HOW TO FIGHT HARMFUL MICROBIAL BUGS AND SUPERBUGS?

EDITED BY: Alain Fischer, Michel Goldman and Paul-Henri Lambert
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HOW TO FIGHT HARMFUL MICROBIAL BUGS AND SUPERBUGS?

Topic Editors:
Alain Fischer, Assistance Publique-Hôpitaux de Paris, France
Michel Goldman, Université libre de Bruxelles, Belgium
Paul-Henri Lambert, Université de Genève, Switzerland

The evolution of human beings has been shaped to a large extent by microbes. A number of microbes are innocuous or even contribute to our health equilibrium. This is the case of bacteria and viral phages present in our gut. However, several bacteria, viruses, parasites, and fungi are damaging our bodies, causing a number of acute and chronic diseases. Until recently, these bugs represented the main causes of death. Better hygiene, vaccines, antibiotics and other anti-microbial drugs have resulted in a better control or cure of many infections. However, malaria, tuberculosis, and AIDS still represent major threats in several countries and the recent epidemics of Ebola and Zika demonstrate how vulnerable we are to newly emerging viruses. Furthermore, diarrhea and pneumonia caused by bacteria or viruses still kill millions of children worldwide. Most importantly, bacteria resistant to existing antibiotics are multiplying at a high pace and these superbugs are expected to kill more and more people in the coming years.

Clearly, we need to develop more effective approaches to tackle bugs and superbugs. Better hygiene and better vaccine coverage must be considered first and education of kids is essential in this respect. This is the main objective of this series of papers published in Frontiers for Young Minds under the heading "How to Fight Harmful Microbial Bugs and Superbugs?". Another key objective of the collection is to elicit the interest of children for research on innovative anti-microbial therapies and vaccines.

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HEALTH
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VACCINES, SHOTS THAT PROTECT YOU

***Marie Neunez*[1]*, Michel Goldman*[1]**, Sylvie Goldman*[2] *and Paul-Henri Lambert*[3]**

[1] *Institute for Interdisciplinary Innovation in Healthcare, Université libre de Bruxelles, Brussels, Belgium*
[2] *Department of Neurology, Columbia University Medical Irving Center, New York, NY, United States*
[3] *Center of Vaccinology, University of Geneva, Geneva, Switzerland*

YOUNG REVIEWERS:

FLORIMONT

AGES: 15-16

Tomorrow, your mother will take you to the doctor to receive your vaccines. Why do you need these shots since you are healthy and have already received some shots when you were just a baby? In this article, you will discover the reasons why booster vaccines are crucial, to protect you, your brothers and sisters but also your classmates and your friends.

VACCINES, ONE OF A KIND DRUGS

While medicines are usually given to a person who is sick, **vaccines** are injected to healthy children or adults to keep them from getting diseases that are transmitted by tiny living organisms named **microbes**. Vaccination is the best way to date to prevent diseases that are called infectious diseases.

VACCINES

Substances that protect from diseases caused by microbes.

MICROBES

Microorganisms that cause infections and diseases such as measles.

MEASLES, A FORGOTTEN INFECTIOUS DISEASE

MEASLES

Disease affecting unvaccinated children.

VIRUS

Small microbe.

When your grandparents were your age, many children suffered from **measles**, a disease caused by a **virus**. Most often, they would heal from it, but sometimes, the disease caused serious complications, involving the lungs or the brain, that could be deadly. Thanks to vaccination, measles nearly disappeared completely. This is also the case for several other childhood illnesses, such as poliomyelitis that caused paralysis of the legs. To date, we count more than 10 infectious diseases that are prevented thanks to vaccines. Unfortunately, not all children have the chance to be vaccinated: either because they live in areas of the world where vaccines are not available or difficult to access, or because their parents are against vaccination.

SOME MICROBES CAUSE CANCER

In certain individuals, long-standing infections can cause cancer. For example, women infected with the human papilloma virus may develop cancer of a part of the uterus, an essential organ for human reproduction. Vaccination is the most efficient way to prevent this cancer from occurring.

MICROBES JUMP FROM ONE PERSON TO THE NEXT

Microbes can be transmitted from person to person, through different routes. In the case of measles, an infected individual can potentially contaminate up to 20 other persons by spreading the virus in the air. This is what "contagious" means when we talk about an infectious disease. The more contagious is the disease, the more important the vaccination will be.

VACCINATED CHILDREN: A WORLDWIDE CHAIN OF SOLIDARITY AGAINST INFECTIOUS DISEASES

When you are vaccinated, not only are you protected against the microbe, but you also decrease the risk of transmitting that disease to your friends and family. This is called herd protection (Figure 1). If the majority of the population is vaccinated, microbes will not succeed in propagating. It is believed that when 9 individuals out of 10 are vaccinated, the entire population is protected so that the disease becomes "invisible." However, the disease can resurface at any point if the proportion of vaccinated individuals decreases. Sadly, this is what is happening today with measles and other infectious diseases: within

Figure 1

Herd protection.

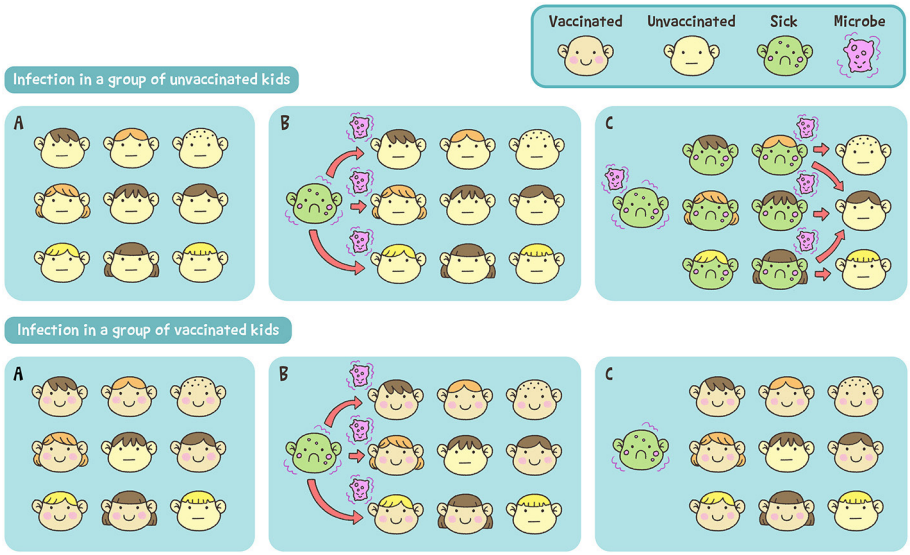

Figure 1

the first 6 months of the year 2018, more than 40,000 Europeans contracted measles while some thought that it had disappeared for good.

Hence, vaccination is critical, have you ever discussed it with your parents? Indeed, vaccination does not stop after childhood. It remains crucial to follow-up and have booster vaccines throughout your life to maintain the benefits of vaccines. This will be explained in the following pages.

THE ROLE OF THE IMMUNE SYSTEM IN INFECTIOUS DISEASES

To discover what is a vaccine, you first need to understand how our natural defenses work, that is how our immune system acts against dangerous microbes. Within a short time after penetrating our bodies, microbes usually multiply and infect our cells, preventing them from functioning properly. In most cases, we succeed in fighting that enemy thanks to the army of cells that compose our immune system. In some cases, the immune system does not succeed in sufficiently and rapidly getting rid of those aggressive microbes, resulting in the onset of a disease.

When a microbe enters into our bodies, several types or cells come into action. Cells named ***lymphocytes*** recognize small pieces of the microbes, the so-called ***antigens***. Each lymphocyte recognizes a specific antigen and then attacks microbes that present this antigen at their surface. Certain lymphocytes act by releasing biological weapons known as ***antibodies***. These weapons that resemble arrows target antigens at the

LYMPHOCYTES

White blood cells that produce antibodies and kill microbes.

ANTIGENS

Parts of the microbes that are recognized by antibodies.

