

A REPORT FROM
THE AMERICAN ACADEMY
OF MICROBIOLOGY

HUMAN MICROBIOME

FAQ



AMERICAN
SOCIETY FOR
MICROBIOLOGY

FAQ

ABOUT ASM FAQs

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FAQ reports are based on the deliberations of 15-20 expert scientists who gather for a day to develop science-based answers to questions the public might have about topics in microbiology. The reports are reviewed by all participants, and by outside experts, and every effort is made to ensure that the information is accurate and complete. However, the report is not intended to advocate any particular position or action, nor to replace the advice of an individual's health care provider.

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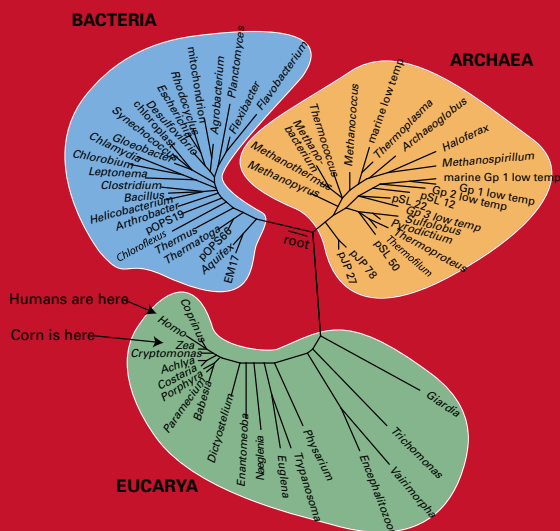
1) What is the human microbiome?

If you think back to your high school biology class, you probably remember learning about cells. You learned that the human body is made up of many different kinds of cells — skin cells, muscle cells, neurons, and blood cells, for example. You might even remember learning that each of these different kinds of cells develops and functions in accordance with the directions encoded by a single set of genes shared by all human cells and that the full set of these human genes is called the human genome.

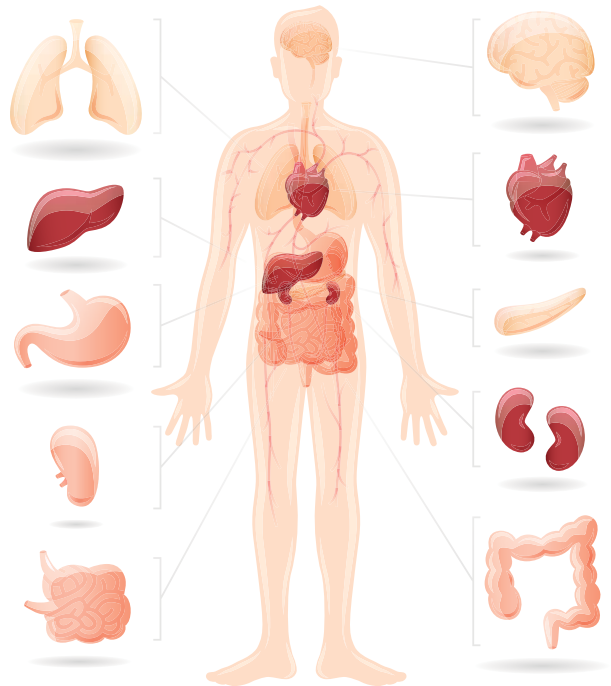


Wait a minute, what's a microbe?

The term "microbe" is used to describe organisms that are too small to be seen with the naked eye. Microbes include bacteria, archaea, fungi, protists, and viruses. Bacteria and archaea are single-celled organisms that do not enclose their genetic material in a nucleus. Although similar in appearance, at the genetic level bacteria and archaea are only very distantly related. Together, these two life forms represent a huge proportion of the diversity of life on Earth, each constituting a major branch, or domain, of the tree of life. The third major branch, the Eukarya, includes all the plants and animals you can see (including humans). There are also many microbes on the eukaryotic branch of the tree of life, including some fungi (like yeast), some algae, amoebas, slime molds and protozoa. Finally, viruses are also considered microbes. Because viruses can only reproduce by infecting cells and hijacking the cell's own machinery to make new viruses, there is debate as to whether they can be considered alive and they are not included in the universal tree of life. Undoubtedly, though, viruses play many important, even essential, roles in biological systems, so they must be taken into account as important participants in microbial communities.



Norman R. Pace, A Molecular View of Microbial Diversity and the Biosphere. Science 276, 734 (1997)



What you almost certainly did not hear about was that the human body also contains trillions of cells that are not human, but microbial, each of which has its own unique complement of genes. Together, these microbes constitute the human microbiome and scientists are now finding that they play an important role in human health. If you need a little refresher course on the definition of microbes, please take a look at the box entitled "Wait a minute! What's a microbe?"

The bottom line is that the human body hosts a huge number of microbes of many different kinds. These microbes play a role in many fundamental life processes. The collection of microbes that constitute the microbiome is not random; the human microbiome is made up of a particular set of microbes that complement each other and the human host. Systematic study of the human microbiome is a very young science and scientists are just beginning to address the questions of what constitutes a normal microbiome, how the microbiome changes over time, and how the composition and activity of the microbiome affect health and disease. What is already clear is that the effect of the microbiome on its human host is profound and multifaceted. Indeed, it is reasonable to characterize the microbiome as a newly recognized organ, with a great range of metabolic activities.



