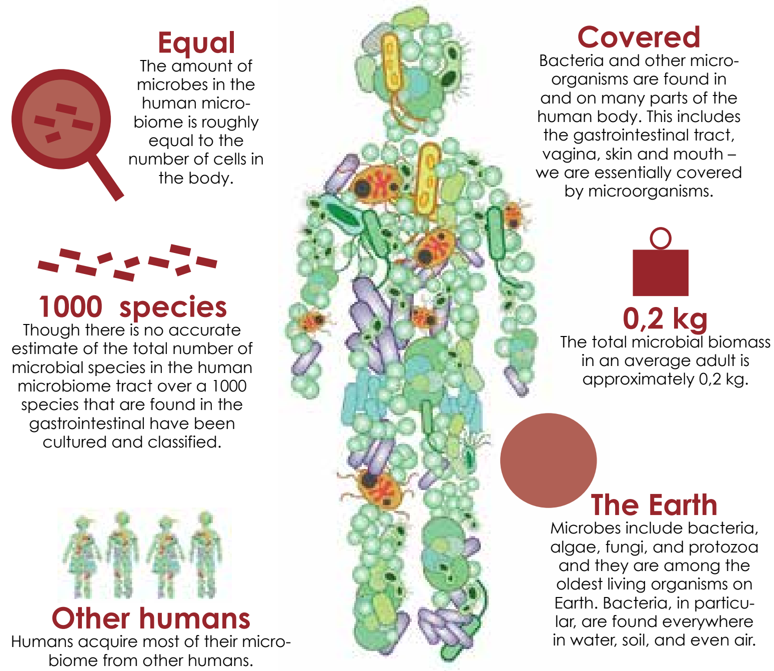
All you wanted to know about microbes but were afraid to ask…

The human microbiome

Life on Earth depends on microbes. If we modify their relationship with the environment or eliminate them, we endanger all life on the entire planet. Microbes are the oldest inhabitants of Earth, constituting an invisible world – complex, challenging and diverse. They represent an unknown microuniverse full of puzzle and beauty, which need to be explored from multiple perspectives.

We humans need the microbial world to strengthen our defences, to degrade and remove waste and to produce substances essential for life. We carry roughly as many bacteria on and in our bodies as human cells. The bacteria in us are as vital to us as our kidneys, hearts or brains, and can rightly be viewed as an organ like these – the Microbiome.



The Basics

What are microbes?

Microorganisms or 'microbes' are small living organisms that we need a microscope to see. Microbes include bacteria, algae, fungi, and protozoa and they are among the oldest living organisms on Earth. Bacteria, in particular, are found everywhere in water, soil, and even air. They are capable of living in extreme conditions, such as boiling water, frozen ground, acid volcanoes, and at the bottom of the ocean. Some can reproduce by doubling every 20 minutes; others can survive for centuries in a resting stage.

What are the microbiome and microbiota?

Microbes permeate not just the entire planet but are also found in large quantities inside and on the human body[1]. This ecosystem is collectively known as the human microbiome and its microbial inhabitants are called the microbiota. However, the term microbiome is used ambiguously to also mean the total pool of genes carried by the microbiota, also known as the metagenome.

How many microbes live in the human body?

The amount of microbes in the human microbiome is roughly equal to the number of cells in the body. The total microbial biomass in an average adult is approximately 0.2 kg[2].

Though there is no accurate estimate of the total number of microbial species in the human microbiome, over a 1000 species[3] from the gastrointestinal tract have been cultured and classified. The composition of bacterial species in the human microbiome changes over time and when a person is sick or takes antibiotics, these changes may be substantial[2].

Where is the microbiome located?

Bacteria and other microorganisms are found in and on many parts of the human body. This includes the gastrointestinal tract, vagina, skin and mouth – we are essentially covered by microorganisms. However, the vast majority of bacteria reside in the human large bowel[2], and this is also the most studied part of the human microbiome.

How do we get a microbiome?

Humans acquire most of their microbiome from other humans. Babies probably encounter microbes already in their mother's womb, but the colonisation begins at birth with a flush of bacteria from their mothers when they are born vaginally. Their next sources are breast milk and family – especially siblings – and as they continue to grow and are exposed to different foods, other people, pets and other environmental microbes, their microbiome becomes more established[4].