ANTIBODIES

Weapons that we produce to attack microbes.

surface of microbes and eventually kill them (Figure 2). After the fight, several lymphocytes remember and record the microbe. This memory enables them to rapidly release large amounts of antibodies in case of a future attack. If the latter occurs, those microbes will be destroyed even before you realize that you have been infected.

Figure 2

Antibodies produced by lymphocytes bind antigens and kill microbes.

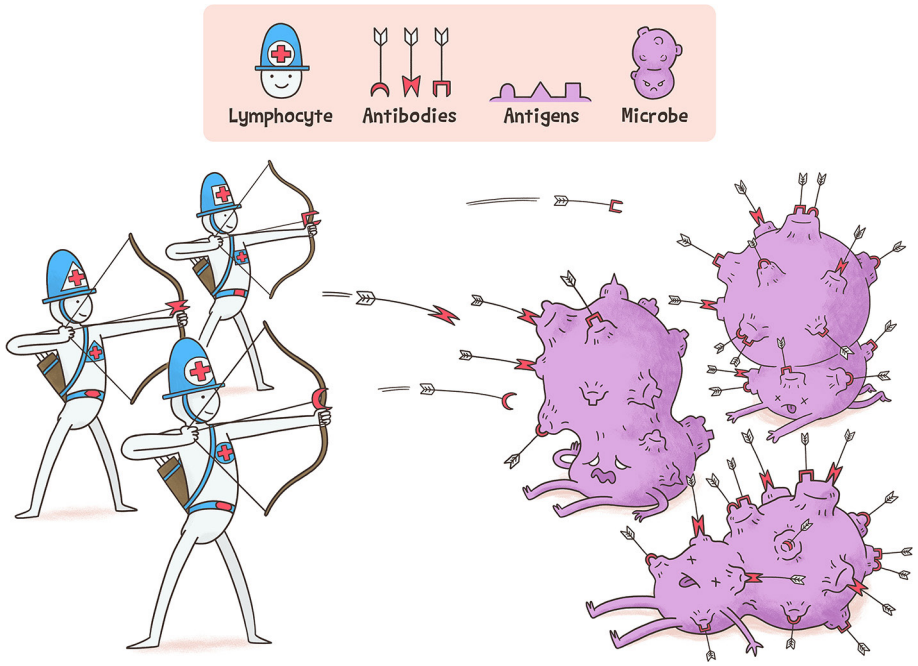

Figure 2

Figure 3

How vaccines work.

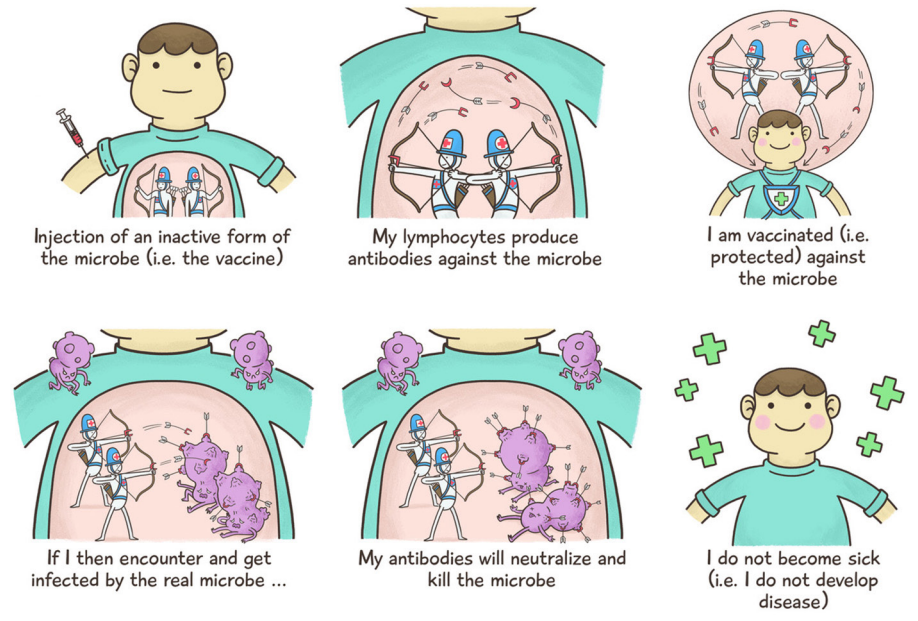

Figure 3

WHAT ARE VACCINES AND HOW DO THEY WORK?

Vaccines stimulate your immune system without requiring your body to be sick [1]. They contain harmless antigens that provide you with double protection: first, vaccines trigger the production of antibodies that last very long in your body; second, they enable memory of the immune system. This is why when your body encounters the microbe, you immediately kill it (Figure 3).

WHY SO MANY SHOTS?

As each microbe is different from the other, multiple vaccines have to be used. Do not worry, it is now common to give multiple vaccines in a single shot.

You probably ask yourself: why do I have to receive several times the same vaccine in the course of my life? The answer is simple. As you know, our memory has its limitations and we have the tendency to forget things. This is also true for our immune system. It is therefore necessary to boost its memory by repeating vaccination. Boosters are indeed crucial to maintain effective protection against infectious diseases.

WHO CAN BE VACCINATED?

Most of the children around the world can be vaccinated. Only a few of them should not, because they suffer from a disease that affects their immune system: they are said to be immunodeficient. Thanks to herd protection, when healthy children are vaccinated, they provide protection for those sick children as well.

Nowadays, vaccines are also given to pregnant women to protect their babies. The vaccinated mother transfers her antibodies to her child during pregnancy and then through breast-feeding. This is important to protect newborns before they can be efficiently vaccinated themselves. An example is whooping cough than can lead to severe respiratory infection during the first weeks of life.

WHAT ARE THE RISKS OF VACCINATION?

You should know that vaccines can sometimes lead to mild discomfort, but the pinch of a shot is never as bad as the illness caused by a harmful microbe.

Vaccines that you received have been analyzed in-depth to make sure they are both efficient and safe.

WHY SOME INDIVIDUALS DOUBT ABOUT VACCINATION?

Unfortunately, the information available to the public on benefits and risks of vaccines is often incomplete or even inaccurate, especially on the internet [2]. Some people believe that infectious diseases are not threatening children anymore and therefore deny the need for vaccination. They forget that if vaccines are not used, diseases will rapidly reappear.

Now that you understand what vaccines are, consider talking about this with your parents.

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YOUNG REVIEWERS

FLORIMONT, AGES: 15-16

In our group, there is Zachary, Paul, George, Sarah, Gabriel, Zeynep, and Klara. We are part of the class 2B2 at Florimont. We worked on the vaccines paper and we found this paper very interesting. We learnt a lot from this article!

AUTHORS

MARIE NEUNEZ

I am a part-time research fellow at the I3h Institute and Student in Medicine at the Université Libre de Bruxelles (ULB). I was a Clinical Research Coordinator for 2 years in the Departments of Nuclear Medicine & Radiotherapy at the Institut Jules Bordet (IJB). I also performed a 5-months internship at BASF SE (Mannheim, Germany) in the Human Health & Nutrition department. I hold a MSc degree in Bioengineering with a specialization in Science, Technology and Quality of Food (UCL, Belgium), a Postgraduate degree in Management (ICHEC Business Management School, Belgium) and a certificate in Clinical Studies (Cefochim, Belgium).

