frontiers FOR YOUNG MINDS

HEALTH
Published: 28 August 2019
doi: 10.3389/frym.2019.00111

THE INTESTINAL UNIVERSE—FULL OF GUT HEROES WHO NEED SIDEKICKS

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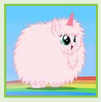
YOUNG REVIEWERS:


AYDEN
AGE: 11


HANNAH
AGE: 10


JOSHUA
AGE: 13


SAHASRA
AGE: 13


ZOE
AGE: 7

You are not, and will never be, alone. A multitude of friends that you cannot see with the naked eye, but who help to keep you healthy, live in your body. They are the bacterial heroes in your most heavily colonized organ, your intestines, living together with gut villains in a fragile balance that, when disturbed, can lead to sickness. This was the case for a young boy born with an abnormally short intestine that allowed unusual overgrowth of gut villains. This boy's disease symptoms persisted even when he took antibiotics (substances that kill bacteria). Only when he was given probiotics—bacterial sidekicks that help to balance good and bad intestinal bacteria—was his health restored. Although this study proved that probiotics can bring our good health back in the context of gut bacterial fights, we should never forget to take care of our intestinal heroes: eat healthy foods and exercise regularly.

Figure 1

You are not alone. Human organs, including the lungs, the intestines, the mouth, and bodily fluids like saliva contain an incredible diversity of microorganisms, which are illustrated in this figure. All the bacteria types shown here have different structures and live together in the lungs, intestines, and bodily fluids.

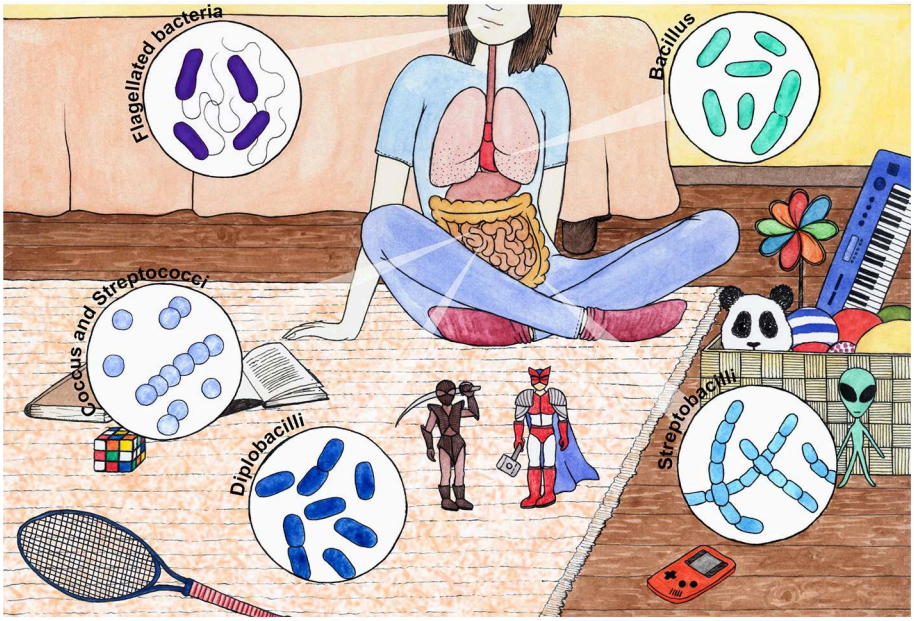


Figure 1

YOU ARE NOT ALONE!

Imagine yourself alone in your room, playing with your favorite superheroes. In this game, you manage to help them in a very critical, everlasting battle against some unearthly villains. You and your heroes save the world! What next, then? The game is over for now. You take a step back, look around the room, and may suddenly start to feel alone. But there is no need for that. What if I told you that you have *never* actually been alone, and you will never be? How would you feel if I told you that each and every one of us has billions of heroes living with us all the time (Figure 1)? There are enormously huge micro-universes on and within our bodies that are full of microscopic heroes and their sidekicks. Right now, there may be no one in your room with you, but instead there are many microscopic creatures in your body that are always with you and fight battles for you. All these microscopic creatures, also known as **microorganisms**, are the smallest living organisms known and are heroes to us, even though we cannot see them with the naked eye. They are so tiny that we need microscopes to see them. Of course, we also have villains in the same micro-universes and these villains are ready to fight at every minute with our heroes. Billions of microorganisms fight for us even if we do not acknowledge them, and all the battles are about our health.

