plant seeds also contain a core set of plant genotype-specific, beneficial endophytes, which are vertically transmitted from one generation to the other (Adam et al., 2016). These seed microbes were shown to have an impact on plant health and were strongly driven by domestication and breeding (Adam et al., 2016). Moreover, some plant phyla cannot germinate without their indigenous microbes, e.g. mosses or orchids. These novel insights suggest that seed endophytes can serve as sources for new targets for agricultural biologicals to translate the "back to the roots" concept that comprises the exploration of the microbiome of wild relatives of crop plant species for the identification of beneficial microbes that got lost during the domestication process and to unravel plant traits involved in microbiome assembly (Pérez-Jaramillo et al., 2016). Thus missing beneficial microbes can be reinstated from wild relatives.

The link between microbial biodiversity and food also has implications for food preservation strategies (Coelho et al., 2014; Melero et al., 2013). Certain microbes naturally protect food such as vegetables against rotting. However, during food storage, the microbiota profile changes (Cauchie et al., 2017; Kergourlay et al., 2015), and this capacity of preservation disappears. Adding "counter-rotting" bacterial strains to food could reduce a huge amount of food spoilage in the world, currently 25% of food production (workshop presentation by Taminiau, 2016). Trials are promising, but the impact on the host microbiota is not known and should therefore be assessed. Moreover, longitudinal impacts on the food industry of these bioprotection systems are not known. It may be advantageous to work with cocktails of strains, probably more potent in preventing food spoilage than individual bacterial strains. Unlike laws and rules regulating health claims and drug development, the legislation for using natural preservative additives makes it easier to use beneficial bacterial cocktails for the prevention of food spoilage.

There is a popular notion that eating seasonal food is good for health. Could this popular concept have a microbiota-related scientific basis? For millennia, seasonal change in microbiota composition was naturally linked to seasonal variation of food availability. It possibly matched seasonal physiological status and helped to adapt the host body to various exterior stresses throughout the year (Ebling, 2015; Follett, 2015; Maurice et al., 2015; Sommer et al., 2016). This should be viewed in conjunction with recent evidence of annual fluctuations in immune system function in humans (a more pro-inflammatory status during the winter period) (Dopico et al., 2015). Moreover, the effect on human health of the specific composition of the microbiota of edible plants (epiphytes and endophytes), and its possible modification by different agro-food systems clearly deserves to be studied more carefully (workshop poster by Massart et al., 2016).

Also, it will be important to investigate how different agricultural systems impact environmental microbiotas and thereby the health of farming and other rural communities. A recent study compared farmers from the same country, with similar genetics, diets and lifestyles, but with very different farming systems. Asthma was ~4 times more frequent in children of farmers practicing highly industrialized agriculture than in children of those practicing traditional family farming with horses as labor force (Stein et al., 2016). The lower risk of asthma could be correlated with higher endotoxin levels in the Amish house dust, which was also effective in blocking allergic responses in a mouse model. This suggests that the different agricultural practices resulted in different microbial composition of the aerosols to which the populations were exposed.

5.3.1. Effect of transgenic plants on environmental microbiota

We also need to consider whether transgenic crops, and other genetically modified organisms or GMO cause unacceptable changes to the microbiota of the host or environment (Azevedo and Araujo, 2003; Kramkowska et al., 2013; Turrini et al., 2015). The issue of spread of antibiotic resistance genes incorporated into many GMO was discussed in Section 3.3 "Microbiota and antibiotics".

In some cases, the transgene product directly modifies the gut microbiota of animals that consume it (for example polyphenol-enhanced apples). In this example the effect is regarded as beneficial to the host, but this will not always be so (Espley et al., 2014). As far as the environment is concerned, there is good evidence that products of GM plants can be exuded from the roots and that some persist in the soil for long periods. Various effects of GM crops on endophytes or on microbes of the rhizosphere have been observed (reviewed in Turrini et al., 2015). These effects can be mediated by the intended products of the transgenes, or by unexpected production of metabolites resulting from pleiotropic effects of the transgene technology (reviewed in Turrini et al., 2015). Results with Bt (*Bacillus thurigiensis*) insecticide-producing GM plants suggest that, in this case at least, it is these pleiotropic effects, rather than the product of the transgene, that modify the microbiota, arguing in favor of the European GMO legislation that assesses the GMOs by "event". However existing studies fail to answer crucial questions: are the effects on the environmental microbiota of a specific transgenic crop greater than the differences that would be found between a range of conventional cultivars under the same tillage and cultivation conditions, and are those effects crucial for soil health? At present it is not clear that the effects seen are harmful, but close scrutiny is essential. Special attention should be given to: - 1) foreseeable impacts on environmental and/or intestinal microbiota of transgene products that have antimicrobial or antifungal effects; 2) foreseeable (on the basis of the transgene function) or unforeseeable (through unexpected pleiotropic effects) impacts on microbial communities that play key ecosystem services in the soil, such as decomposition of crops residues, completion of biogeochemical cycles, maintenance of soil fertility and plant nutrition.

