To be healthy we need exposure to microbes: Reformulation of the "hygiene hypothesis"

Daddy: almost half of the children in my class have hay fever. Is it like that everywhere in the world?

Photo by Andrea Piacquadio: https://www.pexels.com/photo/a-sick-girl-wiping-her-nose-with-tissue-3765115/

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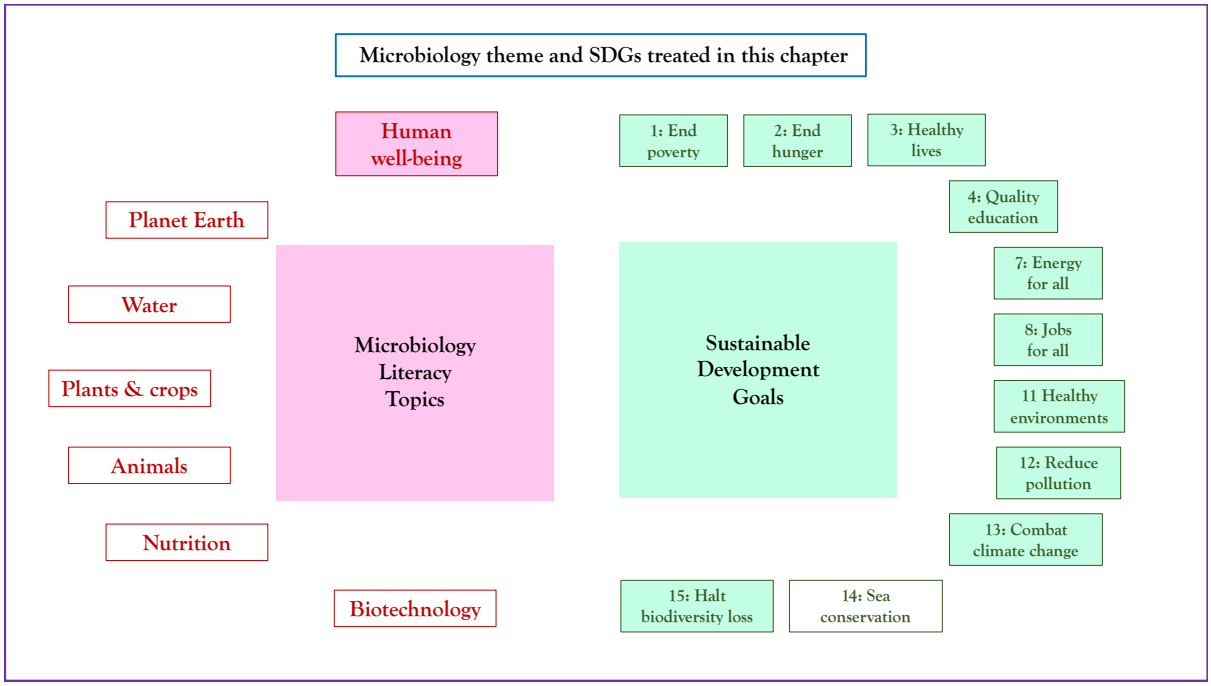
Storyline

In recent decades, particularly in rich countries, there has been a striking increase in the prevalence of health problems caused by our immune systems attacking things they should not attack. The main job of the immune system is to protect us from harmful infections, but we now see it attacking harmless allergens such as grass pollen or peanuts or the neighbour's cat (allergic disorders) or attacking our own tissues (autoimmune disorders such as multiple sclerosis) or driving chronic inflammation in the gut (inflammatory bowel diseases). Moreover, in many people the immune system causes unnecessary chronic background inflammation detectable by measuring cell populations and molecules in the peripheral blood. This state is associated with an increased risk of cardiac, metabolic and psychiatric problems. Much of this failure of the regulation of the immune system is due to reduced exposure to microorganisms that provide data and signals that, in addition to driving development of some organs, including the gut and brain, are essential for "educating" the immune system and in particular, establishing its control mechanisms. Here I discuss how this need for exposure to microorganisms evolved, which organisms we need to encounter, how they promote health, why we are not meeting enough of them and what we can do about this deficit.