We are surrounded by microorganisms. They reside on or within many parts of us, including the skin, mammary glands, placenta, lungs, saliva, and mouth (Figure 1). However, by far, the intestines are the most heavily colonized organ in humans, containing over 70% of all the microorganisms in the body [1]. These microorganisms living in the universe of the intestines (which are also called the **gut microbiota**)

MICROORGANISMS

Tiny living organisms that are mostly one-celled. These include bacteria, some fungi, viruses, and microalgae.

GUT MICROBIOTA

The group of microorganisms that live in the human intestine and do not cause disease in a stable, healthy situation.

can be beneficial or dangerous for people. In this article, we will tell the story of some gut microbiota heroes that got help from their sidekicks while fighting against the villains in the intestines of a young boy, to bring his health back to normal. We will also answer several questions, including how the gut microbiota influences human health, what the role of the gut microbiota is in the body, and how it helps us deal with unhealthy situations.

GUT MICROBIOTA = HEROES + VILLAINS

So, humans co-exist and continuously interact with the gut microbiota, which consists of over one trillion bacteria. If you think about your body as a super-organism composed of both human cells and bacterial cells, your gut microbiota makes up 90% of the total cells in this super-organism! The gut microbiota consists of heroes and villains. Gut heroes are the beneficial microorganisms that have critical roles in the human intestines: they help with digestion, provide essential nutrients, help to the immune system, and fight off food poisoning and sickness [1]. These heroes are in an on-going truce with villains who are also known as **pathobionts**. The interaction between the beneficial and pathogenic microorganisms in the gut is extremely critical to human health and the balance is quite fragile. Unfortunately, under certain conditions when the truce is violated, pathobionts can harm us and cause sickness.

PATHOBIONT

Any potentially disease-causing microorganism which, under normal circumstances, lives without causing any disease.

The truce is strictly under control by several groups of beneficial bacteria. Bacteria called Firmicutes and Bacteroidetes are the most dominant groups in the gut, and to a lesser extent Proteobacteria and Actinobacteria are also major players in the human intestines [2]. The proportions of these four types of bacteria are important for human health. Several features of our modern lifestyle can disrupt the proportions of these four groups of bacteria and contribute to the violation of the truce, including the use of **antibiotics** and other medications, and dietary causes, such as too much refined sugar, processed foods, foods low in digestible fiber, foods containing gluten from wheat, and some seed oils [3]. When these substances are consumed, the interactions between the gut microbiota can change, and the resulting change in the proportions of various types of bacteria can cause a person to experience gastrointestinal illnesses, such as diarrhea, gastroenteritis, irritable bowel syndrome, and inflammatory bowel disease [2]. Although there are many on-going studies to understand the exact roles of the gut microbiota, we have only just started to appreciate several things: (i) how the gut microbiota can affect our health; (ii) how healthy the gut microbiota should be; and (iii) how we should take care of the gut microbiota to keep it healthy.

ANTIBIOTICS

Types of medicines that will seek and destroy bacteria that makes us sick. They work well against bacteria, but they do not against viruses.

SIDEKICKS = PROBIOTICS

Like many heroes, every gut hero needs sidekicks. In the case of human health, those sidekicks are called **probiotics**. Probiotics are

living microorganisms that are good for our health, especially for our **digestive systems**. Probiotics help gut heroes by replacing the beneficial bacteria that are lost, balancing our good and bad gut microbiota, and therefore helping with any digestive-related illnesses. Probiotics add another layer of beneficial microorganisms to the ones that already exist. The best-known probiotic organisms are *Lactobacillus rhamnosus* and different species of *Bifidobacterium.* We actually have some of these organisms in our intestines, but they can also be found in many foods, such as yogurt, bread, kefir, buttermilk, and cottage cheese.