Definitions:

The term “human microbiome” is so new that there is not yet a fully agreed upon definition. But names matter. It’s worth exploring how scientists talk about the microbial communities associated with the human body, because when a new field of study is first emerging, definitions are important. They ensure that everyone is talking about the same thing.

Humans are not the only organisms that have a closely associated microbial community. In fact, there are microbial communities everywhere — in the soil, in the ocean, in every building and water pipe, and on every plant and animal. So the terms below can be used to describe microbial communities wherever they are found.

- **Microbiota:** all the microorganisms that live in a particular environment, for example, the human body. The organisms living on humans were once called the “microflora” but this term is now considered incorrect and misleading, since it implies that humans are colonized with tiny plants. The organisms that constitute the human microbiota are not plants; they are microbes of various kinds.
- **Microbiome:** This term has two definitions, one genetic and one ecological.
 - **Definition 1:** Just as the entire collection of human genes is called the human genome, this definition of microbiome means the entire collection of genes found in all of the microbes associated with a particular host. A broader term, “metagenome” means the entire collection of microbial genes found in a particular environment. A “metagenome” may or may not be host-associated — metagenomes have been generated for sea water, showerheads, and hot springs, among many other environments.
 - **Definition 2:** Ecologists use the term “biome” to describe the collection of plants and animals that live in a particular environment. Thus there are various terrestrial and aquatic biomes (temperate grasslands, or tropical coral reefs, for example) that are characterized by similar climatic conditions and collections of organisms. When microbiome is used in this sense, it refers to the ecosystem made up of microbes within and on the human body — that is, the collection of microbes that live in the human “habitat.”



2) Where does our microbiome come from?



The microbial world may be largely invisible to the human eye, but it is vast almost beyond imagination. There are hundreds of thousands of different kinds of bacteria alone (leaving aside for the moment the other kinds of microbes: archaea, viruses, fungi, and protists), living in every conceivable environment including deep under the seabed, high in the clouds, in the near boiling hot springs of Yellowstone National Park, and in highly acidic drainage from old mines.



Billions of years before multicellular organisms emerged, microbes had seemingly occupied every possible ecological niche. The emergence of multicellular organisms created an entirely new set of habitats — in and on all those animals and plants. The kinds of partnerships between animals and plants and their microbes are just beginning to be explored, but the important thing to recognize is that these associations are not random. Each organism has evolved to have intimate associations with particular kinds of microbes — perhaps not exactly the same species in every case, but with characteristic types. Humans are no exception; of the hundreds of thousands of kinds of microbes on Earth, only about 1,000 have been found associated with humans.

So there are hundreds of thousands of different kinds of microbes in the world, and several hundred different



kinds are generally found in the average human microbiome. How do we get the right ones? Where do they come from?

The short answer is that we get most of them from other humans. Newborn babies encounter microbes for the first time during birth. As the baby is being born, it is coated with microbes from the mother's birth canal. Babies that are born by caesarean section first encounter microbes from the mother's skin and from other individuals who touch the baby. We don't yet know whether the mode of birth has a permanent effect on the composition of one's adult microbiome, but early results suggest that the effects can be long-lasting. The next source of microbes is breast milk. Surprised? Most of us are used to thinking of microbes as dangerous, so finding out that mother's milk contains bacteria may be shocking. But in fact the microbes in milk play an important and very interesting role in the establishment of the baby's healthy microbiome (see box on breast milk).

Newborns also acquire microbes from their fathers, siblings, and caregivers. As babies grow more mobile and begin to explore the world, they encounter both environmental microbes (like those that live in soil and water), and microbes that have been shed by other people, pets, and plants. They also ingest microbes in food as their diet becomes more diverse. The vast majority of environmental microbes will not become part of the microbiome; they are not capable of living in the habitats provided by the human body. Newly encountered microbes that can live in humans have to compete with the microbes that are already established in and on the infant. An important concept to remember is that of "selection" — as the human microbiome becomes established, there is selection going on in multiple directions; newly encountered microbes seek an appropriate environment, which includes both the conditions at the human body site, and the microbes that are already there. At the same time, the human is selecting for microbes that provide needed services and do not cause harm. Microbes sense and interact with specific markers that are secreted by cells or found on their surfaces and use these cues to "decide" where to grow. Thus, there is a role for human genetics in the eventual structure of the microbiome. The exact mechanisms that govern these selection processes are also under active study, but they certainly include a great deal of chemical communication, as well as physical cues like temperature and moisture levels. In any event, the set of microbes that ends up constituting a mature microbiome is far from random — during the first two years of life, there is a process of mutual selection between the baby and the microbes it encounters.



Breast milk: baby's first microbes plus a snack for their friends

Breast milk has been fine-tuned over tens of thousands of years of evolution to provide the ideal nutrition for the developing infant. Replete with nutrients, vitamins, and antibodies, it is the only food a baby needs for the first six months of life. And now it turns out that in addition to providing nutrition, breast milk also supplies many different kinds of bacteria to populate the baby's gut and nutrients that are specifically used by those bacteria to grow and thrive.