The Microbiology and Societal Context

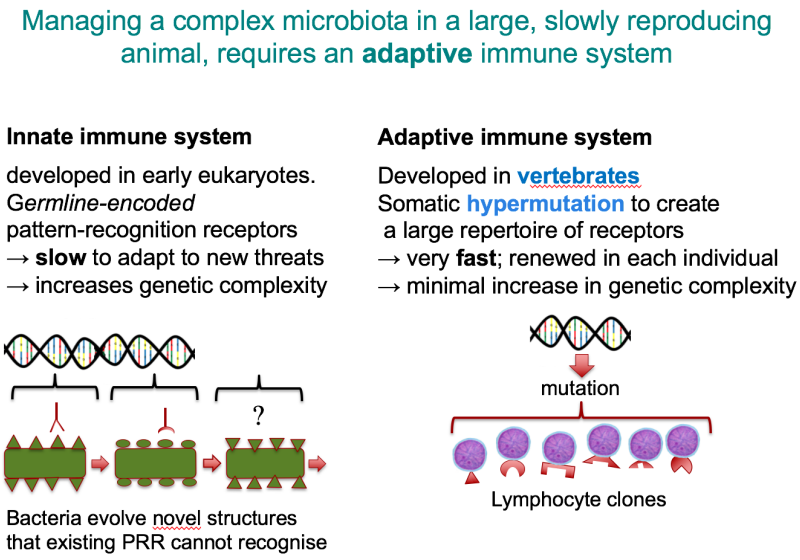
The microbiology: Evolution of the immune system and its relationship to microorganisms; microbiota; mechanisms of the health benefits of microbial exposures; causes of reduced microbial exposures; modern environment; lifestyle; antibiotic exposure; diet. *Sustainability issues:* Microbial exposures in relation to lifestyle and Socioeconomic Status (SES); microbial content of cities; greening of cities; house design to increase microbial exposures; crucial role of food and food production methods; pollution and microbial biodiversity.

Necessary microbial exposures

1. We evolved from and with microbes. About 1.5 billion years ago a bacterium started to live inside another organism, creating the first eukaryotic cells (cells with a clearly defined nucleus). So humans, like all life forms built from eukaryotic cells, evolved from a blend of 2 or more microbes. Moreover the first versions of about 65% of human genes originated in microbes. Not only did we evolve from microorganisms, but we live in a microbial world. Bacteria are second only to plants in terms of total biomass and the total biomass of bacteria, expressed as Gigatons of carbon, is about 1200 x the total biomass of humans. So microbes are everywhere, including in and on ourselves, particularly in the gastrointestinal tract. Our guts contain symbiotic organisms (the microbiota) that are at least as numerous as the human cells in our bodies, and 30% or more of the small molecules in our peripheral blood, many of which have profound effects on our physiology, are products of the metabolism of these microbes. How did this situation evolve?

2. We evolved a close physiological relationship with microbes. Early in evolution the organisms that inevitably found their way into the guts of animals were separated from the host by a chitin barrier, a structure that persists in arthropods and annelids. In chordate invertebrates, such as tunicates, the chitin mesh is embedded in a mucin gel, but the gut bacteria are still separated from the gut epithelium. However, in mammals the chitin layer is lost entirely and complex mucus layers interact with and nourish organisms, many of which adhere to the mucus and modulate the function of the underlying cells. So rather than walling off the microbes, mammals interact closely with them. (It is interesting that this parallels the situation in plants where organisms are attracted and nourished by molecules secreted from the roots, and then take part in symbiotic two-way signaling and exchange of nutrients.) So these microbes, known collectively as the microbiota, have become part of our physiology, like an additional organ.

3. Upgrading the immune system. So the microbiota is like an additional organ that the immune system must maintain and "farm" while simultaneously excluding pathogens. This task requires a very precise system of microbe recognition that can remember the helpful symbiotic organisms, distinguish them from pathogens and set up control systems to avoid attacking the useful ones. Most life forms have an "innate immune system".