6. Microbiota, adaptation and evolution: examples in animal species

Contrary to the main cellular genome of eukaryotes, which is largely static, the microbiome is highly plastic, and can respond rapidly to changes in host diet or environmental conditions. It may thus represent an important source of metabolic flexibility for the host. As such, the gut microbiome is sometimes referred as our "third malleable genome", (the second being the mitochondrial genome), and is increasingly hypothesized to play a role in host ecology and evolution (Carroll et al., 2009). While most biologists agree that microorganisms play an important role in host evolution, the idea that the host and its associated microorganisms form a primary unit of natural selection, and represent two components of a unified genome, is more controversial (Rosenberg and Zilber-Rosenberg, 2016). Especially, how gut symbionts evolve, and whether they undergo natural selection to benefit their

host, is still far from evident. Indeed, the gut microbiota is a complex, heterogeneous and variable community of microbes, which is assembled anew in each host generation through different transmission routes. At one extreme, gut symbionts can be directly transferred from mother to offspring, but most of the time they are randomly picked up from the environment. This molecular dialog between host immunity and gut symbionts plays a crucial role and is starting to be deciphered. These interactions are currently placed in an eco-evolutionary context reflecting the role of the microbiome in host acclimatization and adaptation in fast changing environments (Macke et al., 2017).

First, the invertebrate zooplankton constituent *Daphnia* is an interesting model in which to study symbiotic co-evolution and adaptation of organisms with their microbiota (Callens et al., 2016; Decaestecker et al., 2013). Experiments in this ecotoxicological model have shown that the gut microbiota of these small crustaceans confers resistance against toxins produced in the water by cyanobacteria (workshop presentation by Decaestecker, 2016). Microbiome-linked resistance was increased by previous exposure (selection over generations) of *Daphnia* (containing microbiota) to cyanobacteria, and this resistance was conserved across generations and transferred by the microbiota of resistant *Daphnia* genotypes to susceptible genotypes. Conversely, transfer of the microbiota from susceptible genotypes to germ-free resistant genotypes makes these resistant genotypes sensitive again to cyanobacteria toxins. Altogether, this suggests bi-directional interaction of the microbiota with the Daphnia which can help in the degradation of the harmful cyanobacterial toxins, threatening freshwater ecosystems.

A second example of microbiota mediating increased resistance to biotic stress is found in amphibian populations that are threatened worldwide by the fungal pathogen *Batrachochytrium dendrobatidis* (Bd). This biodiversity problem could generate amplifying ecosystem disturbances. But, the skin microbiota plays a role in amphibian resistance to Bd, and this finding is intensively studied in the hope that it can save this category of animals from extinction (Walke and Belden, 2016). Host factors seem to select for environmental microbes colonizing the skin, which in turn influence Bd infection or are influenced by it. Experiments have demonstrated that an augmented protective microbiota can reduce morbidity and mortality in amphibians exposed to Bd. Bacterial metabolites were shown to inhibit Bd zoospore colonization or development. Interestingly, the anti-Bd metabolite tryptophol was produced when *Bacillus* sp. and *Chitinophaga arvensicola* were grown together, but not when either was grown in isolation, illustrating the necessary interaction between different microbes to ensure beneficial effects for the host.

The promising protective effect of probiotic isolates was found to depend on context, including temperature. This animal microbiota model can also teach us about the protective functions of the human microbiota. Interestingly, just as in humans, the amphibian microbiota was shown to be shaped by transmission from parents, other individuals, diet, habitat, other environmental factors and, notably, to change with the seasons. Lessons from these studies that bring together researchers from a variety of disciplines (including ecology, microbiology, biochemistry, amphibian biology), could also be applied to other organisms affected by pests, from wildlife to agricultural crops, in addition to humans. Fungal diseases are increasing in incidence and are a major threat to biodiversity in bees, bats, snakes, corals, and a variety of economically important crops (Fisher et al., 2012).

Importantly, it has been observed recently that treating bees with tetracycline, a broad spectrum antibiotic that is commonly used in commercial beekeeping, results in dysbiosis, increased susceptibility to pathogens, and increased mortality (Raymann et al., 2017).

7. The ocean; the planet's microbiome gene bank?

We cannot consider the microbiota of soil and terrestrial fauna and flora without bearing in mind the fact that the oceans are the largest reservoir of microbiota on the planet (Fig. 1). Evidence for direct effects of ocean microbiota on human health has emerged. Living by the coast yields health benefits (Wheeler et al., 2012), and ocean spray is a rich source of microbial biodiversity (Leck and Bigg, 2005; Prather et al., 2013), and it is possible that this is one reason for the health benefits. On the rare occasions that marine aerosols contain toxic brevetoxins, clinical effects can be observed some distance inland, proving that physiologically relevant doses or marine organisms are routinely inhaled (Kirkpatrick et al., 2008). Moreover, airborne ocean microbiota can travel a lot further than the coast. Air samples from the upper troposphere have been shown to contain bacteria from many sources, including the ocean (DeLeon-Rodriguez et al., 2013). The global kinetics of ocean bacteria and their ability to reach humans directly via the rain or the air, or indirectly through the food chain warrants further investigation.

Moreover the ocean microbiota plays key roles in biogeochemical processes, like carbon and nutrient cycling, essential for the food web in the ocean ecosystem. The mass of this microbiota feeds the plankton at the base of the ocean food web. Moreover, photosynthesis in the ocean provides about half of the oxygen present in the Earth's atmosphere. It is difficult not to make a link with the alarming depletion of the ocean's oxygen during the last fifty years that could compromise the ocean's ecosystem services (Breitburg et al., 2018).