In addition to bacteria, breast milk also contains a number of complex carbohydrates (oligosaccharides) and glycosylated proteins that actually cannot be digested by the infant. However, they are readily consumed by bacteria of the *Bifidobacterium* species. *Bifidobacteria* are the dominant species in the infant microbiome and are thought to play a role in coating the intestinal surface and preventing the attachment of pathogens. Thus, breast milk contains both probiotics (beneficial microbes) and prebiotics (compounds that support the growth and establishment of beneficial microbes).



3) How big is the microbiome?

The microbiome is big by almost any measure — number of organisms, total volume, species diversity, and genetic diversity.

NUMBER OF ORGANISMS:

The microbiome includes approximately 100 trillion bacterial cells. That's 100,000,000,000,000! You may have heard that there are 10 times more microbial cells than human cells in the human body, but that commonly-cited ratio was based on an estimate of 10 trillion cells in the human body. More recent estimates suggest that the human body actually is made up of about 37 trillion human cells. Thus at any given time, the average human body is carrying around 3 times more bacterial cells than human ones. But the microbiome includes more than just bacteria. Remember that it also includes plenty of viruses, fungi, archaea, and single-celled eukaryotes. There is general agreement that viruses outnumber bacterial cells, maybe by as much as 5 to 1. There are thought to be about 10-fold fewer fungal cells than bacteria. All of these numbers are estimates and because the microbiome is a dynamic community, the numbers may change under different circumstances. However, by whatever measure, the microbiome is big!

TOTAL VOLUME:

The microbiome is also pretty big in terms of the space it occupies and its total weight. Even though each individual member is microscopic, those large numbers do add up. Most estimates put the weight of an average human microbiome at about 2.5 pounds. In volume, if consolidated, the microbiome would occupy about 3 pints. Keep in mind though, that the microbiome is not all consolidated in one place, and the density of the various microbial communities varies greatly from body site to body site. Blood and lymphatic fluids are practically sterile, while the intestines and colon contain one of the densest known microbial communities on Earth. What

is the secret to that high density in the intestinal tract? Surface area. The inner surfaces of the human intestine and colon are highly convoluted. If you were to flatten out the entire inner surface of the intestine, it would be the size of a tennis court! Dense microbial communities coat that entire surface and also fill the interior spaces of the intestines, resulting in a very dense community.

SPECIES DIVERSITY:

The microbiome is also diverse — a normal microbiome includes around a thousand different species. Thinking back again to your high school biology class, you might recall learning about three basic kinds of bacteria: rods, spheres, and spirals. Certainly bacteriologists developed and used a much more detailed classification system that took into account bacterial physiology and metabolism, but until quite recently, known bacterial diversity was confined to the approximately 5,000 bacterial species that could be grown in the laboratory. Technological advances, especially the capacity to sequence genetic material from environmental samples, have allowed scientists to explore the bacterial world at much greater depth and resolution. Scientists now estimate that there are at least a million species of bacteria and there may be many more. Because bacteria are so small, and look so similar under the microscope, it may be difficult to grasp just how different these bacterial species are from each other. But at the level of their genetic blueprints, even quite similar looking bacteria can be as different from one another as humans are from roundworms (see "Looks can be deceiving").

The extraordinary diversity of bacteria stems from the fact that they have been evolving for over 3.5 billion years, during which time they evolved the capacity to live in wildly different environments. Just as polar bears are adapted to the cold and cacti to the desert, different kinds of bacteria have evolved to thrive in virtually every environment on Earth including places where there is no light, virtually no water, and temperatures from well below zero to near boiling. Given how different those environments are, it starts to make sense that these bacteria must be very different from each other.

Kinds of cells in the human body



Out of that vast diversity, only a tiny fraction is adapted to live in and on people. So while the human microbiome includes many hundreds of species of bacteria, these represent only a small subset of all of the different kinds of microbes on Earth.

The diversity of viral and fungal species in the human microbiome has not yet been studied as thoroughly as that of bacteria, but these populations also include hundreds or perhaps even thousands of different species. Bacteriophage — viruses that infect bacteria — are often highly adapted to particular host bacterial species, so it is possible that the viral component of the microbiome is as, or even more, diverse than the bacterial.

GENETIC DIVERSITY:

The human genome — the full set of genetic blueprints that each baby inherits from its parents — includes about 20,000 genes. The collective genomes of all the bacteria, fungi and viruses in one person's microbiome are thought to include as many as 8,000,000 genes. Thus for every human gene, there are up to 300 non-human genes. If you think of each gene as a set of instructions to produce a protein that can do a particular task, this means that the microbiome provides each of us with an enormous reservoir of genetic capability that does not have to be encoded by the human genome itself.

What does this mean in concrete terms? Let us take as an example the digestion of carbohydrates. Carbohydrates like sugar and starch are a class of chemical compounds that are synthesized by all living organisms and are extremely diverse. The plants that humans eat, for example, contain carbohydrates with thousands of different chemical structures. During digestion, those carbohydrates are broken down to their simplest components to provide us with energy. The human genome, however, has fewer than 20 carbohydrate-digesting enzymes. On their own, then, human cells cannot break down most of the carbohydrates we consume. By contrast, the genome of just one gut bacterium — *Bacteroides thetaiotaomicron* — has over 260 such enzymes! It's as if the human genome has just a few Allen wrenches while the *B. thetaiotaomicron* genome has a whole hardware store. Hundreds of other gut microbes have genes for even more carbohydrate-digesting enzymes. Carbohydrate digesting enzymes are just one example of the genetic tools that humans gain access to via the microbiome.