MICHEL GOLDMAN

I graduated as a Medical Doctor (1978) from the Université Libre de Bruxelles (ULB), Belgium, and received my Ph.D. in medical sciences (1981) from the Université de Genève, Switzerland. From 1990 to 2008, I was the chairman of the Department of Immunology at Erasme Hospital in Brussels, and from 2004 to 2009 I served as the first Director of the Institute for Medical Immunology of ULB. From 2009 to 2014, I served as the first Executive Director of the Innovative Medicines Initiative (IMI) a joint undertaking between the European Commission and the European Federation of Pharmaceutical Industries and Associations. Managing a budget of €2 billion, I was responsible for the launch of 59 public-private consortia in areas of major importance for public health. Currently I am a Full Professor at ULB where I was the Founding Director of the Institute for Interdisciplinary Innovation in Healthcare (I3h). *mgoldman@ulb.ac.be

SYLVIE GOLDMAN

I graduated in 1984 from the Department of Psychology & Pedagogical Sciences, Université Libre de Bruxelles (ULB), Belgium. I obtained my Ph.D. in Developmental Psychology from the City University of New York, Graduate Center in 2002. From 2002 to 2009, I held a position of developmental psychologist at the McCarton Center for Developmental Pediatrics. I obtained my post-doctoral training in neuropsychology under the mentorship of Dr. Isabelle Rapin at Albert Einstein College of Medicine, Bronx NY, USA where I became the Co-director of the NIH-Human Clinical Phenotype Core of the R. F. Kennedy Intellectual and Developmental Disabilities Research Center. I am currently an Assistant Professor in the Division of Child Neurology, department of Neurology at Columbia University Irving Medical Center. I am a teaching faculty for the Parent-Infant Psychotherapy Program in Child Psychiatry at Columbia University Irving Medical Center. My current clinical activities and research address the disparities and delays in the diagnosis of autism in girls and minorities.

I am a member of the Columbia University Research Consortium on Autism Spectrum and Related Neurodevelopmental Disorders and the Columbia Population Research Center (CPRC). I am the recipient of multidisciplinary seed grants from the Irving Institute, the Department of Neurology, the Columbia Center of Science and the Presidential Scholars in Society and Neuroscience.

PAUL-HENRI LAMBERT

I am now associated with the Centre of Vaccinology in the Department of Pathology and Immunology at University of Geneva. I am particularly interested in vaccination strategies and evaluation of adverse effects. I am directing the International Advanced Course of Vaccinology (ADVAC) organized under the auspices of the Fondation Mrieux and University of Geneva. I am a member of the Governing Board of the Tuberculosis Vaccine Initiative (TBVI) and chairman of the Human Vaccine Committee of the International Association for Biologicals (IABS). My native is Belgium where I was boarded in Internal Medicine (University of Liege). I joined Frank Dixon at Scripps Institute, La Jolla, California, for my training then moved to University of Geneva Medical School where I became Professor in the Departments of Medicine and of Pathology. My research activities lead me to decipher immunological mechanisms involved in autoimmune and immune complex-mediated diseases, in the pathogenesis of malaria and in new strategies to optimize vaccine immunogenicity. In 1987, I was appointed as Chief Microbiology and Immunology at the World Health Organization and in 1994, Chief, Vaccine Research and Development, WHO Global Programme for Vaccines and Immunization. I was then deeply involved in co-ordination of research aiming at the development of vaccines against diseases of major importance in developing countries. I am an author or co-author of 455 publications, member of several international scientific boards, foreign member of the Royal Academy of Medicine in Belgium and Fellow of the American Association for the Advancement of Science.

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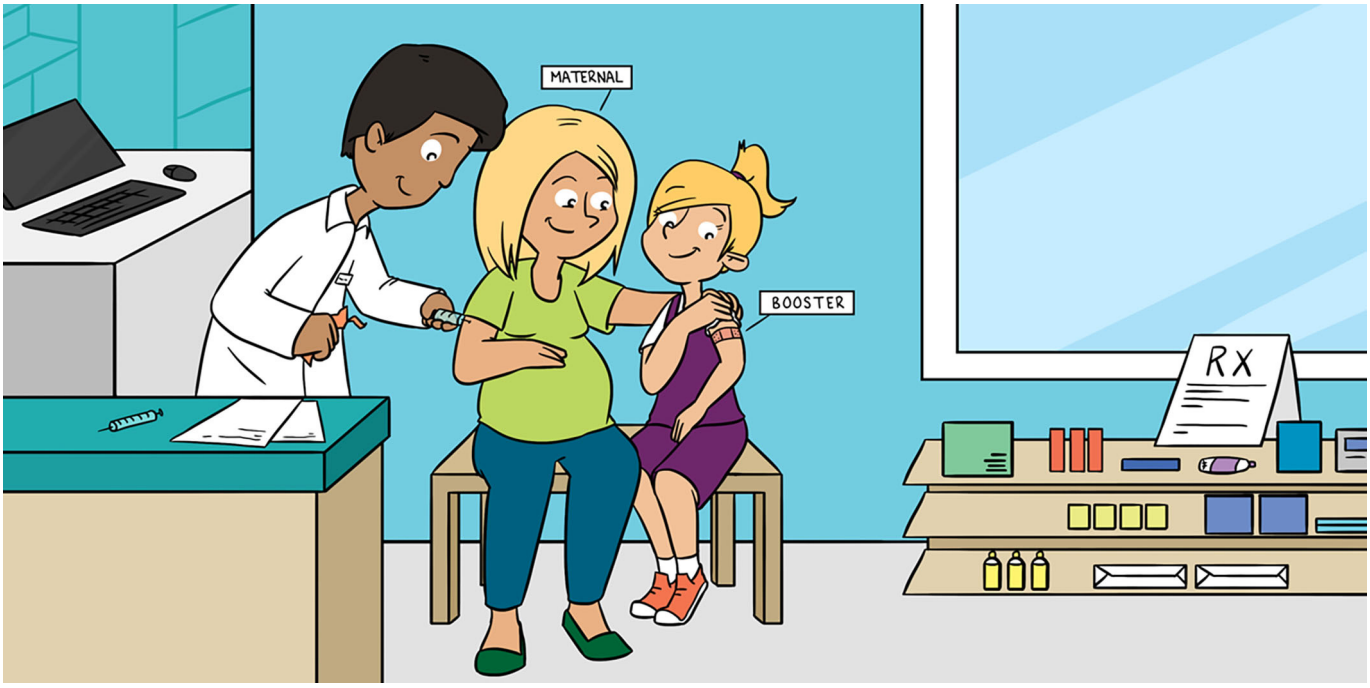

WHAT IS WHOOPING COUGH AND HOW CAN WE PROTECT OURSELVES?

Nicole Guiso *

Institut Pasteur, Paris, France

YOUNG REVIEWER:

SAHASRA

AGE: 14

Whooping cough is a very contagious respiratory disease, caused by a bacterium called *Bordetella pertussis*. Babies <3 months of age can die from whooping cough, and it is also particularly dangerous for seniors. Children are protected from whooping cough if they have the tools to eliminate the bacterium when they come in contact with it. These tools are cells and antibodies in the blood, and this protection can be acquired by vaccination. There are two types of vaccines against whooping cough: one contains whole bacteria that have been inactivated by heat or chemicals, and another contains inactivated factors removed from the bacteria. After vaccination with either vaccine, children are protected against the bacterium. However, after several years, the protective cells and antibodies decrease or disappear, and it is important for children to get revaccinated. These revaccinations are called vaccine boosters, and they are recommended for children, adolescents, adults, seniors, and pregnant women.

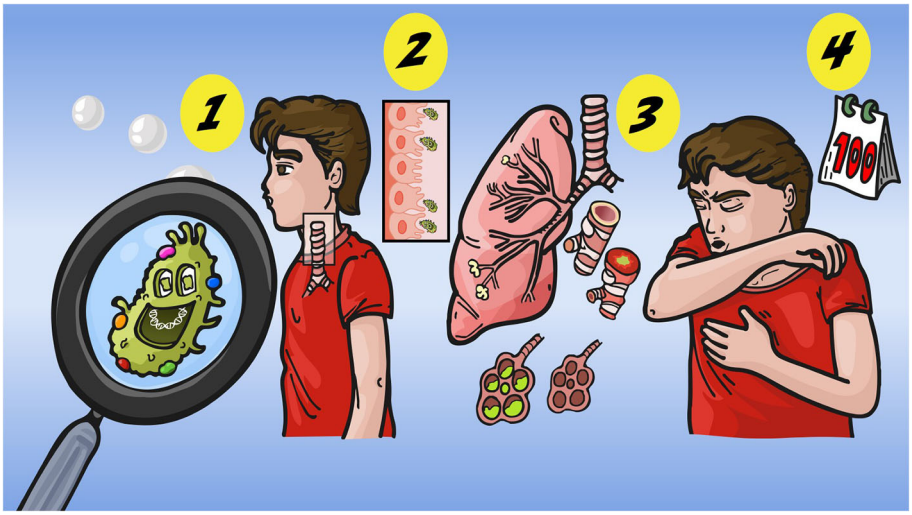

Figure 1

Figure 1

The different phases of whooping cough. First, contact with aerosols from an infected person; then the bacteria contained in the aerosols multiply in the trachea and damage it, inducing only very few symptoms like a cold; then the bacteria secrete factors inducing a terrible cough, vomiting, and after a few weeks, the cough will gradually decrease. The disease can last 100 days in a non-vaccinated person.