Innate and adaptive immune systems

This relies on inherited germline encoded pattern recognition receptors (PRR) that recognise and bind to common microbial components and trigger an inflammatory response. The problem is that rapid bacterial evolution can give rise to pathogens not recognised by existing PRR. The innate immune system can try to catch up by duplicating the gene for a PRR and selecting a modification that is able to recognise the new pathogen, but this process is slow and the genome becomes cluttered with duplicated PRR genes. So the "adaptive immune system" evolved, as described in the next paragraph.

4. ***The adaptive immune system.*** The development of the "adaptive immune system" in vertebrates provided a way to create a very large repertoire of different receptors with a minimal increase in genetic complexity. This is achieved by somatic hypermutation involving the genes encoding the receptors of B lymphocytes and T lymphocytes. These random mutations create large numbers of distinct T and B lymphocyte clones bearing a huge diversity of receptors. This keeps the genetic load low, but it creates several other problems. For example, random mutation can result in vast numbers of useless lymphocytes that recognise nothing and so waste metabolic resources and space. Worse still, there can be lymphocytes that recognise the host's tissues and so mediate autoimmunity. However, the diversified receptors generated by mutation are expressed clonally. Each lymphocyte clone expresses only one receptor, so that if that receptor turns out to be useless or autoreactive, the relevant cell line can be eliminated. The autoreactive cells are mostly eliminated in the thymus, where self-antigens are expressed. However, in order to decide which other lymphocyte clones to keep for managing, "farming" and tolerating the microbiota, while eliminating pathogens, the adaptive immune system requires data from contact with the symbiotic microbiota and microbes in the environment. The subtlety of this arrangement is that each new individual develops an immune repertoire that is matched to the microbial world into which s/he is born.

Mechanisms of microbial benefits

Evolution tends to turn the inevitable into a necessity. So the presence of this additional "organ", the microbiota, has become a necessity. Why? What are these organisms doing for us? Briefly, they digest things we cannot digest, they break down toxins we cannot metabolise, they make vitamins we cannot synthesise, and they release metabolites that have powerful effects on our physiology and on the development of our organs. These metabolites include short chain fatty acids (SCFA), various metabolites of bile salts, and metabolites of tryptophan and tyrosine which are amino acids used by the brain for the synthesis of various neurotransmitters. These are huge topics that cannot be reviewed here, but in the context of this chapter there is another important function; setting up the immune system and its crucial control mechanisms.... The control mechanisms that are failing in rich modern societies.

5. ***Our immune systems require educational inputs from microbes.*** So our immune systems need inputs of data about the molecular components of microorganisms in the environment so that relevant, useful lymphocytes can be maintained, while dangerous or useless lymphocytes are eliminated. At the same time microbial signals ensure that the various immune system mechanisms are set up at levels of activity that are matched to the organisms sensed in the environment.

Inputs from microbes	Effects on the immune system
Organisms	
Diverse organisms from mother, family and the environment	Populate microbiota. Drive organ development, digestive functions, vitamin synthesis, short chain fatty acids (SCFA). Set up regulation of metabolic and immune systems
Spores of gut-adapted strains	Trapped by mucus and cilia, swallowed. Expand or restore the gut microbiota. Drive Treg, SCFA
Pathogens, at less than the infectious dose	Disarm in airways, swallow. Immunity to common pathogens
Signals **from microbes**	
Microbial components (e.g. some LPS & muramic acid derivatives)	Signals via Pattern Recognition Receptors (PRR): Tolerance, immunoregulation, regulation of the innate immune system
Data **from microbes**	
Diverse microbial *epitopes* from symbiotic organisms, pathogens, and environment	Select and expand diverse repertoire of useful lymphocyte clones. Expanded lymphocyte repertoire to recognise novel pathogens and distinguish pathogens from partner organisms that must be tolerated
Pathogens and vaccines	
Infection with pathogens	Death or immunity. Non-specific post-survival benefit after some infections. Intermittent immune system activation by some persistent infections.
Vaccines	Immunity to the pathogen. Epigenetic adjustments to innate immune system. Non-specific survival benefit after live vaccines
Other inputs from microbes	
Bacteriophages	Phage-driven regulation of composition of gut microbiota. Perhaps also drive formation of antibody to phages which might modify phage-driven regulation of strain abundance in gut microbiota
Microbial DNA by horizontal gene transfer (HGT)	Adapt organisms to gut. Adapt gut ecosystem and metabolic repertoire to diet