Bacterial genomes can change dramatically more quickly than the human genome. Bacteria that are distantly related can exchange genetic material

Looks can be deceiving



Bacteriodes fragilis



Escherichia coli

Shared genes = 40%



Caenorhabditis elegans
(nematode)



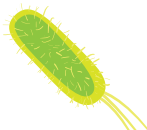
Human

Shared genes = 38%

They may look alike, but the two species of bacteria *Bacteriodes fragilis* and *Escherichia coli* are about as similar at the genetic level as humans and nematode worms.

in several ways, allowing genes that provide a selective advantage in a particular environment to spread throughout mixed bacterial populations. This phenomenon is why antibiotic resistance is such a big problem; if one bacterium evolves resistance to an antibiotic, the responsible gene can be transferred to other bacteria, rendering them resistant too. While antibiotic resistance may be an undesirable trait from the human point of view, the capacity of bacteria to share genes means that the microbiome can change over time at the level of individual genes in addition to changing mixtures of species. Theoretically, because the microbiome can change much more quickly than the human genome, the microbiome provides a much more rapid means for humans to adapt and thrive when environmental conditions change.

One example of such an adaptation is the discovery of a gene for digesting seaweed in the microbiome of some Japanese people. The gene is rarely found in human microbiomes outside of Japan. Where did it come from? It is usually found in environmental bacteria that feed on seaweed in nature. At some point, one such environmental bacterium, possibly while passing through someone's gut on a piece of seaweed, transferred some of its genes to a normal bacterial constituent of the human microbiome. The gene conferred the ability to digest the seaweed that is a common part of the Japanese diet, a capability that is now part of the genetic capacity of the human microbiome in Japan.



4) Where is the microbiome located, and what is it doing?

Wherever the human body is exposed to the outside world, there is a microbial community. That means that the entire surface of the skin, and the linings of the nasal passages, lungs, digestive and urogenital tracts are all home to microbial communities. Some of these communities are extremely dense and others more sparse. And because the living conditions are very different in these different sites, it is no surprise that each one has its own characteristic set of microbes. What the microbiome is doing also varies from place to place and many of its functions have not yet been worked out. Here are some examples of human microbiome communities:



SKIN:

Microbes live on all skin surfaces as well as within pores and sweat glands, and along hair shafts. The composition of the skin microbiome varies from place to place, with dry areas like the arms and legs having fewer and different microbes than moist or oily areas like the armpits or nasal creases. There are indications that some commonly found skin microbes can help keep away pathogens. For example, the frequently found *Staphylococcus epidermidis* has been shown to produce compounds that inhibit the related, but pathogenic, *Staphylococcus aureus*.

MOUTH:

About 1000 microbial species have been found in the human mouth, with any individual person usually hosting 100-200 species. Like the skin, the mouth contains many different microhabitats including tooth surfaces, tongue, cheeks, and gums. Most of these habitats are exposed to the air, but the pockets formed where teeth emerge from the gums can be anaerobic and permit the growth of microbes that can grow without oxygen. In what is emerging as a common theme when it comes to the human microbiome, the line between oral health and diseases like dental caries (cavities) and periodontal (gum) disease seems to depend on maintaining a well-functioning community of microbes that exists in harmony with the immune system. When this balance is disrupted, pathogens can gain a foothold.

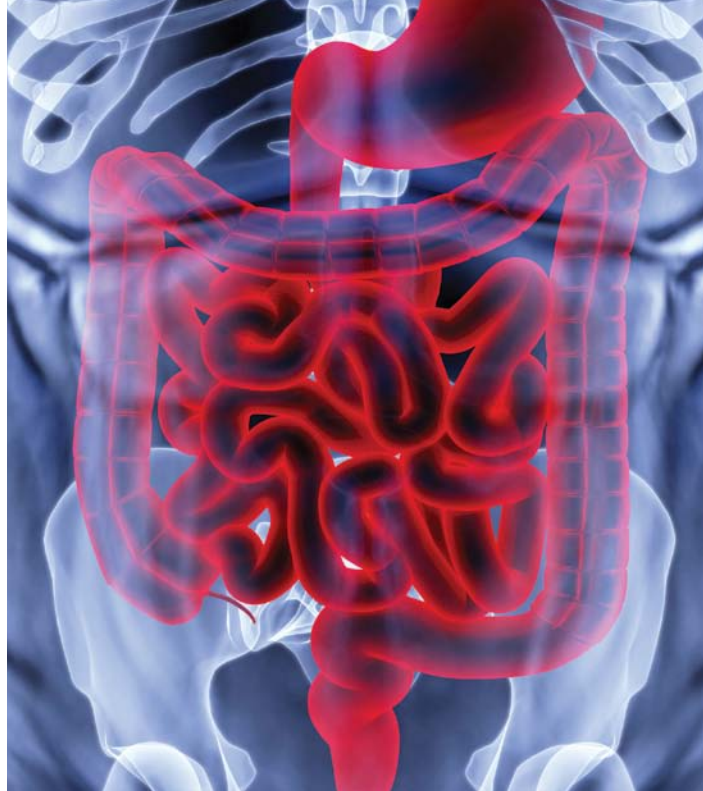


GUT:

The gut is the best-studied site in the human microbiome and it contains the largest, densest, and most diverse microbial community in the human body. In fact, the microbial community in the human large intestine, at up to 100 billion to one trillion cells per milliliter, is among the densest microbial ecosystems ever observed. The gut microbiome acts as a highly efficient bioreactor, helping to extract energy and nutrients from the food we eat. Like the microbial communities elsewhere on the body, the gut microbiome protects against pathogens and is in constant communication with the immune system.