WHAT IS WHOOPING COUGH?

Whooping cough is a human **respiratory disease** that spreads very easily between people and affects the human respiration in particular the parts of the respiratory tract, such as the trachea and the lungs. Whooping cough is transmitted by **aerosols** which are suspensions of liquid in air that are sprayed by infected persons who are coughing. After the bacterium infects a person, it can take around 1 week before the person develops symptoms. When symptoms develop, they include a bad cough and runny nose, kind of like a cold, with no fever. Then the cough gets worse, and people can develop difficulty breathing. The noise that is made because of the breathing difficulty is called the whoop. Vomiting can also result. Symptoms often get worse at night. It takes a long time to recover from whooping cough, with a decrease in whoops and coughing happening slowly over the course of 2–5 weeks (Figure 1). The symptoms of whooping cough are what give the disease its Latin name, **pertussis**: "per" means intensive and "tussis" means cough.

RESPIRATORY DISEASE

Any of the disorders that affect human respiration.

AEROSOLS

Suspensions of liquid in air that are sprayed by infected persons who are coughing.

PERTUSSIS

The Latin name of whooping cough (Per for intensive and tussis for cough).

Whooping cough can be especially serious and even deadly for babies <3 months of age. During the nineteenth century, whooping cough caused 1 out of every 1,000 children to die. It is also dangerous for seniors [1].

WHAT CAUSES WHOOPING COUGH?

The agent of whooping cough is a bacterium. The bacterium causing this disease was identified in Paris in 1900 by J. Bordet, a Belgium physician and researcher. This bacterium was only isolated and grown in the lab 6 years later, after the development of a special substance on which the bacteria could easily grow outside the body [2]. This

bacterium was called *Bordetella pertussis* in honor of its discoverer, J. Bordet.

IS THERE A VACCINE AGAINST WHOOPING COUGH?

One of the best ways to protect people against an infectious disease is to develop a vaccine. Vaccines can either contain the whole organisms that causes the disease, in a weakened or killed form, a piece of the disease-causing organism, or an inactivated toxin produced by the organism. Because the disease-causing organism is not active, vaccinations do not cause the symptoms normally observed during the disease. Instead, injection of the vaccine causes an immune response in the vaccinated individual. This means that the vaccinated person builds defenses against the disease agent. In the case of whooping cough, these defenses include antibodies that can bind to *Bordetella pertussis* and eliminate it, as well as cells of the immune system that can kill cells infected by the bacterium. When people are vaccinated they are armed to fight the disease. That means that when they encounter the live, infection-causing bacterium, they will be able to eliminate it quickly without getting sick.

FIRST WHOOPING COUGH VACCINE: A WHOLE CELL VACCINE

wPV

Whole cell Pertussis Vaccine.

The first vaccine developed against pertussis was made of whole bacteria that had been inactivated by heating or chemicals. This whole cell vaccine was called **wPV**, which stands for whole pertussis vaccine. This vaccine was given as three injections to babies at 2, 3, and 4 months and one injection at 18 months. The last injection we call a booster, i.e., an injection to boost the immune response of the child.

The pertussis vaccine was combined with the diphtheria and tetanus vaccines and was used in the U.S. starting in 1948. It was a huge success and deaths from whooping cough decreased by 99%. A decade later, wPV was used in Europe with the same success. Due to the success of wPV, in 1977 the World Health Organization created the Expanded Program on Immunization, with the goal of vaccinating all children around the world [3].

However, two decades after universal use of wPV began in the U.S., some bad news emerged. First of all, wPV was found to cause some side effects, such as fever after vaccination, pain and swelling at the site of infection, and problems with the nervous system. Secondly, 25 years after the introduction of vaccination against whooping cough, the number of babies hospitalized for this disease began to increase again. Why? Researchers found that the immune defenses created by wPV decreased as time went on. Before vaccination became a common

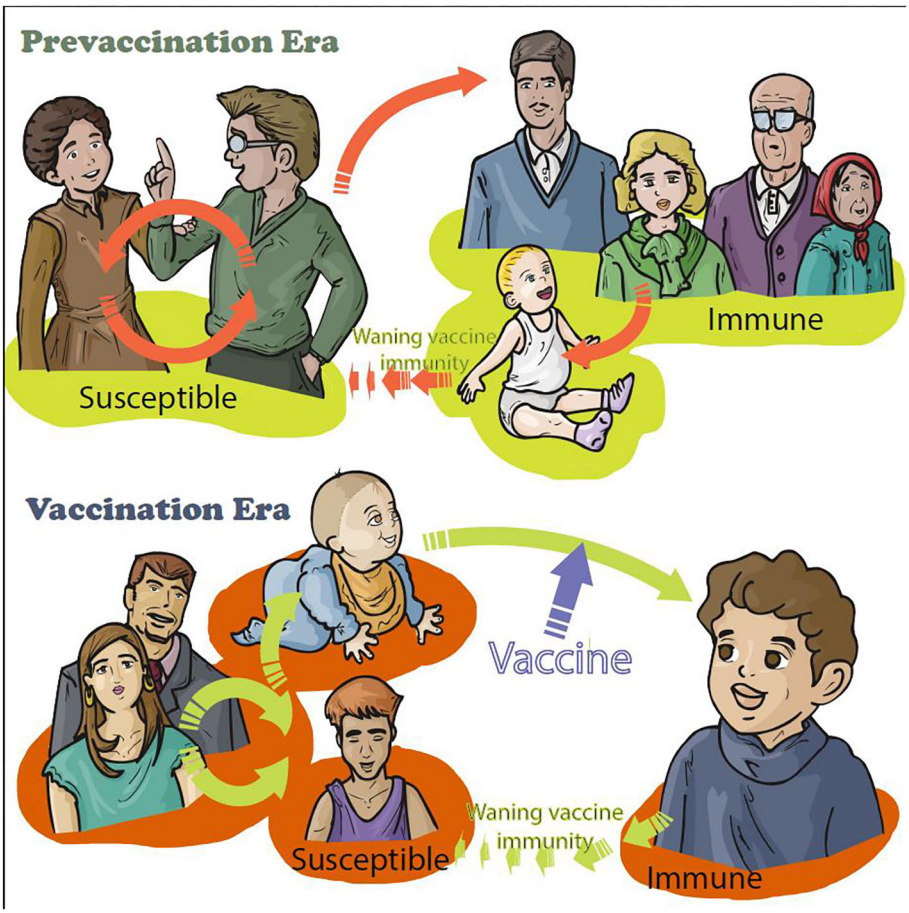

Figure 2

Figure 2

Change of transmission of whooping cough after vaccination of babies before vaccination, around 80 years ago, children were contaminated by contacts with infected children (yellow color around children). After the introduction of vaccination with wPV only for babies and very young children, the mortality decreased a lot and it was a success. However, a change occurred: children were protected against the disease (orange color around the child) but adolescents were not anymore because the protection induced by vaccination is not life-long. Adults did not have any more contact with infected children or babies <8 weeks old who cannot be vaccinated yet (yellow color around the family members). Then a new vaccine was developed. This aPV vaccine was used to introduce regular boosters for young children, adolescents, adults, and pregnant women in order to protect the whole population as well as babies <8 weeks old (orange color).

practice, people who survived whooping cough when they were young were often in contact with infected young children, because whooping cough was still common. These contacts stimulated their bodies to produce new immune cells and antibodies as they got older. These stimulations are called natural boosters (Figure 2). However, after vaccination started, people no longer came in contact with children with whooping cough, and without these natural boosters, their immune defenses began to fade. Then, if they did become infected with the bacterium, they could get sick just as if they had never been immunized. The even bigger problem was that infected adults could spread the bacterium to young, unvaccinated babies, for whom the disease is very dangerous (Figure 2).