6. ***Which microorganisms do we need to encounter?*** A huge amount of research is aimed at giving precise answers to this, but the bottom line is that we need to encounter microbes from our mothers and other family members, and microbes from the natural environment, particularly in early childhood while the immune system is being set up.

The term "hygiene hypothesis" emerged in 1989 when it was observed that children with older siblings, especially dirty older brothers, were less likely to develop hay fever. It was suggested that the protection might be due to exposure to the common infections of childhood (measles, mumps etc) brought home by the siblings. However epidemiological studies show that these infections do not drive regulation of the immune system, but seem rather to activate it, and often trigger or exacerbate allergic conditions of the respiratory system. Moreover, these infections are mostly "crowd infections" that did not exist in human populations until large urban human communities evolved so it is unlikely that humans are in a state of evolved dependence on them. (Measles, for example, might not have emerged until the 11th or 12th century, or perhaps a few hundred years earlier during the Roman empire). The "crowd infections" may be relevant to non-specific innate immune system activation (a role now at least partly replaced by the non-specific effects of vaccines discussed in Section 10), but there is no evidence that they drive the immunoregulatory functions that are deficient in children with allergies or autoimmunity. (The idea that we need exposure to parasitic worms seems to be another failed hypothesis.). So neither the common infections of childhood nor parasitic worms seem to be the organisms that we need to meet. There is however powerful evidence that we need to encounter microbes from our mothers and other family members, and microbes from the natural environment, particularly in early childhood while the immune system is being set up. So what is going wrong in the modern world?

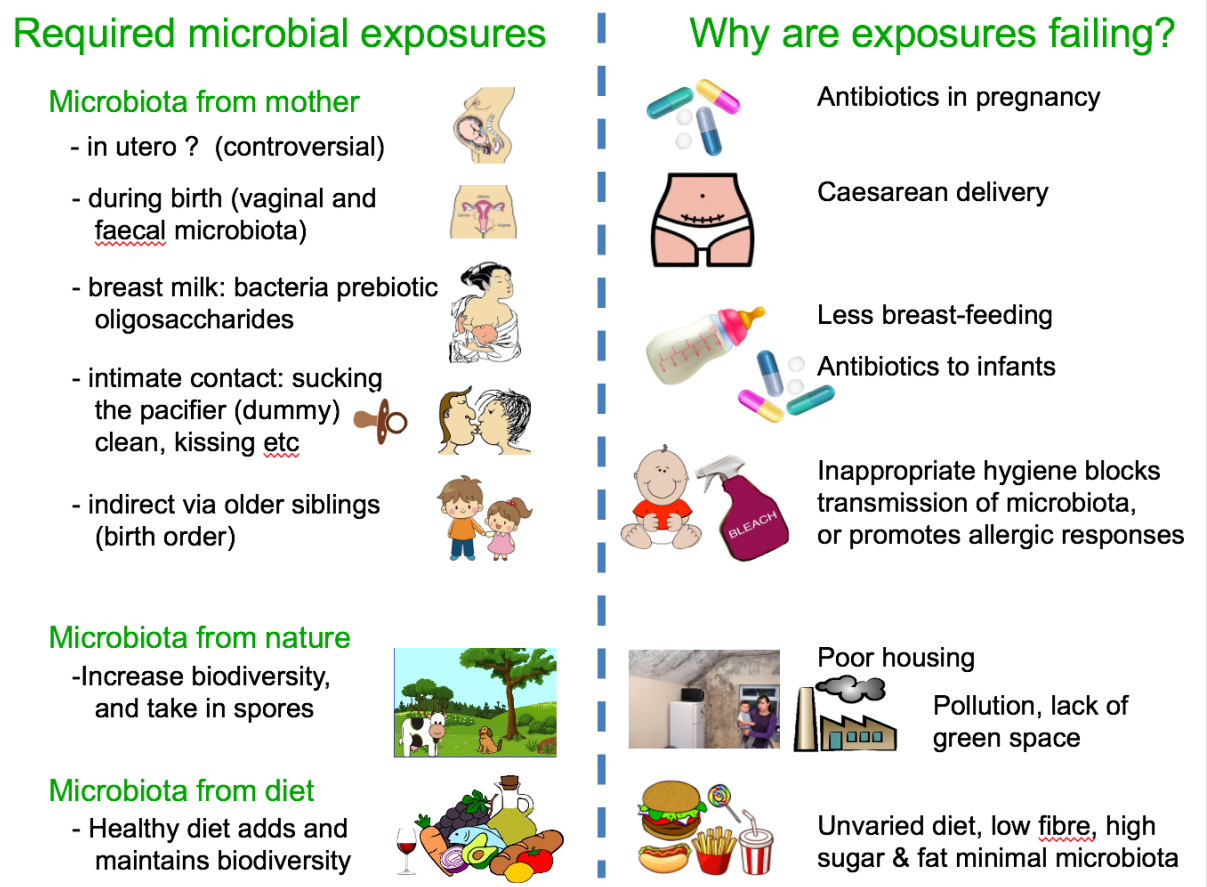
Why we probably do not need to be infected with helminths