In terms of temperature, chemical composition, nutrients, depth and pressure, the ocean water is a rather variable environment that favors a large biodiversity of both microbial and eukaryotic marine life. It thus offers a living laboratory to facilitate comparative analysis of microbial composition between ecosystems and to study the impacts of environmental changes, and the capacity for adaptation of microbial communities that play essential roles in the health of our planet.

Samples from epipelagic and mesopelagic waters across the globe, have yielded new data on the microbial composition of the ocean (Sunagawa et al., 2015). A biodiversity rich microbial reference gene catalogue of >40 million non-redundant, mostly novel sequences, contained in >35,000 prokaryotic species, was generated. The ocean can thus be viewed as a microbial gene bank.

A core of gene families that accomplish stable core functions was distinguished from gene families that are involved in variable, adaptive functions. Curiously, >73% of the stable core functionality is shared with the human gut microbiome, despite the physicochemical differences between these two ecosystems (mostly anaerobic and heterotroph microbes in the gut; mostly aerobic and autotroph microbes in the ocean). Only the proportion of some functionalities varies (genes for defense mechanisms, signal transduction, carbohydrate transport and metabolism more abundant in the gut; genes for transport mechanisms and energy production, more abundant in the ocean). This suggests that most microbes' fundamental functionality has not changed much during their evolution and that replacement of one microbial community by another after environmental change can be accomplished without excessively difficult adaptation. This is important as we face climate change. This study revealed that the major environmental factor shaping taxonomic and functional microbial communities is temperature (Sunagawa et al., 2015). Therefore, new communities of microbes may be able to fill the void left by others as ocean temperatures rise. We might speculate that genes facilitating adaptation to different temperatures could be pinpointed in this gene bank. But the worry is that these shifts in the microbial community might cause changes in the nutrients available in the food web of the ocean and so lead to changes in other fundamental functions accomplished by the ocean microbiota that impact life and health on earth. For example, we now know that ocean microbiota and their metabolic products are present in marine aerosols where they are important modifiers of raindrop nucleation, and therefore of cloud formation and climate change (Cochran et al., 2017). The health of the ocean thus deserves to be closely monitored at the level of its microbial

life in conjunction with its macro-life and with other environmental perturbations.

8. Influence of chemical substances on the microbiota: still a lot to explore

Effects of antibiotics and other pharmaceutical products on gut and environmental microbiota were already mentioned in previous sections. Here we consider other classes of pollutant derived from chemicals that are used as pesticides, fertilizers, plasticizers, lubricants, dispersants, or emulsifying agents, or added to personal care products, or to food. Recent publications indicate that early-life exposure to environmental chemicals and alterations of microbial colonization during the perinatal period may promote dysregulated immune responses in later life (Gascon et al., 2013; Maurice et al., 2013; Menard et al., 2014). These findings suggest that the adverse health effects of environmental chemical pollutants, including endocrine disruptors, may not be restricted to direct toxicity on host cells. Some of them may be mediated by effects on our microbiota.

Specific members of numerous chemical classes have been shown to alter the composition and/or metabolic activity of the internal microbiota in animals (mostly mice) or in SHIME models (Simulator of the Human Intestinal Microbial Ecosystem). The physiological disturbances caused were sometimes linked to the altered metabolism of these molecules by the microbiota as described in Section 2.2.3, and commonly included inflammatory disorders, and disturbed energy metabolism typical of diabetes (reviewed in Claus et al., 2016; Velmurugan et al., 2017). Endocrine-disrupting properties have been associated with most of these chemicals, and strong epidemiological studies, supported by defined biochemical pathways, link the physiological disturbances they cause to rapid increases in type 2 diabetes in many parts of the world (reviewed in Velmurugan et al., 2017). For some of these chemicals, interaction with the AhR (aryl hydrocarbon receptor) was demonstrated to be a fundamental step in the induction of dysbiosis and metabolic disturbance (Zhang et al., 2015). We list below some of the compounds that have been shown to evoke dysbiosis associated with metabolic alterations (reviewed in Claus et al., 2016; Mnif et al., 2011; Velmurugan et al., 2017).

- POPS (persistent organic pollutants), in particular a polychlorinated dibenzofurane (TCDF; tetrachlorodibenzofuran), polychlorinated biphenyls (PCBs), and chlorothalonil (an organochlorine fungicide).
- Organophosphates, less persistent and thus used as 2nd generation insecticides and herbicides, such as the insecticides diazinon and chlorpyrifos (Joly et al., 2013), and the herbicide glyphosate (see below).
- Carbamates and Pyrethroids (3rd generation pesticides, considered still less toxic), like the fungicide carbendazim and the pyrethroid insecticide tau-fluvalinate. The latter caused disturbed bacterial diversity in bees but host metabolism was not studied.
- Bisphenol A (used as plasticizer in various plastic products, including water bottles and toys). Its toxic effect as endocrine-disruptor has been recognized officially in the European Union, so bisphenol S has been proposed as an alternative. However, recent tests show some disturbances in the caecum of male animals and the liver of females (European Chemicals Agency (ECHA), 2014). This sex difference (also observed for the effects of diazinon, cadmium and lead (Velmurugan et al., 2017)) might suggest endocrine disrupting mechanisms, that could operate via the microbiota.
- Phthalates, used in plasticizers, lubricants, dispersants, and personal care products (e.g. cosmetics, perfumes, nail polishes). In addition to dysbiosis, exposure of rats to diethyl phthalate led to consistent weight loss.
- Non-caloric Artificial Sweeteners (NAS), like aspartame, sucralose, saccharin
- Emulsifiers, like carboxymethyl cellulose and polysorbate-80
- Disinfection products like trichloroacetamide
- Heavy metals, in particular tested cadmium, arsenic, and lead (Lu et al., 2014), contained in synthetic fertilizers.