The gut microbiome is also important because of the many chemical reactions that can be carried out by microbes. Compounds that humans cannot digest on their own can be broken down by microbes. Evolutionarily, these microbial capabilities allowed humans to benefit from a wider variety of foodstuffs. The metabolic diversity of microbes also has a contemporary impact. Gut microbes have been found to affect the metabolism of some drugs, such as digoxin (a heart medication often used to treat atrial fibrillation) and acetaminophen (used to treat pain and fever). A drug used to treat advanced colorectal cancer, called irinotecan, or CPT-11, which is normally detoxified by the liver, is turned back into its active form by gut microbes, causing extensive cell death in the intestines and thus severe diarrhea. Prescribing an additional drug that inhibits the microbial enzyme responsible for re-activation may allow cancer patients to be given higher doses of the anticancer drug.

Finally, the gut microbiome has complex effects on human metabolism and changes in its composition have been linked to a number of diseases including inflammatory bowel disease, *Clostridium difficile* infections, autoimmune disorders, and even diabetes and obesity. In most cases, the associations between the microbiome and these diseases are just that — associations. Many specific mechanisms have been demonstrated in animal models, but it is not yet known which are most important in humans. What is certain is that the microbes of the gut are extremely metabolically active in their own right and many of the chemical compounds they secrete — known as metabolites — pass through the gut wall into the bloodstream and circulate throughout the body. There are intriguing indications that the gut microbiome may affect sleep patterns, mood, and other behaviors. Again, the science is still young, but it is clear that the microbiome has many systemic effects.



Do I still have to wash my hands and brush my teeth?

YES! The vast majority of microbes that you encounter in your daily life are harmless or even useful for replenishing your microbiome. Many studies suggest that increasing levels of hygiene in the past 100 years may actually have deprived humans of contact with the rich range of microbes that our immune systems evolved to expect and contributed to the relatively recent rise of allergies and other autoimmune disorders. Be that as it may, even though a healthy microbiome helps prevent pathogens from becoming established, it's still important to give your microbiome a hand when it comes to avoiding microbes that might make you sick. So, by all means, wash your hands frequently and thoroughly (with warm water and regular soap), especially when you have been in situations that would be likely to expose you to pathogens or when you are likely to come into contact with individuals who have compromised immune systems. And yes, you should still brush and floss your teeth just like the dentist orders. There is no need to use special "antibacterial" soaps or rinses. It is also important to avoid the unnecessary use of antibiotics because they can disrupt your microbial communities and potentially leave them vulnerable to invasion by pathogens.



5) Is everyone's microbiome the same?

Yes and no.

Each individual's microbiome carries out many similar functions, but the jobs are not necessarily done by the same microbial species in each person. Also, the species carrying out the various functions in any given individual may change over time. The situation is analogous to any other kind of ecosystem — if you were to compare forests from all over the world, you would find trees, ground cover, birds, insects, and animals in each forest. Some might be dominated by oak trees, others by spruce, but the various ecological niches that make up a forest would all be filled. Another useful analogy is that of a city: every city has firefighters, police officers, bus drivers, and garbage collectors, but different people

fill those roles in each city. In the human microbiome, certain broad functional capabilities are always found, but they are not always carried out by the same microbial species. Some functions are quite specific — for example, the ability to metabolize a particular drug or digest a specific dietary compound — and these functions are not found in everybody, or at all times.

The first five years of the Human Microbiome Project, a research program funded by the National Institutes of Health, examined the microbiomes of 242 healthy individuals at 15 (male) to 18 (female) body sites and found them to be quite diverse, both from individual to individual and from body site to body site. What did they find out?

- There is quite a bit of variation from one person to the next, but one's own microbiome is fairly stable over time.
- The microbiomes of various body sites are similar in everyone. Thus, your skin microbiome is more similar to other people's skin microbiomes than to your own gut microbiome.
- When microbiomes are classified by the bacterial species they contain, they look very different from person to person. If they're classified by the presence of various functional capabilities — the ability to digest different kinds of carbohydrates, synthesize vitamins, or break down toxins, for example — they look more similar from person to person.

The Human Microbiome Project focused on healthy individuals with the goal of establishing a baseline description of a "normal" microbiome. Ongoing studies are starting to look at whether particular microbiome compositions correlate with particular diseases, disease risks, and responses to drugs or other treatments. Furthermore, microbiome studies are moving beyond identification of "who's there" — that is, microbial species composition of the microbiome — to "what are they doing?" — that is, understanding their functions.