Another failed hypothesis is that we all need to be infected from birth with parasitic worms.... helminths. Helminths downregulate inflammation to avoid fatal immunopathology, and some authors think that we are in a state of evolved dependence on this helminth-mediated immunoregulation. But this is very unlikely, because different helminth species live in blood, tissues, bladder or gut, and each species downregulates inflammatory responses via a different mechanism. Moreover the loads of helminths differ wildly between individuals, even when they live in similar geographical locations. Therefore there is no constant "inevitable" helminth-associated factor that could drive evolution of a human germline encoded genetic dependence on helminths. Although evolution tends to turn the inevitable into a necessity, evolution does not turn erratic or occasional exposures into necessities, because that merely leads to gene-environment mismatch. In fact temporary environmental or infectious stresses are coped with via epigenetic adaptations in the developing immune system that can fade over several generations, or be renewed if required. This probably explains why clinical trials with helminths for treating multiple sclerosis work in developing countries where helminth infection occurs in early infancy, and epigenetically encoded dependence on helminth-mediated immunoregulation is present, but the trials fail in rich countries where helminths have been rare for generations. However this issue remains controversial.

7. ***Failure of microbial inputs in modern urban life.*** First, contact with mother's microbiota is decreased by caesarean deliveries and lack of breast-feeding (breast milk contains microorganisms). Moreover the numbers of antibiotic courses in early childhood correlate with increases in immunoregulatory disorders. Then poor unvaried diet reduces the diversity of the microbiota. For example lack of fibre (plant cell walls and some other complex polysaccharides) distorts the microbiota.

The role of the microbiota of the natural environment has been revealed by studies of allergic disorders of children brought up in farming or non-farming environments, and recently by a clinical trial of directly exposing children in their playgrounds to earth and leafy material from a forest floor. The exposure increased biomarkers of immunoregulation in the childrens' peripheral blood. Keeping pets also increases exposure to the microbiota of the natural environment because they bring it into the home. Modern city dwellers get less exposure to the microbiota of nature because they (and their pets!) spend little time in biodiverse natural environments.

8. ***Cleaning the home.*** We need exposure to the microbiota of mother and family, and the microbiota of the natural environment. But what about the microbiota of the modern home? Are we too clean for our own good? The answer is no. A clean home does not block encounters with our mothers or with the natural world. The lifestyle changes that do that are listed in the previous paragraph. A modern home, built with biocide-treated timber and plasterboard, is not a natural environment, and the microbiota of such homes is not something with which humans evolved. If the home is deteriorating and damp the microbiota often includes organisms, especially moulds, that are toxic to humans. This can be manifested as sick building syndrome. When very detailed studies of home cleaning are done it emerges that the incidence of allergic disorders is not related to removal of microbes from the home, but rather to the cleaning agents themselves, and many studies have been misinterpreted.