Children who are born via caesarean section do not receive the initial flush of bacteria (mainly lactobacilli) from their mothers, and are instead colonised by bacteria from the skin of the parents and staff. Thus their microbiome is very different during the first years of their life.

The Microbiome and Human Health

Bacteria play important roles in the digestive, hormonal and immune systems of the human body[5]. For example, bacteria in the gastrointestinal tract, allow humans to digest foods and absorb nutrients that otherwise would be unavailable[1].

Humans have a symbiotic relationship with their microbiomes, where we affect our hosted microbes, and the microbes affect us.

Effect of diet

Our diet contributes to the similarities and diversities in microbiome in populations across the world. Some foods are prebiotic, beneficial for bacterial growth in general. And the types of foods we eat – carbohydrates, proteins and fats – will affect which bacterial species will thrive. For example, the seaweed-digesting gene is rarely found in the human microbiome. But in the people living in Japan, where seaweed forms a staple diet, it is common[6].

Production of neurotransmitters

Human brain development and behaviour is believed to be influenced by the human gut microbiome. Although studies to determine the exact mechanisms responsible for microbiome-nervous system interactions are still ongoing, available data suggests that the gut microbiome is producing neurotransmitters such as serotonin and dopamine[7].

Conversion of nutrients

The microbiome located in the human gut is responsible for catalysing digestion and metabolism of various food groups into simple absorbable nutrients. For example, the human gut produces less than 20 carbohydrate-digesting enzymes, known as CAZymes. Were it not for the over thousands of carbohydrate-digesting enzymes in the microbiome it would not be possible for us to digest most of the carbohydrates that we eat[8].

Helping the immune system

A healthy microbiome on and within various body parts can help protect the human from pathogenic microorganisms. When the ecological niches are adequately colonised with "friendly" bacteria, there is less room for pathogenic microorganisms to establish themselves and cause disease.

The Microbiome and Disease

Just as the microbiome can contribute to human health, it can also contribute to the development of diseases and disorders. Much research is being done, and the magnitude of the contributions of the microbiome is often unknown. Below are some examples of such diseases:

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterised by chronic and relapsing inflammation in the intestine[9]. Besides hereditary factors and the environment, disturbances or dysbiosis in the microbiome have been associated with the development of IBD. It is however still unclear if the inflammation itself causes dysbiosis or if the dysbiosis leads to inflammation in the gut[10].

Asthma and allergy

Asthma and allergy are local tissue inflammations determined by hereditary factors and the environment, making them complex diseases[11]. The microbiome is believed to play an important role in the development of asthma and different allergies especially in early life[12]. Insufficient exposure to microbes necessary for the immune system may lead to the development of allergic diseases and asthma[13,14].

Obesity

Obesity is a multifactorial disorder and a major global concern. Growing evidence suggests that the microbiome may have a role in nutrient acquisition, fat storage and energy regulation, which are contributing factors to the development of obesity[15]. The exact mechanisms and the role of microbiome on obesity are not yet fully understood, but it seems like different compositions of the microbiome may have different impacts on obesity[16].

Effects of Antibiotics on the Microbiome

All antibiotics kill both pathogens at the site of infection and bacteria belonging to the normal microbiome. This may cause several unwanted side effects and diseases described below:

Decreased diversity

A cornerstone of any well-functioning ecosystem is high diversity. Exposure to antibiotics can lead to changes and/or destabilisation (dysbiosis) in the human microbiome. This can in turn lead to diseases not necessarily directly caused by a single pathogen but caused by disruption of the composition and diversity the microbiome[17].

Selection of resistant bacteria

Whenever a population of bacteria is exposed to an antibiotic, any bacteria that are resistant to it, either by mutation or transferred resistance, gain an advantage. As many other bacteria die, the resistant ones are able to increase in number. Widespread use of antibiotics leads to selection of bacteria that in turn may spread and cause infections that are difficult to treat[18].

Transmission of resistance

Many bacteria are capable of transferring genetic material to each other via three routes: conjugation, transduction or transformation. Due to these processes, when one bacterium carries a gene causing resistance to a given antibiotic, the resistance gene can be passed on to other bacteria[19].

Antibiotic-associated diarrhoea

Clostridium difficile (C. diff) is an example of a bacterial pathogen that is also found in healthy individuals. However, use of antibiotics, especially broad-spectrum antibiotics, even at appropriate doses can cause dysbiosis allowing the pathogen to grow. This can result in severe diarrhoea and gastrointestinal infections[20].