Does everyone have a microbial "fingerprint"?

Will there soon come a time when forensic scientists will be able to identify a suspect by matching crime scene evidence to his or her microbiome? Or will it be possible to tell where someone has traveled by testing for characteristic microbes? At present, these scenarios are purely hypothetical. We do not yet know enough about how much variation there is between individuals' microbiomes, nor do we know how much or how quickly microbiomes change over time, to use such data in a forensic setting. So it will probably be quite a while before microbiome evidence appears in a real-life trial — although a study that matched office workers with their computer keyboards by analyzing the microbes transferred from their skin to the keys did find its way onto a television drama! Valid use of microbiome information for forensic purposes will require a much larger reference database than is currently available.



6) Does the microbiome change over time?

The microbiome definitely changes dramatically between birth and the age of about two years, when it begins to look like a typical adult microbiome. The situation is not unlike what happens after a fire or volcanic eruption in a natural environment; certain plants and animals are predictably the first to colonize the cleared area, with others arriving as the conditions change. After some years, the cleared area will resemble areas around it that were not disturbed.

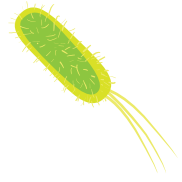
It is worth noting that this natural succession of species may proceed differently in an area where there has been a lot of human activity. In such a situation, weeds, pests, or other invasive species may arrive first and out-compete the native plants. The area may never regain the native mix of species.

During the first two years of life, infants gradually acquire a microbiome that resembles the typical adult microbiome. Soon after birth is a unique time when, for example, rare microbes can become established — later they would be out-competed. The recognition that these early years are a crucial time for the establishment of the microbiome has drawn new attention to practices that are fairly recent human introductions — caesarean delivery, formula feeding, and, especially, the use of antibiotics early in life. The long-term impact of different practices on the microbiome is unknown. Indeed, it appears that the process of acquiring a functional microbiome is quite robust as the vast majority of babies, whether born vaginally or by caesarean, breastfed or not, do just fine. Nevertheless, long-term and detailed surveys will be required to determine whether such recent healthcare and nutritional practices have unintended consequences that are predictable, and possibly preventable.

After the adult-like microbiome is established, does it change over time, or can it be intentionally changed? On the simplest level, the answer to both questions is yes. The microbiome can change as a result of changing diet, treatment with antibiotics, or a move to a new environment, whether these changes are intentionally aimed at changing the microbiome or not.

The microbiome can change in different ways — some species will be found at all times while others will come and go. Certainly, the proportion of different species or groups of species will change. Characteristic distributions of certain groups of gut bacteria correlate closely with obesity and the microbiomes of individuals who lose weight will gradually come to resemble the microbiomes more characteristic of lean people. What is harder to measure, but certainly also true, is that the function of the microbiome can change even if its composition does not. This is because the microbes that make up the microbiome are complex organisms with diverse genetic capabilities. When conditions change, they will activate different metabolic pathways. That, in turn, will affect the microbes around them, and the human host.

Understanding how the microbiome can change over time requires getting into the mindset of an ecologist. Together a human host and its microbiome form an ecosystem — actually, many interacting ecosystems. Changes in any one member, or in the external environment, ripple through the community in ways that scientists are only beginning to unravel. The ultimate goal is to understand what constitutes a healthy human-microbiome ecosystem and then to develop the means to keep it healthy and repair it when necessary.



7) What is the relationship between the microbiome, health, and disease?

Any suggestion that complex conditions like diabetes or obesity can be explained simply by the composition of the microbiome is likely to be misleading. There have been many studies that show a correlation between certain mixtures of microbes and certain disease states, but evidence that any particular microbial community actually causes a particular disease is still limited. What is clear, however, is that the microbiome is probably an important factor in many diseases, a factor that has been neglected in the past. A better understanding of the microbiome will deepen our perception of human health and likely contribute to new kinds of treatments and more effective ways to deploy traditional treatments.

The early history of microbiology was dominated by the quest to identify the microbes responsible for disease, and find ways to stop them. As far back as 1890, the microbiologist Robert Koch and colleagues advanced the then-revolutionary idea that particular microbes caused particular diseases. The implications of this insight were profound. Identification and study of causative agents was the first step in developing ways to prevent and cure infectious diseases, certainly one of the public health triumphs of the 20th century.

Koch developed a set of postulates laying out the conditions that had to be fulfilled in order for a disease to be attributed to a particular microbe. Still used today, Koch's postulates rest on the assumptions that each disease can be attributed to a particular microbe and that disease-causing microbes are not found in healthy individuals. The "one microbe-one disease" concept is so strong that many diseases are actually named for the microbe that causes them — for example, polio is caused by the polio virus and strep throat by the bacterium *Streptococcus*.

Koch's postulate #1:

The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.

Koch's postulate #2:

The microorganism must be isolated from a diseased organism and grown in pure culture.