These observations convinced researchers to try to develop a new type of vaccine against whooping cough—one that had fewer side effects and could be used to boost regularly people whose immune defenses against pertussis were fading, which was not recommended with wPV because of its side effects [4].

SECOND WHOOPING COUGH VACCINE: AN ACELLULAR VACCINE

aPV
Acellular Pertussis Vaccine.

The second type of vaccine created against whooping cough is called the acellular pertussis vaccine (**aPV**), since it is composed only of a few factors produced by the bacterium. To prepare the aPV, it is necessary to purify all these bacterial factors without destroying their structures and then to inactivate them so that they cannot harm people.

After several tests, aPV was found to be as effective as wPV and it caused fewer side effects. This meant that aPV could be used for boosters [3]. A short time after it was developed, aPV booster vaccines for older children, adolescents, and adults were rapidly introduced in Europe, North America, Japan, and Australia, but not in many other parts of the world, because the aPV are expensive. Today, the world is divided in two: the countries using wPV with the old vaccine strategy of vaccinating only young children (mostly Africa, Asia, and South America) and those using aPV with the new vaccine strategy that includes booster vaccinations (Australia, Europe, Japan, and North America).

However, 20 years after the start of vaccinations with aPV, we are again seeing an increase of the number of infants hospitalized with whooping cough, as we saw with wPV. Of course, the number is very low as compared to the time when children were not vaccinated at all, but even one death or 3-weeks hospitalization of a baby is unacceptable!

We now know that the immune protection caused by aPV, similar to that induced by wPV, is not a life-long protection. Vaccine boosters are still extremely important. Today, we are seeing that the protection provided by whooping cough vaccines is not high enough in adolescents and adults. Deaths of young, unvaccinated babies are still occurring: babies cannot be vaccinated before 6–8 weeks of age, and they thus can become infected by their parents, grandparents, siblings, or babysitters before being old enough to get vaccinated.

WHAT CAN BE DONE TO PROTECT BABIES IN 2020?

COCOONING STRATEGY
Vaccination strategy consisting of vaccinating all persons in contact with a baby before their birth.

Researchers are still trying to develop a new vaccine that can provide longer-lasting protection against whooping cough. In the meantime, it is important to develop new strategies that can be used with the existing vaccines to protect babies between their birth and 8 weeks of age.

One of these is called the **cocooning strategy**. When a couple decides to have a baby, this strategy consists of vaccinating the future parents

and all the people who will be in contact with the baby. This includes family members, babysitters, and the medical staff.

MATERNAL VACCINATION

Strategy of vaccinating a pregnant woman before the birth of their baby.

Another strategy is called **maternal vaccination**. This strategy consists of vaccinating the future mother at least 3–4 months before delivery. If the mother is vaccinated, she will produce immune cells and antibodies and will not transmit the disease to the baby. Furthermore, she will transmit part of her immunity to the baby, especially the antibodies. The mother's antibodies will protect the baby for at least 3 months after birth, until the baby is old enough to be vaccinated.

LESSONS LEARNED

Several important lessons have been learned since the introduction of vaccination against whooping cough. First, we have discovered that: whooping cough is not only a pediatric disease: a person who has not been vaccinated or whose immune defenses have weakened can be infected at any age. We have also learned that vaccination is the best way to be protected against whooping cough, so it is extremely important for all of us to get our vaccines at the recommended times. And lastly, we need to keep an eye out for whooping cough outbreaks, even if we have an effective vaccine. If we are paying attention, we can catch new outbreaks early and change the vaccine strategy if needed—possibly by using techniques like maternal vaccination and cocooning [5].

In conclusions, whooping cough is a very dangerous disease, in particular for babies and seniors. We have effective vaccines able to protect us against the disease. However, the immunity induced by these vaccines is not life-long. It is the reason that the vaccine calendar is regularly adapted by adding vaccine boosters in order to suppress mortality due to this disease. It is therefore very important to follow the vaccination recommendations from the Public Health authorities.

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YOUNG REVIEWER

SAHASRA, AGE: 14

Hello, I am Sahasra, rising tenth 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 or healthcare.

AUTHOR

NICOLE GUISO

Nicole Guiso obtained her Ph.D. and then her Thesis in Microbiology in 1980. She became Director of Researches in 1991. She created and was the Director of the National Pertussis Reference Centre from 1993 till 2015 at the Institut Pasteur in Paris. Nicole Guiso has authored more than 300 articles in international peer-reviewed journals and 20 book chapters. She is presently the President of the Perilic project aiming to build reference laboratories in several Instituts Pasteur around the world. *nicole.guiso@pasteur.fr

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HEALTH
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VACCINATION OF PREGNANT WOMEN: PROTECTING BABIES EVEN BEFORE BIRTH!

Kirsten Maertens, Marjolein Orije and Elke Leuridan *

Centre for the Evaluation of Vaccination, Vaccine & Infectious Diseases Institute, University of Antwerp, Antwerp, Belgium

YOUNG REVIEWER:

LILI

AGE: 10

Vaccines protect humans against microorganisms that cause disease. Usually, vaccines are given to infants, toddlers, or older children at regular intervals. For example, you probably know about the tetanus vaccine, which is given to you when you are hurt, or beforehand, to protect you from disease in case you get hurt. Maternal immunization means vaccination of a woman during pregnancy. This can protect the pregnant woman and her unborn child from disease, and can also protect the new-born baby. The protection is provided by antibodies, which are substances made in the mothers' body after vaccination, and are transported through the placenta and the breastmilk to the baby. Some vaccines are advised to be taken during pregnancy and, in the future, some vaccines might even be specifically designed to be used during pregnancy. This article will explain how vaccination during pregnancy works.

WHY DO WE VACCINATE DURING PREGNANCY?

VACCINE

A substance given to a person to prevent a specific infectious disease caused by a specific microorganism.

MATERNAL IMMUNIZATION

Vaccination of a woman during pregnancy, which can protect both the woman and her unborn baby. Babies continue to be protected for a few months after birth.

Vaccines are substances that can protect your from infectious diseases caused by microorganisms. Many vaccines are safe for everyone and can even be used in pregnant women. **Maternal immunization** means vaccination of a woman during pregnancy. This type of vaccination can protect the pregnant woman and her unborn child from certain diseases, and can also protect the new-born baby for several months after birth.

There are a few vaccines that are already used during pregnancy, including vaccines against flu, tetanus, and whooping cough (pertussis) [1, 2]. These vaccines can often be received at the pharmacy. Flu, tetanus, and pertussis vaccines are given to pregnant women because the diseases they protect against are particularly risky, either for pregnant women, their unborn babies, or for new-born babies.

VACCINES USED IN PREGNANCY

The first vaccine to be approved for use in pregnancy was the tetanus vaccine. Tetanus is caused by a bacterium called *Clostridium tetani* that lives in dirt and in soil, as well as on rusty surfaces. When you injure your foot on a rusty nail, for example, you could get tetanus. The bacterium *Clostridium tetani* causes neonatal tetanus disease, which means tetanus disease of the new-born baby, and often leads to death. Pregnant women are advised to get the tetanus vaccine to protect themselves and their new-borns from this disease.

A second vaccine that is recommended during pregnancy is the whooping cough vaccine. This vaccine is recommended in pregnancy because whooping cough disease is more severe for babies in their first weeks of life, often leading to hospitalization and even death. The bacterium causing whooping cough is called *Bordetella pertussis*. Neither the pregnant woman nor the unborn baby are in danger when they are infected by *Bordetella pertussis*, yet the new-born baby is! Vaccination during pregnancy can protect new-born infants from birth until they are old enough to be vaccinated themselves.

Last, the flu vaccine is recommended in pregnancy mainly because pregnant women can become more severely ill if they get flu, which is caused by the influenza virus. Contracting flu during pregnancy can endanger the pregnant women and her unborn child.