PROBIOTICS

A group of microorganisms (bacteria) that help to maintains and restores beneficial bacteria to our intestines when they are consumed.

DIGESTIVE SYSTEM

A team of organs that digests food to obtain nutrients and energy and that expels the remaining waste as feces. In humans, the digestive system consists of the stomach, intestines, tongue, salivary glands, pancreas, liver, and gallbladder.

In some disease conditions, such an ear infection or diarrhea, doctors prescribe antibiotics, which are a type of medicine that kills bacteria. Using antibiotics helps people fight a bad infection, but they can harm the beneficial gut microbiota, too. Taking a probiotic can actually help to replace the beneficial gut microbiota that are killed by the antibiotics, restoring the natural balance to the gut microbiota. In addition, probiotics may keep people healthy by decreasing the number of disease-causing bacteria in the gut [4]. Probiotics are mostly safe, but some people can experience side effects, such as gas, bloating, diarrhea, and minor skin and allergic issues, which are usually mild and short-lived. However, it is important to consult a doctor about any severe or persistent side effects.

A DEFEAT WITH THE HELP OF SIDEKICKS

The human intestines have about the same surface area as a tennis court, but all coiled up to fit inside the abdomen. The intestines are divided into the small and large intestine. The small intestine is a tube about 6 m long and the large intestine is shorter, but much wider. The intestines are perfect places for microbes to live, because of the constant temperature and richness of nutrients that can be used as food by the gut microbiota. In some people, the small intestine (also known as the small bowel) can be shorter and cause a disorder called short bowel syndrome. In short bowel syndrome, the small intestine does not function properly, because it is not long enough to adequately absorb nutrients. The primary symptom is diarrhea, which can result in dehydration, malnutrition, and weight loss. In some cases of short bowel syndrome, some of the pathobionts in the gut may grow and cause build-up of acidic molecules in the blood. These acidic molecules lead patients to suffer from something called **D-lactic acidosis**, which could result in severe damage to the nervous system if not treated properly. To understand what D-lactic acidosis is, let us think about the production of the yogurt you might eat at home. The acidic taste of unflavored yogurt results from the controlled transformation of lactose—a sugar found in milk—into lactic acid, by bacteria, such as *Lactobacillus.* The limited amount of acid in yogurt does not harm you, but the uncontrolled build-up of acidic molecules in the blood stream of patients suffering from

D-LACTIC ACIDOSIS

A metabolic complication occurring our intestines due to the malabsorption of carbohydrates. This leads to accumulation of D-form of lactic acid that can be extremely harmful to us.