Koch's postulate #3:

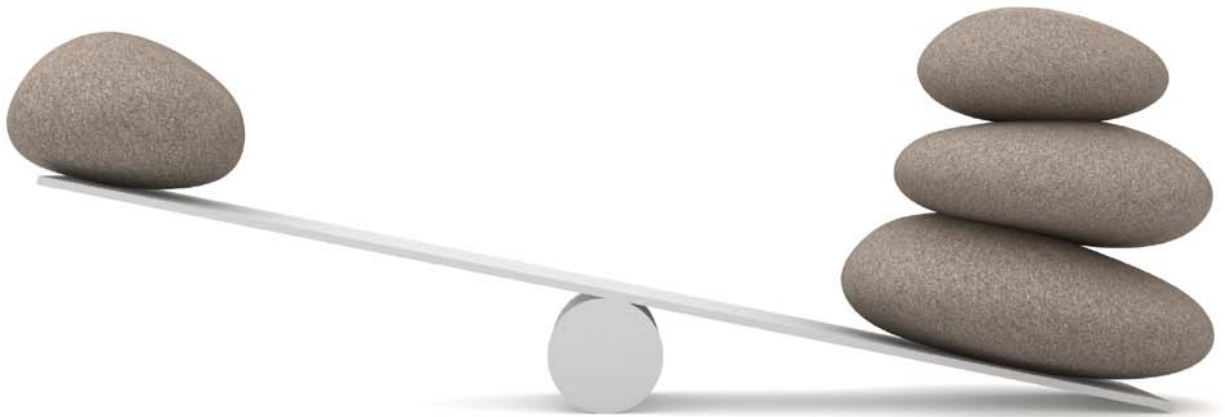
The cultured microorganism should cause disease when introduced into a healthy organism.

Koch's postulate #4:

The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

If you read Koch's postulates with an awareness of the magnitude and multiple roles of the microbiome, you can see that their ability to describe the relationship between microbes and disease has become less universal. What is becoming clear is that not all





microbially-associated diseases are “infectious” in the traditional sense. Some diseases are caused by microbes that are normal constituents of the microbiome, so they are found in both healthy and diseased individuals. *E. coli*, yeast, *Staphylococcus aureus*, and *Clostridium difficile* are all examples of potential pathogens that can be found in healthy individuals, but cause disease only when the microbiome is disturbed or the microbes gain access to a part of the body where they do not normally live. The role of the microbiome in crowding out or otherwise inhibiting pathogens is another reason that mere presence of a pathogen does not necessarily mean disease. A pathogen may not cause disease if it is introduced in the context of a healthy microbiome, or, conversely, a dramatically smaller dose of the pathogen may result in disease if the microbiome is disturbed. For example, the infectious dose of *Salmonella* is one-thousand fold lower for individuals who are on antibiotics.

Some diseases may be the result of disturbance of the microbial “community” that makes up the microbiome. In this case, the symptoms are not caused by a particular microbe, but by altered proportions of various normal constituents or altered behaviors of the normal constituents under conditions of stress. For example, the discomfort that many people experience after taking broad-spectrum antibiotics is the result of a disturbance of the normal microbial community in

the gut that leads to gastrointestinal inflammation and diarrhea, and sometimes sets the stage for infections by pathogens like *Clostridium difficile*.

A corollary of the fact that human health depends on maintaining a good relationship with a complex set of microbes is the recognition that microbes can contribute to disease in previously unexpected ways. Many human diseases in which microbes were not previously thought to play a role have recently been shown, largely in animal models, to be at least partially influenced by the microbiome. Diseases as different as asthma, diabetes, obesity, cancer, and heart disease have been shown to be influenced by the microbiome. In mice, there are even intriguing, if very preliminary, indications that the microbiome may play a role in conditions like anxiety and insomnia.

The gut microbiome is not the only one with a role in disease and health; the microbiomes of the mouth, skin, vagina, lungs, and stomach are also altered in various disease states. The microbes in these body sites are not simply passive bystanders but are playing active roles in the dynamic balance between health and disease. In the majority of cases, the underlying mechanisms by which the microbiome affects health have not yet been determined, but highly suggestive correlations have been found. Research on model organisms, especially mice, is ongoing in an attempt to better understand exactly what is going on.





8) Spotlight on the role of the gut microbiome in digestion and metabolism

Complicating the effort to understand the role of the microbiome in many non-infectious diseases is the fact that most such conditions are multifactorial. Changes in the microbiome may be a major contributor in some patients or under certain conditions, but not all. Obesity, for example, has genetic, environmental, hormonal, neurological and many other contributing factors, in addition to the role of the microbiome.

Nevertheless, obesity is a disease in which the study of the microbiome could have profound implications for human health. Much of what scientists know, or suspect, about the roles of the human microbiome in metabolism come from studies in mice. Many experiments can be done with mice that would be impossible or unethical to impose on humans. For example, mice can be raised without a microbiome (such mice are called “germ-free”); microbes can be introduced in a defined manner (these mice are called “gnotobiotic” to signify that the composition of their microbiomes is precisely known); microbiomes can be swapped between mice; and diet can be completely controlled. Studies in mice suggest that there are very strong feedback loops connecting diet, the microbiome, and metabolism. Among the results that point to important roles for the microbiome in obesity and other metabolic conditions are:

- Mice that are maintained in the germ-free state are leaner than mice with microbiomes even when they are fed more food or a high-fat, high-sugar diet. Without a microbiome, much of the food passes through undigested.