In addition to the above, combustion of organic materials and accumulation of petrochemical products lead to contamination of the environment with polyaromatic hydrocarbons (PAH). Soils experimentally contaminated with creosote, (a rich source of PAH), contained higher levels of Proteobacteria and lower levels of Actinobacteria and Bacteroidetes. Similar alterations in the relative abundance of phyla in human microbiota have been associated with adverse health outcomes, including immunological disorders. It is therefore conceivable that negative health effects of PAHs could be partly attributable to changes in environmental microbiota leading secondarily to changes in human microbiota (Parajuli et al., 2017).

Thus we need to explore how the various agrochemical residues in food may affect our gut microbiota, either directly, or indirectly via their influence on the microbial composition of soil and edible plants (Claus et al., 2016; Kruger et al., 2013). Impacts of pesticides on the microbiota of animals have been reported to increase their susceptibility to infections with high morbidity or mortality and threaten biodiversity and ecosystem equilibria (Walke and Belden, 2016). Similarly, effects on pollinators and human food security are important in this context (Engel et al., 2016).

It is worrying that the list quoted above includes chemicals used in food and cosmetics, that were previously considered safe for humans. Sweeteners and emulsifiers have been reported to alter the composition of the microbiota, with potential effects on obesity and other cardiometabolic diseases (Chassaing et al., 2016; Roca-Saavedra et al., 2017; Suez et al., 2014; Suez et al., 2015). Similarly, recent studies highlight doubts about several substances that are very common in the human environment. Experiments were performed in rats using diethyl phthalate (DEP), methylparaben (MPB), or triclosan (TCS), because DEP is used to stabilize fragrances in perfumes and hygiene products and increase the flexibility of plastics, while MPB and TCS are used as preservatives and microbicides. The rats were exposed, from birth to adulthood, at doses equivalent to human exposure. There were significant changes in overall gut bacterial composition in adolescent rats, and smaller changes were seen in adults (Hu et al., 2016). Treatment with mixtures of these compounds resulted in a distinct microbiome shift different from that caused by the individual chemicals or attributable to a simple additive effect, suggesting biological interaction between these chemicals or their effects.

Some pollutants reach humans via aerosols. For example experiments in mice reveal that ingestion of airborne particulate matter (urban PM10), already known to impair lung health, also changes the gut microbiome (Kish et al., 2013). This change was accompanied by inflammatory responses in the intestine linked to enhanced intestinal permeability (Kish et al., 2013). Further study will be required to prove the cause-effect relationship between the changed microbiota and the inflammatory responses, but such a relationship has been demonstrated elsewhere (reviewed in Erdman and Poutahidis, 2015).

Potential positive or negative effects on our health of cumulative interactions of chemical substances with the microbiota should not be neglected. For example, it has been reported that the microbiota can exert an adjuvant effect on cancer chemotherapy (Iida et al., 2013; Viaud et al., 2013). Other studies have focused more specifically on the susceptibility to antibiotics of bacteria when they are exposed to sublethal doses of commercial formulations of herbicides (Dicamba, 2,4-Dichlorophenoxyacetic Acid, and Glyphosate) (Kurenbach et al., 2015). Changes in the minimal inhibitory concentrations (MIC) of various antibiotics were observed, through direct action of the herbicides on the phenotype of the bacteria. One mechanism noted was an effect on the efflux pump used by bacteria to move antibiotics from inside the

organism to the external environment. The changes seen (e.g. increasing or decreasing MIC) depended on the herbicide, the antibiotic and the bacterial species. The effects were observed with herbicide concentrations above current food allowed maximum residues, but within application levels for all herbicides, and additive effects were observed with combinations of some of these products. These effects undermine antibiotic therapy and drive, in some cases, greater use of antibiotics for farm animals. This in turn leads to increased exposure of useful insects like honeybees, and favors the selection of genotypes resistant to these antibiotics. When the MIC is increased, it raises the survival of populations exposed to 'normal' (when tested alone) lethal concentrations of the antibiotic. When the MIC is decreased, it creates a selective force for the development of resistant genotypes at lower antibiotic concentrations than otherwise.

These combined effects suggest that we should broaden our view of the environmental contributors to the evolution of antibiotic resistance, and rethink risk evaluation protocols and regulations for herbicides and pesticides. Moreover, chemicals influencing health via effects on our microbiota can come from various sources. Sewage sludge is treated and then applied to agricultural land. After application of treated sludge to soil there was a high risk of contamination by residual estradiol, antibiotics, caffeine, triclosan and triclocarban (Verlicchi and Zambello, 2015). Thus we need to evaluate the impacts of doses of chemicals that occur in the real world, and we must also test long-term effects of exposure to low doses and to combinatorial effects. Attention must be given to the comparability of methodology in order to avoid confounding factors that could lead to inconsistent results (Koskinen et al., 2016). On the basis of various observations made in this paper, effects on the microbiota, in particular on its biodiversity and functionality, should be included in these evaluations.