In addition to these three recommended vaccines, several other vaccines can be used in pregnancy if the pregnant woman has a specific individual risk. For example, when a pregnant woman must travel and needs vaccines to be protected against diseases present in other countries, certain other vaccines are safe to

Figure 1

When a vaccine is given to a pregnant woman, she makes antibodies. The antibodies are transported through the placenta to the unborn baby and remain in the baby's blood, where they can provide protection before the baby is born and during the first few months after birth.

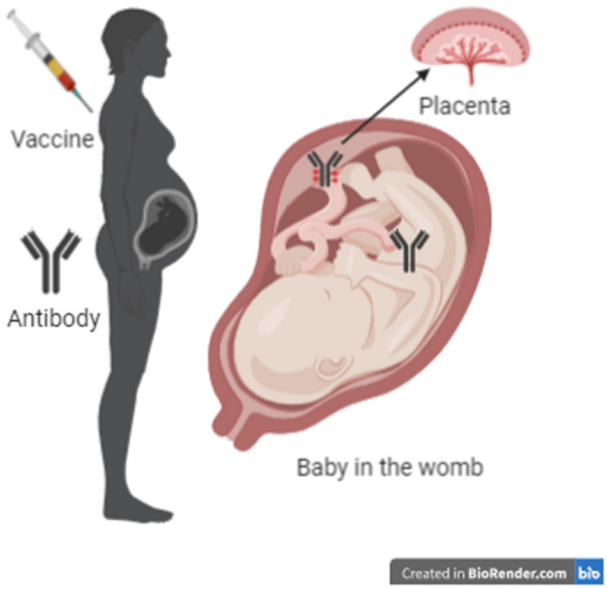

Figure 1

give during pregnancy, such as meningococcal vaccines and hepatitis vaccines.

ANTIBODIES

Molecules produced by the body to attack disease-causing organisms.

IMMUNE SYSTEM

The system in your body protecting you against disease, based on biological processes.

PLACENTA

An organ that grows in the womb during pregnancy, which allows the baby to get nutrients and antibodies from the mother's blood.

HOW DOES MATERNAL IMMUNIZATION WORK?

When we give a person a vaccine, the person will make **antibodies**. Antibodies are molecules made by the **immune system**, and they are one of the body's weapons against disease-causing organisms. When we vaccinate a pregnant woman, she will produce a lot of antibodies. These antibodies will not only protect her from the disease, they will also be transported through the placenta to the unborn child (Figure 1). The **placenta** is an organ that grows in the womb during pregnancy and its role is to provide the baby with blood containing nutrients to help the baby grow. The placenta also has a special transport mechanism that actively transports antibodies from the mother's blood to the baby. In fact, if the pregnancy lasts the full 40 weeks, the baby will have higher levels of antibodies than the mother!

Other antibodies produced in the mother are specifically designed to be transported to the baby through the breastmilk (Figure 2). These antibodies can provide additional protection to the baby during the first weeks and months after birth, when the mother is breastfeeding her child. The amount of maternal antibodies transferred to the new-born through both the placenta and the breastmilk depends on the timing of vaccination during pregnancy [3], the health of the mother and their placenta, and the amount of antibodies the pregnant woman has. For maximum transfer of maternal antibodies to the unborn child, the concentration of antibodies in the mother's

Figure 2

When a vaccine is given to a pregnant woman, she makes antibodies that end up in her breastmilk. When she breast feeds her new-born child, those antibodies are transferred into the baby.

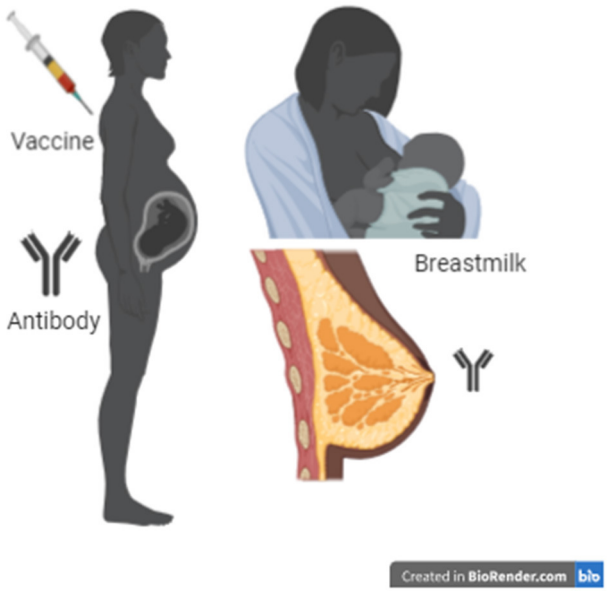

Figure 2

blood should be high, which means that vaccination should be performed well in time, and thus preferably not near the end of the pregnancy.

Maternal antibodies do not last forever in babies. They decrease over 6–12 months after birth. But that is OK, because maternal antibodies only need to protect babies until they are old enough to receive their own vaccines [4, 5].

IS IT SAFE TO VACCINATE DURING PREGNANCY?

Vaccination during pregnancy is very safe. Many studies have been carried out to look at the safety of the vaccines that are used in pregnancy and they were all proven to be safe. Certain vaccines cannot be used in pregnancy. Some vaccines contain live versions of the disease-causing organism, and these cannot be used for maternal immunization. These live vaccines include those against measles, rubella, mumps, smallpox, and yellow fever, to name a few [6, 7].

WHAT ABOUT FUTURE VACCINES?

Will the new vaccines still being developed and tested today also be safe to use during pregnancy? Hopefully, many of them will! In addition to the three vaccines that are currently given during pregnancy, many more could be of value to the pregnant woman and her baby. For example, infection with respiratory syncytial virus (RSV) causes severe lung problems in young babies. There is currently no cure for RSV infection, but if an RSV vaccine could be used during pregnancy, it

would be easier to fight this disease. You can probably think of other diseases for which maternal immunization might be important, such as Covid-19 and Zika virus disease.

MOST PREGNANT WOMEN SHOULD GET MATERNAL IMMUNISATIONS!

Vaccination has long been known to protect people against dangerous infectious diseases. Maternal immunization is a safe way to protect both the pregnant woman and her unborn baby against diseases like flu, tetanus, and whooping cough. The antibodies the unborn baby receives from the mother can persist even after birth and can often last until the child is old enough to receive his or her own vaccinations.

Many women are being vaccinated during pregnancy, but we still need more people to understand why maternal immunization is necessary. Many people, including health care workers, often think of vaccines as something primarily for children, and do not yet automatically associate vaccines with pregnant women. Therefore, it is important for public health officials to continue to organize campaigns to raise awareness of the importance of vaccination during pregnancy. As more health care workers and pregnant women begin to appreciate the value of maternal immunization, more women and babies will be protected from dangerous infectious diseases. The existing maternal vaccines, and new vaccines still in development, may help to improve the health of mothers and new-borns all over the world [8].

AUTHOR CONTRIBUTIONS

MO and KM were responsible for the writing of some of the sections. EL was responsible for the general structure of the article, the writing of sections, as well as the homogenization of the whole text.

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YOUNG REVIEWER

LILI, AGE: 10

Hi, I am Lili. I love nature and I really enjoy going out and investigating wildlife. I am keen on biology and I have even visited a research laboratory. I am also fond of painting and I have won several art competitions where I had to draw wildlife. I am trying to do everything to protect the environment. In the future, I would like to write a book about helping the environment and I would also like to study at a veterinary college.

AUTHORS

KIRSTEN MAERTENS

I am a post-doctoral researcher at the Centre for the Evaluation of Vaccination at the University of Antwerp in Belgium. My research focuses on all aspects of vaccination in pregnancy including immune responses in both pregnant women and infants, the safety of vaccinating pregnant women, coverage and acceptance of this vaccination strategy in pregnant women... This research is very important to be able to improve current recommendations for vaccination in pregnancy and to develop new and better vaccines that can be used during pregnancy in order to offer better protection to pregnant women and newborns against infectious diseases.

MARJOLEIN ORIJE

Marjolein R. P. Orije graduated in 2016 at the University of Antwerp as a major in Biomedical science. Afterwards, she has been working as a Ph.D. fellow on the topic of maternal immunization at The Center for the Evaluation of Vaccination.