- Germ-free mice that are inoculated with the microbiome of an obese mouse or human donor gain more fat than those that receive the microbiome of a lean control, even when both receive the same amount of food. Co-housing these two groups of mice allows bacteria from the lean donor to invade the obesity-associated gut microbiome, blocking the increase in body fat.
- Microbiome composition changes within a single day when mice or humans are fed high-fat diets. When the resultant “high-fat” microbiome is transferred into a germ-free mouse, that mouse will be fatter than a littermate given the microbiome of an adult on a normal diet.

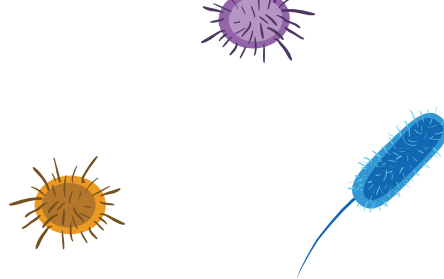
These and many other observations in mice, humans, and other animals suggest not only that the microbiome has a major effect on body fat, but that it is possible to shift the microbiome in ways that either encourage or discourage the accumulation of fat. It should be noted, however, that at this point, most studies, even in mice, are looking at correlations between gut microbiome composition and factors like weight, insulin sensitivity, and other metabolic measures. And, of course, while mice are excellent model organisms for understanding human health, they are not perfect and it is not clear how the human and mouse microbiomes will differ in their effects on the host’s health and metabolism. Exactly how the microbiome exerts these effects is the subject of intense study as is the question of whether the composition of the human microbiome can easily

be shifted from one state to another. The prospects, however, are intriguing.

In addition to obesity, studies examining the gut microbiome in humans have found a number of interesting correlations between microbiome composition and several diseases related to inflammation of the gut including inflammatory bowel and Crohn’s diseases. Disorders related to auto-immune reactions, including celiac disease, asthma, and other allergies have also been related to differences in microbiomes, or correlated to factors that affect microbiome composition like vaginal vs. caesarean section birth, or extent of antibiotic exposure. Disruption of the gut microbiome by antibiotics has been implicated in the development of persistent *Clostridium difficile* infections, but not everyone who takes high dose antibiotics develops this condition. A great deal of work remains to be done to determine the role that particular microbes or combinations of microbes play in any or all of these conditions. The answers are likely to be complicated because the microbiome does not exist in a vacuum and no two human microbiomes are the same. There is a dynamic relationship between the microbiome and many other factors. One’s individual genetic make-up may affect which microbes your body will encourage, tolerate, or reject. Major changes in diet do not only affect the microbiome — they affect the host as well, setting up a complex web of feedback interactions. Environmental factors like exposure to antibiotics and other drugs, or moving to a new geographic location, may also change or even destabilize the microbiome.



9) How can I take care of my microbial partners?



Now that you know about the trillions of microbes that call you home, and play such an important role in health, you may be wondering what you can do to keep them happy. The answer, for the moment, is that we just don't yet know what characterizes a healthy microbiome, or how our behavior affects it. There are a few things we can say, though. Broad-spectrum antibiotics can have a profound and often long-lasting effect on the microbiome. They can also be life-savers. The key is to use antibiotics only when necessary.

We also know for certain that your diet can affect your microbiome in two ways. First, just as we say that a pregnant woman is eating for two, it is absolutely true that you are eating for yourself and trillions of microbes. The foods you consume are also feeding your microbes. Some foods encourage the growth of microbes that are associated with good health — these foods contain certain compounds, like specific

carbohydrates, that “feed” desirable microbes. The compounds are called “prebiotics.” Thus, one of the ways that a diet rich in fiber, fruits, and vegetables contributes to good health is that it also encourages a healthy microbiome. Second, consuming microbes can change your GI microbiota. Fermented foods like yogurt, cheese, and sauerkraut actually contain microbes that are similar to those found in your GI tract. There are also supplements that are made up solely of microbes, called “probiotics.” There is lots of evidence that probiotics can contribute to health, but caution is called for. Probiotics are not regulated like drugs, so labels may not accurately reflect which microbes are present, whether they are viable, or how many are in a serving. For many prebiotics and probiotics, the kind of rigorous clinical testing that establishes whether a drug is effective, how much is needed, and how often it should be taken has not been performed. Measuring health and testing health claims can be a challenge given that medical knowledge about what defines “healthy” pales in comparison to what is known about disease. Probiotics are sometimes marketed as undifferentiated “cure-alls,” as if any microbe or mixture of microbes will be helpful for any condition. But probiotics are probably more analogous to any other kind of therapeutics, like drugs. After all, you don't just take a random drug if you are ill; you seek out the right drug for that disease or symptom. Over time, clinical testing will reveal which probiotics are effective for which conditions, in which patients. Indeed, some specific mixtures of microbes have already demonstrated effectiveness in treating irritable bowel syndrome and ulcerative colitis in randomized clinical trials.

As scientists and physicians learn more about the microbiome, the activities of pre- and probiotics will be better understood and it will be possible to apply more rigorous standards. Then it will be possible to give the public better guidance on how best to care for their microbiomes. Study of the human microbiome is a rapidly advancing field of science with new and exciting discoveries emerging constantly. You can be sure that you'll be hearing more and more about the essential microbial partners that make up your microbiome.



FAQ

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