8.1. Glyphosate

One agrochemical that deserves special mention is glyphosate for which there are conflicting reports regarding its hazards for human health (Tarazona et al., 2017). This commonly used herbicide inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase. Since mammals lack this enzyme, glyphosate was thought to be harmless to humans. However, many microorganisms do have enzymes that are affected by glyphosate, and glyphosate formulations have been patented as antibacterial compounds (Abraham and Monsanto Technology Llc, 2010). Therefore, we have to consider whether glyphosate is causing significant changes to soil, plant, animal and human microbiota, and if so, whether these changes are damaging to our health (Cuhra et al., 2016). For example, the shikimate pathway, when present in bacteria, is involved in the synthesis of aromatic compounds like tyrosine and tryptophan that are key intermediaries in systemic effects of our microbiota (see previous section in this review). Tested in vitro, and at relatively high concentrations, glyphosate formulations had more deleterious effects on beneficial bacteria from chickens and cattle than on pathogenic ones, though it was not clear why this occurred (Kruger et al., 2013; Shehata et al., 2013). Similarly, other experimental work has revealed additional potentially harmful mechanisms and effects, but it is not clear whether these involve concentrations that occur in human communities. While still speculative, the potential effects of this widely used herbicide on the environmental and internal microbiota warrant further investigation (Cuhra et al., 2016; Vandenberg et al., 2017).

For example, In addition to some specific actions of glyphosate mentioned above, this molecule and commercial formulations of it are reported to act as endocrine disruptors (reviewed in Mnif et al., 2011). Beside various endocrine-related disturbing effects in vertebrates and invertebrates, numerous epidemiological correlations have been made between exposure to different pesticides and occurrence of endocrine-dependent cancers or other disturbances of endocrine-dependent functions in humans (Mnif et al., 2011). In some of the studied cases, correlations are also found with dysfunctions of the immune and central nervous systems, which could suggest effects on the systemic influences of the microbiota.

9. Conclusions

A large body of evidence suggests that our microbiome, that some authors consider as our "second" or "third genome" (~100 times more genes than our primary genome), plays key roles in the developmental phase of eukaryotes and potentially in that of their progeny (Miller Jr, 2016). The microbiota is at the interface between the environment and our internal world (Fig. 1), can adapt itself and its hosts to different and changing environments, and may contribute towards a good OneHealth/EcoHealth relationship between our body and the external environment. We summarize our suggestions for further research in Table 1, while in the following paragraphs we consider other aspects of policy and planning.

9.1. Microbiota research and policy in the EU

At the international level, large research consortia have been created to study the microbial genome in relation to health, notably the International Human Microbiota Consortium (IHMC, 2008). At the EU level, transnational projects Metacardis and MyNewGut (Metacardis, 2012; My New Gut, 2013) aim to study the relationship between microbiota and health (with multi-omics methods) and to reveal how the microbiota changes with different pathologies and lifestyle factors, including diet, drug therapies, hygiene practices, travel, and disease. These projects involve large samples sizes, and the creation of biobanks and meta-datasets (workshop presentation by Dao, 2016; workshop poster by Sanz, 2016). A workshop was held in Belgium in 2016, co-organized by OCDE and EWI (Department Economy, Science and Innovation of the Flemish Government). This aimed to identify gaps in our understanding at the scientific and regulatory levels in order to facilitate progress in the microbiota field, and to contribute to an innovative bioeconomy sector developing preventive medical interventions that target the gut microbiota (workshop presentation by D'Hondt, 2016a, b). It discussed existing consortia and initiatives at the international and European levels.

9.2. Interdisciplinary transnational research and intersectoral policies

To increase understanding of all components of external and internal microbiota-host interactions and their implications for human health we need interdisciplinary and transboundary studies. Specialized medical doctors and veterinarians (including oncologists, neurologists, (neuro-)gastroenterologists, endocrinologists, diabetologists, allergologists, pneumonologists, rheumatologists, psychiatrists) and other health care professionals (nutritionists, food hygiene specialists, psychologists), should collaborate with (micro-)biologists, immunologists, ethologists, anthropologists, zoologists, biotechnologists, bioinformaticians, engineering specialists, and of course botanists, environmentalists, ecologists, phytopathologists, and agronomists. In addition, ethologists, anthropologists, socio-psychologists, and generalist medical doctors should be involved, as well as architects and political scientists.

Such inter- and trans-disciplinary approaches may provide knowledge that will enable us to use microbiota composition as an indicator of related present or future health issues. Similarly, this knowledge will enable the exploitation of microbes or their products as preventive or therapeutic strategies. Such strategies may involve interventions related to food, pharmaceuticals and the environment, and targeting chronic diseases at the population level or in at risk subgroups. By easing the financial burden of such diseases this knowledge could contribute to the economy as well as to public health. It could simultaneously provide human health data to support progress towards sustainable

Table 1
(Part 1) urgent research goals.

A. Further research to better understand and exploit the symbiotic relationship between microbiota and host

- what constitutes a "healthy" or "health-promoting" microbiota composition?
  - what is the influence on the human microbiota of:-
    - genetics, age, season, geographic location and local parameters affecting symbiotic evolution?
    - quality of the living environment (natural environments, biodiversity, pollution etc.)?
    - food production systems, diet and lifestyles?
    - exposure by various routes to a range chemical substances, additives and xenobiotics?
  - can we develop population level microbiota monitoring?
  - how can we use knowledge of the microbiota in the management/prevention of diseases?