ELKE LEURIDAN

Dr. Elke Leuridan is a Professor at the Vaccine & Infectious Diseases Institute, Centre for the Evaluation of Vaccination, University of Antwerp, Belgium. She is a Medical Doctor and obtained a Ph.D. at the University of Antwerp, working on vaccine preventable diseases and maternal antibodies. She supervises several projects on all aspects of (pertussis) vaccination during pregnancy in Belgium and abroad (Vietnam, Thailand). She is member of the Belgian National Health Council, working group vaccination, and participates in the decision-making process on current and future immunization programs in Belgium. She combines working in research with general practice. *elke.leuridan@uantwerp.be

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MATHEMATICS
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WHY IS MEASLES VACCINATION SO IMPORTANT?

Emma Slack[1], Markus Arnoldini[1], Daniela Latorre[2], Selma Aslani[3], Valentina Biagioli[3], Tania Cruz[3], Naomi Elina Dünki[3], Antonia Chiara Jeanne Eichelberg[3], Matthias Goldiger[3], Nicole Howald[3], Giovanni Marastoni[3], Thierry Marti[3], Vega Peterhans[3], Lavanja Selvakumar[3] and Anna Winterberg[3]*

[1] *Institute for Food, Nutrition and Health, ETH Zurich, Zurich, Switzerland*
[2] *Institute for Microbiology, ETH Zurich, Zurich, Switzerland*
[3] *ETH Zurich, Zurich, Switzerland*

YOUNG REVIEWERS:


ALAA
AGE: 11


FRIESS LAKE ELEMENTARY
AGE: 9

Measles is a dangerous and nasty disease caused by the measles virus. The virus spreads quickly from person to person, and there is no cure. A successful vaccine had almost completely eliminated the disease from America and Europe. Unfortunately, due to scare-stories and fake news, many people stopped getting the vaccine. This has allowed the disease to come back. Here we explain: (1) what measles is; (2) how the vaccine works; and (3) why the scare-stories are not true.

WHAT IS MEASLES?

Do you remember the last time you were sick? Maybe you had pain or a fever? Maybe every noise and touch felt horrible? Maybe you could not sleep, or you could not stay awake? You may have experienced these feelings a few times in your life, due to different infections. Measles is a particularly bad infection. It causes a high fever, a bad cough, red and itchy eyes, and a red, flat skin rash. If you are lucky, the symptoms

start to go away after about 10 days. In really severe cases, measles infection can spread to the lungs and brain, leading to death [1]. In the late 1990s, measles had been almost completely wiped out from the western world because of a successful **vaccine**. However, due to fake news, not enough people are vaccinated today, and the disease is coming back.

Measles cannot be cured. The only thing we can do for people who are sick with measles is to treat the signs of their illness, for example reducing their fever and keeping them hydrated. This means that the only way to avoid getting sick from measles is to not get it in the first place.

Measles can be spread through coughs, sneezes, and saliva from other people who are sick with measles. The measles **virus** causes this disease. A virus is an extremely small **microorganism** that invades the body. Different viruses also cause diseases, such as chicken pox and flu. Imagine the virus as a burglar and the human cell as a house. The burglar enters the house and uses everything in it to make a bunch of copies of himself. This destroys the house. After destroying the house, every single burglar-copy invades a new house and the cycle begins again. Eventually the entire city (your body) gets damaged. This damage to cells makes you feel sick.

HOW DOES THE MEASLES VACCINE WORK?

Luckily, your body has a police force called the **immune system**. The immune system patrols the body day and night to catch all kinds of bad microorganisms, such as the viruses or bacteria that cause infections. Each one of these microorganisms (for example the chicken pox virus, the flu virus, and the measles virus) uses different tools to infect us, and therefore the immune system police need specific training to recognize and "arrest" each different microorganism.

More than 200 years ago, scientists realized that the immune system could be trained to recognize dangerous microorganisms. This training can happen if the body encounters weakened versions of the microorganisms that are not capable of making the person sick—this is the idea of a vaccine. Vaccines look identical to the real virus or bacteria, but they are changed in the lab to make them weak so they cannot cause disease. The measles vaccine has been changed so that it cannot copy itself properly [2]. When you get the measles vaccine, your immune system sees and investigates this weakened virus and the weak virus in the vaccine does not damage your cells. This vaccination trains the immune system to recognize and "arrest" the real measles virus, if you ever come into contact with it.

In fact, you can think of this immune system training as the police developing a special type of handcuffs that exactly fit the measles

VACCINE

A weakened or dead microorganism, or a part of a microorganism, that can train the immune system to recognize and defend the body against the actual microorganism.

VIRUS

Tiny microorganism that can only grow inside the cells of another organism. Some viruses can infect human cells and cause disease.

MICROORGANISM

A life-form that is very small and cannot be seen with the naked eye, only with a powerful microscope. Bacteria and viruses are microorganisms.

IMMUNE SYSTEM

The system in the body that protects it from microorganisms. Some parts of the immune system can be trained by vaccines to recognize infectious microorganisms.

Figure 1

The measles vaccine trains the immune system to produce anti-measles antibodies. **(A)** The immune system recognizes the vaccine. **(B)** Antibodies are produced that bind to the measles virus. **(C)** If you encounter the actual measles virus, it is immediately arrested by antibodies!

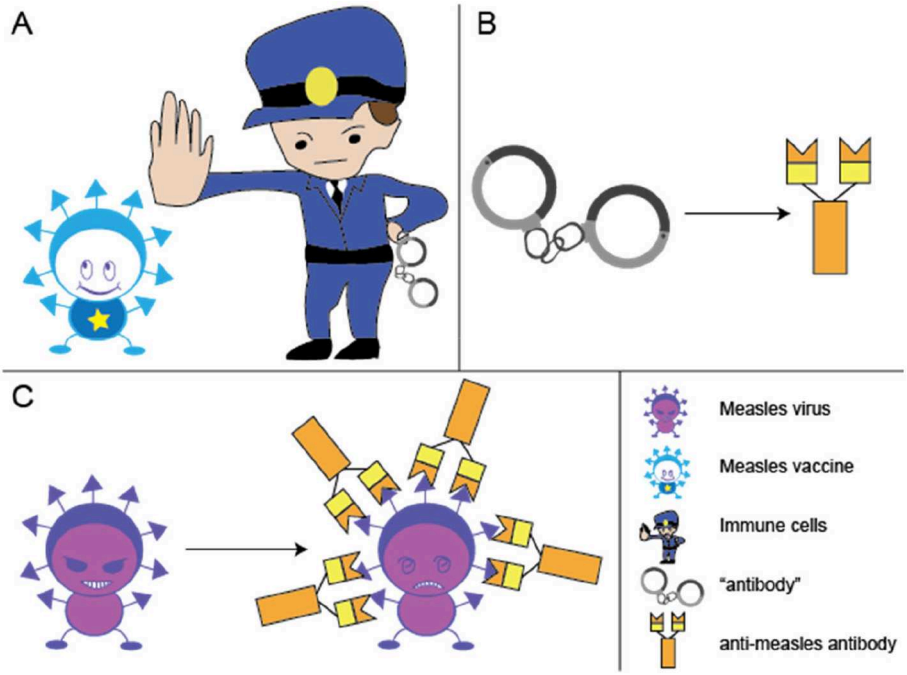

Figure 1

ANTIBODY

When your immune system encounters a microorganism, it generates proteins able to precisely bind to the microorganism. These proteins are called antibodies.

viruses. Biologists call these handcuffs **antibodies**. Antibodies are large Y-shaped proteins present in the blood, and they can recognize and stick to viruses, making the viruses safe and easy for the body to get rid of. When the immune system arrests a measles virus, it puts handcuffs (antibodies) on it. A handcuffed virus cannot break into the cell and cannot start an infection (Figure 1).

If you have been successfully vaccinated against measles, antibodies that bind to the measles virus will be present in your blood for the rest of your life. If these antibodies ever come across a real measles virus, they react extremely quickly and protect you from getting sick.