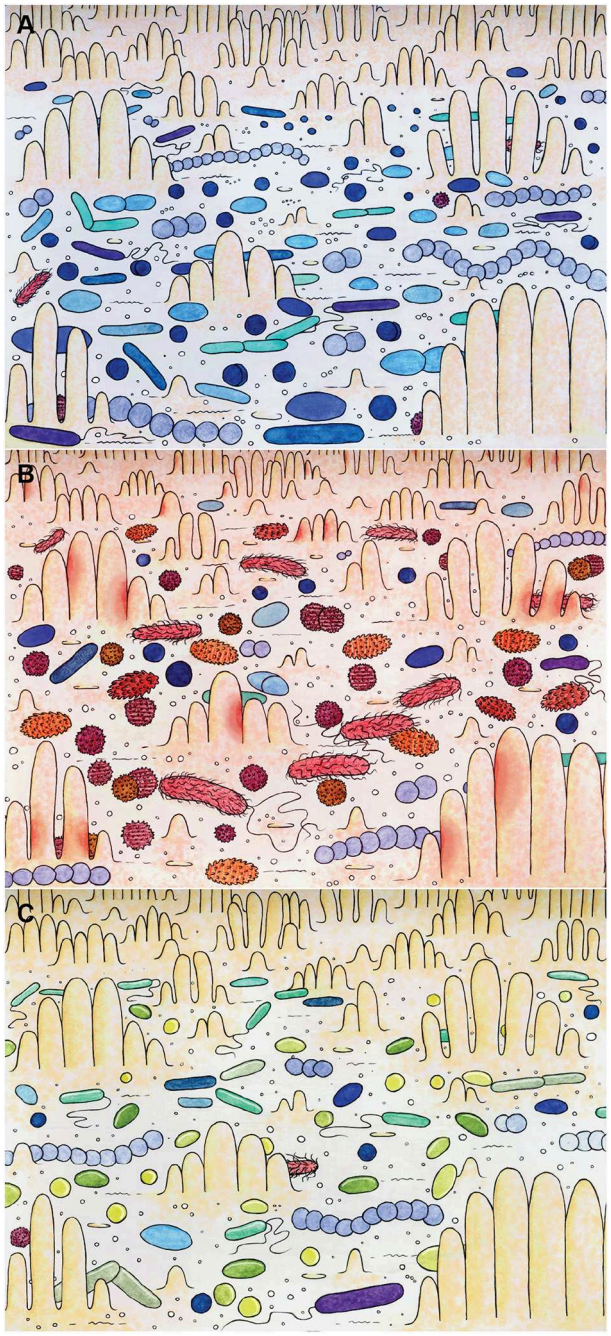


Figure 2

Changes in gut microbiota that influence human health. **(A)** Healthy intestines with rich microbial diversity and lots of gut heroes (represented in various shades of blue). The heroes prevent the spread of *Lactobacillus* villains (in red). In this situation, the gut heroes and villains are in a balanced, but fragile, truce. **(B)** Unhealthy intestines with abnormal overpopulation of *Lactobacillus* villains (in red) in the gut. **(C)** Re-establishment of healthy microbiota through the administration of probiotics as sidekicks for the gut heroes—a combination of *Lactobacillus* and *Bifidobacterium,* shown in various shades of green. These sidekicks help to fight against and decrease the abundance of gut villains.

D-lactic acidosis can result in symptoms including **delirium**, **ataxia**, and slurred speech.

The young boy in our study [4], who was born with short bowel syndrome, developed symptoms of D-lactic acidosis from time to time, due to the overgrowth of *Lactobacillus* villains that overpopulated his small bowel. These villains are almost non-existent in healthy individuals (Figures 2A,B). The villains in this story could not be defeated by the gut microbiota heroes and the boy's symptoms persisted even when his doctors tried to fight back by continuously

DELIRIUM

A serious condition of mind involving severe confusion and changes of behavior usually because of a high fever or other illness.

ATAXIA

An inability to coordinate voluntary muscular movements.

administrating antibiotics. We were in a critical situation and, in order to restore the boy's health, we desperately needed help from sidekicks. These sidekicks quickly became legends: D-Lactate Free Multi-Strain Probiotics. In only 3 weeks of the boy receiving these probiotics on a daily basis, the main villain that was causing his symptoms started to disappear from his intestines (Figure 2C). After 323 days of probiotics, there was no detectable trace of any villain in the boy's stool (poop). Even today, the boy is healthy and free of episodes of D-lactic acidosis. In summary, we managed to help the gut heroes by introducing sidekicks to help in the battle against the villains in the intestines.

BE KIND TO YOUR GUT HEROES

Over the last decade, the importance of gut heroes has become a big focus of research in human health. However, only a few studies have examined the microbiota in patients with short bowel syndrome. With our study we showed that, in some unhealthy situations, gut heroes might need help that can be provided by probiotics. For the young boy in our study, probiotics were the key to the long-term decrease in the number of villains in his gut. However, in most cases, antibiotics are still the most important way to fight against bad infections. Although probiotics can help to restore our health, it is important to remember that we still need to learn how to keep ourselves healthy. We should always follow the instructions of our doctors, and never forget to take care of our gut heroes every day: eat healthy foods and exercise regularly!