B. Recognizing the full spectrum of the beneficial effects of a "health-promoting" microbiota. Understanding the interactions of the internal microbiota with the host

- characterize effects on human and animal health and disease of
  - microbiota components
  - bioactive metabolites produced by microbiotas
  - identify changes in microbiota associated with
    - a wide range of diseases
    - predisposition to disease in prospective studies.
  - explore
    - physiological pathways involved in interactions of microbiota with the host, and the dynamics of these effects
    - using the microbiota as a disease risk diagnostic and prognostic tool
    - using microbes or derived host-microbe metabolites as disease preventive approaches or treatments
    - mechanisms of adaptive co-evolution potentially brought by the microbiota to their host, and their relationship with health outcomes

C. Putting microbiota research in the broader environmental-ecological context

- Characterize
  - the short and long term influence of the environmental microbiota on the human microbiota
  - unrecognized routes of human exposure to microbiota in the environment
  - the effect of contact with nature, particularly in urban contexts, on our microbiota
  - the effect of the built environment and materials on our microbiota
  - the influence of the external microbiota on our internal microbiota
  - the load (time and magnitude) of external microbiota exposures necessary to change our microbiota
  - the links between such microbiota changes and health parameters
  - microbial species interactions outside and within human body
  - exterior and internal microbial diversity
  - More generally, evaluate the role of the microbiota in the impacts of nature on various dimensions of human health, and the interlinkages between those impacts.

D. Characterizing the effects of food production systems, food, diet & nutrition, and lifestyle (e.g. stress) on our microbiota

- Explore/compare effects on the human microbiota of:-
  - food produced by conventional agriculture and by agroecological systems
  - different varieties and breeds utilized (modern, traditional).
  - industrialized foods/food components & additives compared to more traditional diets
  - interactions with other factors of the modern life style (e.g. stress, low physical activity, etc.)
  - diets rich in vegetables versus animal products.
  - Ensure that plant and animal breeding strategies reflect the importance of microbial diversity for natural resistance to disease and pathogens

E. Study the impact of chemical substances (drugs, pesticides, additives, endocrine disruptors) on human microbiota and health; study their combinatorial effects

- Explore the impact of current antibiotics on:-
  - the general environmental and internal microbiota
  - "defensive microbes", and related health impacts on infectious and NCDs
  - Resituate the resulting knowledge in the current world problem of antibiotic resistance (see session of the workshop: Cross-pollinating agro-eco-human health)
  - Investigate potential effects on health parameters and the microbiota of:-
    - non-dose related impacts of endocrine disruptors and other xenobiotics and chemicals
    - amplified impacts on the endocrine system and (directly or indirectly) on other physiological functions
    - glyphosate (and its commercial formulations and compounds), currently the most used herbicide at the planetary level, on our microbiota and consequent impacts on our health
    - early life exposure to various environmental pollutants
    - chronic exposure to low doses vs acute exposure to high doses
    - transgenic foods
  - Re-evaluate molecules which are considered safe (e.g. additives for food, drugs, cosmetics) to identify effects on human microbiota and health
  - Generate additional data and tools for risk assessment and, thereby, inform existing regulations, in particular European Union legislation, on:-
    - effects on microbiota of pesticides (declared active molecules and commercial formula) and endocrine medicine wastes and disruptors: explore potential relationships with current and increasing NCDs
    - additives: explore their effects on the microbiota and potential links with NCDs.
    - combinatory effects of various of these substances (among other pesticides + antibiotics, in the evolution of antibiotic resistance).

agricultural practices, ecological consciousness and more natural lifestyles and urban environments.

Education should prepare future scientists for inter- and transdisciplinary work and enhance their capacity to listen to, understand, communicate and put in place ways of thinking and approaches to problem solving, that are essential for collaboration across disciplines. While scientific specialization is useful and at present unavoidable, specialists should be trained to understand the bigger picture. The curriculum of studies in universities should be adjusted accordingly.

A huge budget has been allocated to studies on the microbiota in the USA (Handelsman, 2016). This is not the case in the EU. We call upon EU policy makers to reinforce integration of the relevant policy sectors (health, environment, agriculture, land use planning, housing, food security and nutrition) in order to generate support for financing interdisciplinary microbiota research. There is also an urgent need to support longitudinal population-wide studies to monitor the drivers of the transition from health to disease and the underlying biological processes affecting host-microbiota cross-talk. Such studies could generate collections of microorganisms (biobanks) that could be exploited to characterize a healthy microbiota, to identify normal variation and dynamics of adaptation to changes in the environment, and to characterize specific functional microbes and their products. Such research will also set the baseline for standardization of collection, storage and analysis of samples and data. This will lead to the required identification of biomarkers corresponding to health or disease, and of clinical endpoints that can be used for early prediction, diagnosis and prognosis of disease, and for validating the efficacy of preventive and therapeutic interventions.

9.3. Changing behavior among the public, health professionals and other professional sectors

On the basis of current knowledge, unsoundly exaggerated hygiene measures in daily life should be reconsidered, while strict hygiene practices in clinical settings remain essential. We have to move to more "targeted hygiene", focusing on routes of transmission and on sites where pathogens accumulate, especially at the start of epidemics (Stanwell-Smith et al., 2012). It should be emphasized that hygiene is not a major cause of disruption of our exposures to appropriate microbial inputs. Accumulated data suggest that the general impoverishment of the biodiversity of our microbiota and the consequent deleterious health impacts are mainly due to antibiotic use (especially in pregnancy and early life), the western diet, caesarian birth, lack of breast feeding, and reduced exposure to the natural environment (Haahtela, 2014; Logan et al., 2015; Rook et al., 2014a; von Hertzen and Haahtela,

2006), rather than to exaggerated daily hygiene (Bloomfield et al., 2016).