Modifying the Microbiome

Probiotics

Probiotics are defined as live microbes that cause a health benefit to the host. Commonly used probiotics are species belonging to three genera: *Lactobacillus, Bifidobacterium,* and *Saccharomyces*[21]. In some cases, probiotics have been shown to modulate the composition of the microbiome and help restore or maintain human health by preventing growth of pathogenic bacteria[22,23].

Prebiotics

Prebiotics are substances that are beneficial for microbial growth. All known prebiotics are carbohydrates that are indigestible by mammalians but fermented by the microbiota. In contrast to the probiotics, where live bacteria are eaten, prebiotics help existing bacteria to grow. Examples of prebiotic foods are asparagus, onions and oats[23].

Microbial transplants

In children delivered via caesarean section, concerns are that the lack of early colonisation with lactobacilli and bifidobacteria from the mother may have adverse health effects. Trials have been made where the newborn has been swabbed with the mother's vaginal microbiota. The results show that the babies develop a normal microbiome more rapidly than without the procedure[24].

Faecal transplants have shown to alter the microbiome and be a successful treatment approach for intestinal disorders, especially in patients with *Clostridium difficile* infection[25]. The theory is that a dysbiosis can be restored to a healthy composition by inoculating it with a healthy microbiota.

Environmental Microbiomes

Apart from the human microbiome, researchers are also studying the microbiomes of other systems such as hospitals, animals, different habitats on Earth and even the Earth as a whole. The Earth Microbiome Project[26], founded in 2010, is a massively collaborative effort involving over 500 investigators, using crowd-sourced samples, to understand patterns in microbial ecology across the biomes and habitats of our planet.

The most influential bacteria for life on Earth are found in the soil, sediments and seas. The most well known functions of these are probably providing nutrients like nitrogen and phosphorus to plants as well as producing growth hormones. Also, by producing antibiotic compounds and by their sheer number the beneficial bacteria may keep pathogenic bacteria at bay[27]. By decomposing dead organic matter, they contribute to soil structure. The different compositions in different soils can even affect which plants are able to grow in a certain place[28].

The more spectacular species of environmental microorganisms are capable of living in extreme conditions: salt lakes, hot springs or mud pots near volcanoes, some producing beautiful, vivid colours.

Laguna Colorada in Peru. The water is colored red by microbes/microorganisms.

Antibiotics and the Environment

The myriads of different species of bacteria and fungi found in the soil cause competition for nutrients and living space among the microorganisms. Some species have conjured some competitive advantages by producing antibiotics. These substances are released into the nearest surroundings, inhibiting the growth of other bacteria[29].

Natural antibiotics

Some of these are known to man, and have been harnessed as antibiotics in medicinal use. Examples include penicillin, synthesised by the fungus *Penicillium chrysogenum,* tetracyclines synthesised by *Streptomyces* species, and polymyxins synthesised by *Bacillus polymyxa*. Some estimates claim that approximately 80% of the antibiotics used in human medicine are either originally from the soil microbiome, or modified derivatives of such[29].

The latest substance found from the soil microbiome is teixobactin. The discovery of teixobactin was announced in 2015. It is a substance produced by the previously uncultivable bacterium *Eleftheria terrae*[30].

Antibiotic resistance

The other side of the story of antibiotics is the story of resistance. For an ecosystem containing antibiotic producing bacteria to be in balance, there need to be bacteria resistant to these antibiotics. And so there are. For every class of antibiotics in human use, there are resistant bacteria. Antibiotic resistance has even been found in caves secluded from human influence.

Selection of resistance

With the use of antibiotics in human medicine and food production comes selection of resistance in bacteria, not only in our human microbiome, but also in animals and the environment. When human activities release antibiotics to the environment – through wastewater, manure or release from aquaculture – resistant bacteria and resistance genes are enriched. These bacteria are then able to spread and share the resistance genes to other bacteria they encounter[31].

Antibiotics affect environmental microbiomes

Release of antibiotics to the environment may also affect the composition of the soil microbiome[32]. Spread of antibiotic containing manure has, for example, been shown to inhibit nitrogen-fixing bacteria and cause a shift in the populations in favour of fungi. At high loads of antibiotics near the outlets of wastewater treatment plants, the microbiomes have changed even more, with high degrees of resistant bacteria[33].

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