Lifestyle factors that enhance or reduce microbial exposures

9. ***Misinterpretation of studies relating childhood allergies to clean homes***

Some of the confusion has arisen because the cleaning agents themselves can be toxic to the airways and lungs, causing increased permeability of the epithelium, or even some local cell death. We have known for years that cleaning personnel exposed every working day to cleaning sprays have an exaggerated risk of lung disease. We now believe that low doses of these agents are affecting small children. Recent work has shown that mild toxicity at epithelial surfaces (airways or gut) causes the immune system to set up its fast-acting rejection reaction, manifested as an allergic response. But the immune system cannot make an allergic response to, for instance bleach, and instead targets whatever else was present at the same time as the cleaning agent. This tends to be food items such as milk proteins, or things in the air such as house dust mites, pollen, or cat dander. Subsequently these things are targeted as proxies for the cleaning agent and provoke "immediate" allergic reactions when next encountered. This problem is more common in homes of low socioeconomic status (SES) where mother is cleaning while looking after babies and toddlers, whereas wealthier families employ outside personnel as cleaners. So we should clean our homes, but avoid direct exposure of young children to cleaning agents.

10. SES and distorted interactions with essential microorganisms. Many factors that lead to reduced exposure to the microbiota of the natural environment, and/or lead to distortion of the commensal microbiota, are strongly associated with low socioeconomic status (SES). The most obvious are lack of access to green space, living in proximity to sources of pollution, poor diet and exposure to multiple stressors. These factors all reduce relevant exposures or induce distortion of the microbiota. Reduced education is also a factor because this is associated with smoking, antibiotic misuse, and vaccine hesitancy or refusal. The latter point is important. It

has emerged that an infection such as measles, *if you survive it*, not only drives immunity to that infection, but (after a brief phase of immunosuppression) also causes broad non-specific boosting of the immune system. Many vaccines do the same thing but without the risk of dying from the infection! So vaccines, like mother's microbiota and organisms from the natural environment, are a beneficial microbial input.

SES-associated factors that disturb microbial exposures & microbiota	
Pollution	Traffic, air pollution
	Agrochemicals
	Damp, sick-building
	Exposure to cleaning and hygiene products
Lack of green space	Little exposure to microbial strains and spores from nature
	Less sunlight, vitamin D
Stressors	Drug abuse, violence, heat, noise, sleep disorders
Poor diet	Processed, unvaried, low fibre, low vitamins
	Sugars, artificial sweeteners
	Obesity
Education	Smoking
	Antibiotic misuse
	Vaccine hesitancy and refusal

Low socioeconomic status (SES) is linked to distorted microbial exposures
lifestyle factors that enhance or reduce microbial exposures

11. Increasing microbial exposures: lifestyles. Avoiding the lifestyle factors that reduce microbial exposures is important, if social conditions allow it. The public is becoming aware of the benefits of natural births, breastfeeding and minimising the use of antibiotics. Similarly, a varied diet rich in fibre, plus supplements, such as probiotics (living organisms) or prebiotics (materials that encourage the growth of appropriate organisms in the gut) may increase the biodiversity of the microbiota. The use of Faecal Microbiota Transplants to replace a failing (dysbiotic) gut microbiota with microbiota from a healthy donor is being studied in clinical trials and shows promise in some situations.

12. Increasing microbial exposures: design of houses and cities. We need to modify the way we design our houses and cities so as to cut pollution and increase exposure to the natural environment.

Green spaces in cities, even small ones, will help and green spaces on roofs are beneficial in many ways. Scientists are trying to invent novel "bioreceptive" building materials that can maintain a stable population of algae, lichens and microbes.