Policy makers should also support education of the public and concerned professionals about the new insights into the functioning of microbiotas and the new opportunities this is creating for novel applications and behaviors supporting better health and wellbeing. The public should be helped to understand this new paradigm, in which health is addressed in a holistic way including host-microbiota interactions, and they should understand the role this approach could play in the global challenge of non-communicable diseases, and act accordingly. Socio-psychologists could help to integrate this societal change of paradigm not only into understanding but into practice.

While we clearly need to affect the way of thinking of the public, we also need to avoid exaggerated, sensational, and scientifically unsound press coverage, announcing miracles that could be accomplished thanks to the microbiota. Similarly, misguided press announcements suggesting a general reduction of hygiene practices should be particularly avoided in this period where various societal changes and rapid travel favor the emergence and diffusion of pathogens (Workshop Session, 2016c). We also need to consider other drivers that affect the behavior of humans towards exposure to environmental microbiota. For example, there are health programmes which inform about the risk of disease when in contact with nature; these include those spread by ticks and other vectors. Researchers, authorities and policy makers should make recommendations which take these controversies into account and explain their relationship, and highlight the beneficial aspects of contact with microbiota.

The Global Partnership for Business and Biodiversity (CBD_biodiversity, 2017) initiated by the international CBD (Convention on Biodiversity) since its COP-10 meeting, and completed by commitments for actions at its COP-13 meeting (end 2016) should encourage that partnership for co-responsibility towards biodiversity and its ecosystem services, including those of the microbiota towards human and environmental health. The microbiota should of course be included among the indicators developed by the "Initiative for Biodiversity Impact Indicators for Commodity Production" in the framework of that partnership (CBD_Commodity production, 2017). Related behavioral changes and initiatives by business, coupled to changes in public demand and help from public services, could promote faster societal changes in lifestyle.

9.4. Contact with the natural environment: a disease prevention strategy supported by UN

These insights suggest that we need to encourage the responsible authorities to promote access to, and contact with nature (Rook, 2013). The knowledge collected here places the environmental microbiota as an important concrete element in the health benefits that contact with the natural environment can provide. In particular, for young children raised in urban areas there should be access to parks, squares, gardens, urban farms and other green infrastructures like green walls and roofs. The interior public space (schools, hospitals, work places) should be also enhanced in this regard. Integration of green infrastructures into urban planning could be a simple and cost-effective way to ensure that the living environment contributes to the healthy microbiota (workshop presentation by Furman, 2016). Consistent with the OneHealth/EcoHealth approach, healthy ecosystems may be key to disease prevention and should be viewed as a fundamental pillar of a cost-effective healthcare strategy (von Hertzen et al., 2015).

The United Nations has set sustainable management of our planet's natural resources, as a prerequisite for social and economic development in its General Assembly of September 2015, adopting Agenda 2030 for sustainable development, described in point 33 of the online document (UN General Assembly, 2015). A request for implementing Agenda 2030 is to take into account the interlinkages of the various SDGs (Sustainable Development Goals) and to implement them in an integrated manner. Among the SDGs of UN Agenda 2030 (see Table 2), reaching Goal 3 (that includes reduction of communicable and non-communicable diseases) can be facilitated by practices enhancing diverse microbiota. Moreover, implementation of knowledge of the microbiome, improved by complementary research, could obviously contribute to integrated realization of several SDGs. Taking into account the knowledge compiled in this review, it could indeed participate in Goal 2, Goal 6, Goal 11, Goal 14, and Goal 15 (Table 2). Moreover, through influence on the previous ones, implementation of other SDGs could be helped (Goal 1; Goals 8 and 9; Goal 10; Goal 13). On the other hand, there are SDGs that could help to materialise these goals, such as Goal 4 and Goal 17. Implementing the conceptual framework of UN Agenda 2030, cross-sectoral research on the *lifestyle-natural environment-microbiota-health nexus* should be supported. Such support could contribute significantly when national, regional and global policies, as well as local practices, such as land use planning, are being developed and decided upon. Taking also into account the request of universality of Agenda2030, the role of microbiota in reaching SDGs is important in several regions of the world; in respect of sustainable development, all countries are developing countries.

Table 2
Sustainable Development Goals of the United Nations Agenda 2030.