ORIGINAL SOURCE ARTICLE

Yilmaz, B., Schibli, S., Macpherson, A. J., and Sokollik, C. 2018. D-lactic acidosis: successful suppression of D-lactate-producing *Lactobacillus* by probiotics. *Pediatrics* 142:e20180337. doi: 10.1542/peds.2018-0337

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SUBMITTED: 15 May 2019; **ACCEPTED:** 15 August 2019;
PUBLISHED ONLINE: 28 August 2019.

EDITED BY: Michel Goldman, Free University of Brussels, Belgium

CITATION: Yilmaz B, Carvalho JC and Marialva M (2019) The Intestinal Universe—Full of Gut Heroes Who Need Sidekicks. Front. Young Minds 7:111. doi: 10.3389/frym.2019.00111

CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

AYDEN, AGE: 11
My name is Ayden, and I go to school in New York City. My favorite subjects are History and English because we learn fascinating facts and read interesting books. I ran for my school's track team and came in fourth place out of 20 schools. I also enjoy spending time with friends and playing video games. I like playing golf and enjoy watching professionals play almost every weekend.

HANNAH, AGE: 10
I am in the fourth grade, and I am homeschooled. In my free time, I enjoy competing in tennis, reading, playing with my cousins, and relaxing with my dog and cat. I love visiting restaurants, and spicy Chinese food is my favorite cuisine.

JOSHUA, AGE: 13
I am homeschooled, and I enjoy playing the piano, competing in tennis, and reading. Currently, my favorite author is James Herriot. I own the entire volumes of Bill Watterson's Calvin and Hobbes and Gary Larson's The Far Side.

SAHASRA, AGE: 13
Hello, I am Sahasra, rising ninth grader. I am eagerly waiting to start my high school. I am interested in Science and Language. I love listening to music and reading books. J. K. Rowling is my hero. Playing volleyball is my passion. I play for my school and local club. I would love to pursue my career in life sciences/healthcare.

ZOE, AGE: 7

My name is Zoe, and I will be in the second grade. My favorite hobby is dancing and have danced at the Joyce Theater in New York City. I love traveling and camping with my family. My favorite part about camping is roasting marshmallows! After a long day of school, I love hanging out with my 5 years old Welsh Terrier named Duke.

AUTHORS

BAHTIYAR YILMAZ

I was born in Bulgaria but moved to Istanbul as a young child. I finished my Bachelor's and Master's degrees on Evolutionary Engineering of Yeast at Istanbul Technical University (Turkey) and afterwards received my Ph.D. in Immunology from Instituto Gulbenkian de Ciencia (Oeiras, Portugal). During my Ph.D. study, I discovered that gut microbiota can trigger a natural defense mechanism against malaria, a life-threatening mosquito-borne blood disease caused by a parasite. Afterwards, I moved to Bern, Switzerland where I have been doing research to understand the role of intestinal microbial communities in patients diagnosed with chronic inflammation in the intestines. *bahtiyar.yilmaz@dbmr.unibe.ch

JOANA C. CARVALHO

I was born in Lisbon, Portugal and grew up in a small city in the south. There, an endless curiosity about wildlife and an ever-lasting will to draw all its details led to the decision of studying Biology. In 2015, I graduated in Evolutionary and Developmental Biology, from the Faculty of Sciences of the University of Lisbon. Today, my time is divided between the bench of the lab, studying the immune system of the fruit fly, and the studio desk, using illustration to communicate all that is dear to me.

MARTA MARIALVA

After completing a Ph.D. in Evolutionary Biology, I decided to pivot my career in science and start a new adventure where I could combine my two passions: science and education. This is how I co-founded what I call *the best version of me*: Ginkgo Educa. I use the scientific method and hands-on experimentation to stimulate critical thinking in young minds and to encourage problem-solving attitudes. I truly believe that science education is essential to build the foundations for a more just, tolerant, and green future and it feels good to be with the right people, going in the right direction.