Relevance for Sustainable Development Goals and Grand Challenges

Changes in lifestyles that would enhance essential microbial exposures and promote healthy microbiotas are associated with several SDGs:

- **Goal 1. End poverty in all its forms everywhere.** Poverty and low SES are linked to disturbed microbial exposures and disturbed microbiota via several pathways as outlined above.
- **Goal 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture**. A change towards sustainable, more organic farming will increase microbial biodiversity and reduce exposures of agricultural workers to toxic chemicals, many of which are antimicrobial and disturb our microbial exposures. The problem will be to maintain high productivity so as to reduce hunger and provide good nutritious diets for those at the bottom of the SES scale.
- **Goal 3. Ensure healthy lives and promote well-being for all at all ages**. Improving the lives of those at the lower end of the socioeconomic scale will, for the reasons outlined above, reduce the incidence of immunoregulatory disorders attributable, in part, to inappropriate or diminished microbial exposures.
- **Goal 4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all.** Several factors that damage the microbiota, or distort microbial exposures are closely associated with low educational levels, notably smoking which directly distorts the microbiota of the airways and gut. Vaccine hesitancy is also somewhat linked to low educational level, but we now know that vaccines constitute a valuable microbial exposure for setting up the immune system, in addition to providing protection of an individual against disease caused by a specific infection. Moreover vaccination is known to have several other positive socio-economic effects such as reduced transmission to others, especially family members, fewer lost days from school, resulting in better education and consequential better productivity and societal benefits. Education might also help to teach people to avoid pollutants and agrichemicals that distort microbiota, and to avoid overuse of antibiotics.
- **Goal 7. Ensure access to affordable, reliable, sustainable and modern energy for all** Excessive heat and cold are major stressors that lead to distorted microbiota. Thus cheap energy for air conditioning and heating would reduce stress levels, particularly at the lower end of the SES.
- **Goal 8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all**. Decent work, in addition to providing an adequate wage, should not endanger health by exposing workers to toxic pollutants that, amongst other effects, distort the microbiota. Workplaces can damage health directly, and indirect stress-mediated effects are also a major component of SES-related health deficits.
- **Goal 11. Make cities and human settlements inclusive, safe, resilient and sustainable.** Sustainable cities should include many safe green spaces, accessible to all. Similarly, novel designs for houses and apartment towers should include vegetation, mosses, lichens and other materials that can harbour diverse microbes. Air conditioning systems should

promote the exposure of the occupants to these microbes. Novel bioreceptive building materials are being devised that can incorporate a sustainable microbiota.

- **Goal 12. Ensure sustainable consumption and production patterns.** Pollutants from factories, agriculture and transport directly disturb the microbiota of humans, and also indirectly disturb it by distorting the microbiota of the natural environment, which is no longer "natural".
- **Goal 13. Take urgent action to combat climate change and its impacts**. Healthy diets rich in vegetable, fruit and fibre, with low meat content are beneficial for the microbiota and increase the biodiversity of microbial inputs. Moreover a change to such a diet will simultaneously lead to changes in the balance of agricultural activities that will reduce emission of methane from cattle.
- **Goal 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.** The microbial inputs from the natural environment that are essential education for our immune systems must be "natural". Loss of microbial biodiversity endangers the usefulness of these inputs.

Potential Implications for Decisions

1. ***Individual***

a. Should you exercise in parks where there is exposure to the microbiota of the natural environment, or indoors and in gyms?

b. Would houseplants increase beneficial microbial exposures?

c. Should you eat a varied diet rich in fresh fruit, vegetables and fibre, or processed food rich in fat, meat and sugar?

2. ***Community policies***

a. Community involvement in maintaining and using green spaces for sport, exercise, walking.

b. Urban planning. Increase urban green space and design green houses, especially in areas of low SES.

c. Encourage vaccinations, and reduce incorrect advice from social media.

3. ***National policies***

a. Encourage natural child birth (if medically advised) rather than elective caesarean which diminishes transmission of maternal microbiota.

b. Encourage breast feeding when available (to enhance transmission of maternal microbiota) rather than formula feeding.

c. Teach use of "targeted hygiene" and hand-washing that concentrate on the places and circumstances that risk transmission of infections (toilets, food preparation).

d. Teach avoidance of exposing children to aerosols of cleaning agents. (This is more difficult in small crowded dwellings of low SES where mother does the cleaning while managing small children).

e. Urban planning. Increase urban green space and incorporate plants and other components of the natural environment in innovative house and apartment design, especially in areas of low SES.

f. Reduce exposure to pollution (traffic, agrochemicals etc).