Sustainable Development Goals (SDG)	
SDG 1	End poverty in all its forms everywhere
SDG 2	End hunger, achieve food security and improved nutrition and promote sustainable agriculture
SDG 3	Ensure healthy lives and promote well-being at all ages
SDG 4	Ensure inclusive and equitable education and promote lifelong learning opportunities for all
SDG 5	Achieve gender equality and empower all women and girls
SDG 6	Ensure availability and sustainable management of water for all
SDG 7	Ensure access to affordable, reliable, sustainable and modern energy for all
SDG 8	Promote sustained, inclusive and sustainable economic growth and decent work for all
SDG 9	Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
SDG 10	Reduce inequality within and among countries
SDG 11	Make cities and human settlements inclusive, safe, resilient and sustainable
SDG 12	Ensure sustainable consumption and production patterns
SDG 13	Take urgent action to combat climate change and its impacts
SDG 14	Conserve and sustainably use the oceans, seas and marine resources for sustainable development
SDG 15	Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
SDG 16	Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
SDG 17	Strengthen the means of implementation and revitalize the global partnership for sustainable development

Finally, access to a safe, healthy and ecologically-balanced environment as a human right has been addressed in recent UN meetings. At the 34th session of the Human Rights Council of the General Assembly of the UN (27 February–24 March 2017), the Special Rapporteur transmitted a report on human rights obligations relating to the conservation and sustainable use of biological diversity. It was suggested that full enjoyment of human rights requires ecosystem services provided by biodiversity that promote healthy food and water and a safe, clean, healthy, sustainable environment (Special Rapporteur, 2016). Microbial diversity was explicitly mentioned in this report, as were the links between environmental microbiodiversity and our immunoregulatory circuits, and the increasing incidences of NCDs in all parts of the world. These increases result, at least in part, from loss of microbial diversity (Haahtela et al., 2015; Hanski et al., 2012; Rook, 2013). In its conclusions and recommendations, this report calls for the States to ensure that

their National Strategic Plan on Biodiversity (NB: the European Union adopted a Strategic Plan) implementing the CBD 2011–2020 Strategic Plan reflect the necessary scope and ambition (now including a human rights perspective linked to health) to protect biodiversity. Application of current knowledge on microbiota diversity to improve health should thus now be considered as a policy obligation providing Parties to the UN adopt this report. Research on the *environment-microbiota-health axis* could contribute significantly to the implementation of "good practice" guidelines and to increased understanding and awareness of the links between human rights and protection of biodiversity in the general environment.

As a conclusion and as follow-up to the Environmental and internal Microbiota session of the European OneHealth/EcoHealth workshop 2016 (Workshop Session, 2016b), we suggest in Table 3 how we should prioritize research on the *environment-microbiota-health axis* with a view to promoting preventive healthcare in national, EU and global policies for humans, plants and animals. We highlight an integrated approach where the microbiotas of living organisms and of the environment are important signaling transducers of the communication system that connects all elements of the global ecosystem. As such, the contributions of microbiotas to the health and well-being of humans are of paramount importance.

Table 3
Research and science-policy relationships on the *lifestyle-natural environment-microbiota-health* axis.

Prioritize research and science-policy relationships with a view to promoting preventive healthcare in national, EU and global policies: for humans, plants and animals (ecosystems), in an EcoHealth interrelated approach, involving potential necessary changes in lifestyles and societal habits
• Define a "healthy" microbiota and its role in resilience to NCD development o Composition at the species level, and overall metabolome
• Explore food production and the microbiota in the context of human/animal/-plant health. o are there (significant) differences between the systems (conventional agriculture, organic farming and other agroecological approaches) in this regard? o which system offers the most cost-effective approach? o which practices should be mandated from a public health point of view? o can food products that target the gut microbiota compensate for a bad microbiota heritage?
• Explore the impacts of nature on the microbiota o effects on human health, mediated via the microbiota, of disturbance of ecosystems o effects on the microbiota of spaces or processes which enable good health. o what qualities of green infrastructures in cities enhance human microbiota in ways that benefit health?
• Explore the effects of environmental components and substances/xenobiotics on the external and internal microbiota and the relationship to health (NCDs & infectious diseases; see Table 1), with a view to legislative amendments to risk assessment requirements o antibiotics: - make the link with the world problem of current antibiotics abuse and antibiotic resistance - make the relationship with clinical practice and the food chain (use of antibiotics during husbandry of livestock and honeybees) and human health - assess the risk of developing more infectious diseases but also more NCDs in the long term. o additives, including those presently considered safe o pesticides (declared active molecules and commercial formula), endocrine medicine waste and endocrine disruptors o combinatory effects of various of these substances on the microbiota, and bidirectional interactions between environmental pollutants and our microbiota, to relate to (potential) amplifying and combinatory negative effects of pollutants on health
• Explore the molecular mechanisms underlying all these effects.
• Explore mechanisms that enable a transition in lifestyles towards paths which build on a sustainable *natural environment-microbiota-health nexus*
• Establish a science-policy platform in an integrated policy approach to facilitate the translation of research findings into:- o policy making processes and applications at the national, EU and international levels o health policy (including disease prevention through food) o land management policies (for agriculture, forestry, industrial development) o urban planning policies (sustainable urban development) o educational policies (from daycare to academic) o nature conservation policies (e.g. EU Green Infrastructure strategy), including marine nature

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Authors' contributions

LF co-organized the workshop that included the session on which this review is based; she organized and coordinated this session with advice from ED, TH, and GR. TP, GB, GC, M-CD, ED, EF, SM, HP, and YS made presentations at the workshop. LF initiated the draft report of this session that was followed by further contributions from, and discussions with TP, GB, GC, M-CD, ED, EF, SM, HP, TH, YS, and GR. LF, GR and TP then wrote extensive additional material. GB, GC, M-CD, ED, EF, TH, SM, HP and YS read and commented on several drafts. GR, LF and TP then edited and assembled the paper before recirculating it to all authors. All authors approved the submitted text.

Conflict of interest

None of the authors has competing/conflicting interests in relation to the issues tackled in this paper.

Human and animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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