Pupil Participation

1. ***Class discussions***
    a. Why does exposure to microbes enhances our health?
    b. Why does the modern lifestyle reduce exposure to beneficial microbes, and also distort the gut microbiota?
    c. What are the most obvious things the individual can do to improve this situation?

2. ***Pupil stakeholder awareness***
    a. Policies and changes that make progress towards the SDGs will also increase beneficial microbial inputs. Which of these are most important to you personally/as a class?
    b. Can you think of anything you might personally do to increase your exposure to beneficial microbes from the environment?
    c. Can you think of any changes to your diet that might help you to have a healthy gut microbiota?

3. ***Exercises***
    a. Can you think of ways to redesign cities and houses so that everyone has more contact with the natural environment?
    b. What can the government do to encourage healthy eating…which tends to be more expensive than a bad diet based on processed foods, meat, fat and sugar,

The Evidence Base, Further Reading and Teaching Aids

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Glossary

Annelids: animals (e.g. earthworms and leeches), with segmented bodies
Arthropods: invertebrate animals with a chitin exoskeleton and jointed appendages.
Autoimmunity: an immune response that targets the host's own tissues
Autoreactive: an element of the immune system, such as antibodies or lymphocytes, that recognise the host's own tissues.

B lymphocytes: lymphocytes concerned mostly with antibody responses.
Biocide: a substance designed to kill living organisms, often used to protect vulnerable building materials such as wood and paper.
Bioreceptive: materials designed to encourage the surface growth of plants and plant-like organisms such as mosses and lichens, and their accompanying microbiota
Chitin: a complex polysaccharide found in the exoskeletons of arthropods and in the cell walls of fungi.
Chordate: animals of the phylum Chordata that have a notochord. The notochord is the evolutionary forerunner of the structure that develops into the spine in vertebrates.
Dysbiotic: a microbial imbalance, such as an inappropriate composition of the gut microbiota. This can be overgrowth of non-symbiotic organisms, and a decrease in biodiversity.
Epigenetic: changes in DNA and associated molecules that modify gene regulation without any change in DNA sequence.
Epithelium: one or more layers of cells that cover most internal and external surfaces of the body and its organs, notably the skin, and the lumens of the airways, gut and blood vessels.
Eukaryotic: cells in which the genetic material is situated in a membrane-bound nucleus.
Fibre: dietary fibre is mainly complex polysaccharides, usually of plant cell wall origin, that are poorly digested in the small intestine, but provide nourishment for useful organisms in the large bowel, which ferment them to yield necessary short chain fatty acids.
Germline encoded: encoded in the DNA of the cells that pass on genetic material to the progeny (e.g. egg, sperm).
Immunoregulation: mechanisms that stop "forbidden" or unnecessary immune responses (e.g. autoimmunity and allergies) and terminate immune responses when they are no longer needed, so that inflammation does not persist.
Neurotransmitters: substances involved in transmission of signals from one neuron to another (acetycholine, dopamine etc).
Plasterboard: (also known as gypsum board). Rigid panels of a building material consisting of a gypsum core between layers of fibreboard (wood chip based) or paper.
Prebiotics: substances that encourage the growth of appropriate organisms in the gut, which are able to metabolise them. They may not be metabolisable by the host.
Probiotics: microbes that are consumed alive in fermented foods (such as yoghurt) or as dietary supplements, that maintain or restore beneficial bacteria to the digestive tract.
Somatic hypermutation: any mutation at the cellular level in somatic tissues. These mutations do not involve the germline so they do not pass on to the offspring.
T lymphocytes: many types of lymphocyte involved in immune responses, and in the regulation of those responses.
Tunicates: primitive chordate marine animals such as sea squirts.