Before the measles vaccine was introduced in 1963, there were measles outbreaks infecting more than 3 million kids each year. Every year, tens of thousands of kids were hospitalized and more than 1,000 died from measles infection. Even today, in some countries like Afghanistan and Brazil, which struggle to distribute the measles vaccine, there are severe outbreaks and many people die of measles.

I HAVE NEVER MET ANYONE WITH MEASLES. WHY DO I STILL NEED THE VACCINE?

Measles is normally rare in western countries. Unfortunately, it is still common in many developing countries. The measles virus is therefore always around, because people travel all over the world. If you are vaccinated against measles, you cannot get sick from it. But how about

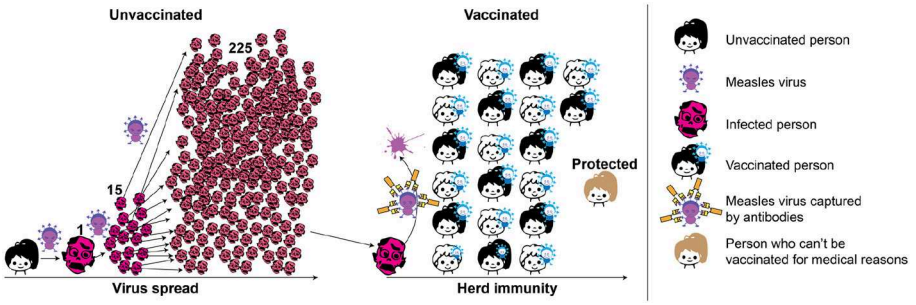

Figure 2

Figure 2

Herd protection protects people who cannot be vaccinated because they are too young or have serious health problems. On the left, you can see how the population of infected zombies would grow if each new zombie infects 15 people. On the right, you see that the vaccinated population protects the most vulnerable people in society who cannot be vaccinated due to very young age or problems with their immune systems.

just avoiding people who travel? Would not that work too? The answer is no, and here is why:

In a typical zombie movie, one zombie infects one new person, who infects the next person, and so on—so you have one, then two, then three, then four zombies. Let us imagine what this would look like if the measles virus, breaking into your cells and making you sick, turned you into a zombie! With measles, each infected person infects on average 15 new people, so you have one zombie, then fifteen zombies, then 225 zombies, then 3,375 zombies, and soon, like an explosion, you reach hundreds of thousands of zombies (Figure 2). Measles spreads very, very quickly! Being vaccinated therefore actually does two things: It protects you from becoming sick, and it also prevents you from spreading the disease. If most people who meet the measles virus are protected, we can dramatically reduce the number of new people who become infected, and hopefully the virus will eventually die out completely (Figure 2). This is what we call **herd protection**. If herd protection is not high enough, we cannot contain outbreaks, and many people are likely to become sick.

HERD PROTECTION

When enough people have been given a vaccine, the disease can no longer spread. This way, vaccinated people protect the few people who cannot be given the vaccine.

Some people are more likely to become very sick from measles but cannot be vaccinated. For example, babies under the age of one, or people whose immune systems do not function properly cannot get the measles vaccine. To protect these people, we need good herd protection: 90–95% of the total population needs to be vaccinated, which means 18 or 19 of every 20 people. Being vaccinated is not only great for you, you are also doing a great job as a barrier to stop the spread of disease. Your immune system is actually working hard to protect the weakest members of our society, who cannot be vaccinated themselves!

BUT I HEARD THAT THE MEASLES VACCINE COULD BE DANGEROUS … IS IT?

Perhaps you have heard that people are afraid that vaccines cause autism? Autism is a mental disorder in which children have difficulties with things like knowing how others are feeling or with using words

to express themselves. Very extensive studies in many of countries, involving tens of thousands of patients, have shown that autism has nothing to do with the measles vaccination (or the combined **MMR vaccine** , which is a vaccine mixture containing the measles vaccine) [3]. So, why do these fears still exist? Largely because it is easy to scare people, and hard to un-scare people.

MMR VACCINE

The combined "Measles, Mumps, and Rubella" vaccine. Mumps and Rubella (also known as German Measles) are two other serious diseases caused by viruses. This vaccine generates protection against all three infections.

This story started with a corrupt doctor named Andrew Wakefield in the late 1990s (luckily, corrupt doctors are very rare!). He was doing research on how measles infections (not the vaccine!) might cause problems in the gut. Wakefield was contacted by a lawyer representing the parents of children with autism [4]. The lawyer paid Wakefield a lot of money to produce data showing a link between vaccines and autism [4]. Wakefield examined just 12 children (autism is estimated to affect 1 in 60 children, or more than 1 million children in the USA [5] alone, so 12 is a very small sample)! Despite the tiny number of children tested, and poor evidence, his work was published in a leading medical journal called The Lancet. Dr. Wakefield gave an exaggerated report of his data to the newspapers and television news [4]. The shocking (but fake) news of his findings spread and generated a crisis. Parents were convinced that the measles vaccine was dangerous and stopped vaccinating their children. Herd protection dropped, and measles outbreaks are back in America and Europe [1]. Even though honest scientists have uncovered his many mistakes and his papers have been retracted, the fear still has not gone away. People continue to spread scare stories via the internet. However, just like zombie movies, these stories are never completely true!

DO NOT BE SCARED—GET VACCINATED IF YOU CAN!

Measles is a serious infectious disease, caused by the measles virus, that spreads extremely fast if not enough people are vaccinated. A vaccine, by definition, is a dead or weakened form of the microorganism. A vaccine will never be worse for you than encountering the real infection. The only exception is if you have a severe allergy to a vaccine ingredient. In this case, you also belong to the small fraction of the population who cannot be vaccinated, and you will need the herd protection of the population to protect you! If you are vaccinated, you can be proud of the work that your immune system is doing to protect you, but also to protect those who are most vulnerable to the infection.

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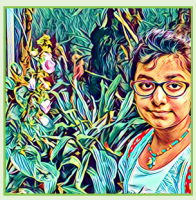
YOUNG REVIEWERS



ALAA, AGE: 11
I love learning. My favorite subject is Science. I am an avid reader and a chocoholic. When I grow up, I want to be a pilot or a scientist. I am a nature fanatic and I love traveling. I have traveled to many fascinating places like Amsterdam, Abu Dhabi, Dubai, Dusseldorf, Frankfurt, London, Vancouver, Victoria and Kelowna and I plan to visit many more in future. I enjoy drawing and coloring, watching cartoons and educational videos. I am a varsity badminton player and I love the game.

FRIESS LAKE ELEMENTARY, AGE: 9
These zany kids love popcorn, rice krispy treats, and science!

AUTHORS

EMMA SLACK

Do you ever wonder about how your immune system can work in your guts? How can we keep the bad bugs out and keep the good bugs in? How does our food affect your health? Can we make effective vaccines that you can swallow? Can we make people and farm animals healthier by changing their gut bacteria? These questions keep my research group and I very busy indeed. We work at ETH Zurich, in Switzerland. I also love to teach and communicate science. This is really important so that everyone, not just the scientists, can keep up to date with the amazing progress that is being made. *emma.slack@micro.biol.ethz.ch

MARKUS ARNOLDINI

These days, everyone knows that we have tiny microorganisms in (and on) our bodies. They are important for our health, but sometimes also make us sick. I am investigating how our bodies and behaviors select which microorganisms live inside us, and how they interact with each other. Are the "good bugs" always good, or can they sometimes also turn against us and cause diseases? I do this research at ETH Zürich in Switzerland. In addition to doing experiments and analyzing the data, an important part of being a scientist is communicating the results: we are responsible for making sure that our findings reach people and that scientific facts can be used as the basis for making informed decisions by the general public.

DANIELA LATORRE

How does the immune system work in the context of infections? Which immune cell population are involved? How can we improve the immune responses to prevent or better treat infections? I have been studying these aspects in healthy individuals and patients affected my immunodeficiencies or autoimmunity. I work at ETH Zurich, in Switzerland. I believe that scientific dissemination to young people and non-scientific community is part of our aim as scientists to help everyone understand science and to avoid spreading of fake news.

SELMA ASLANI

We are students from all over the world, who are studying for a Masters in Food Sciences, or a Masters in Health Sciences and Technology at ETH Zurich. We all took the class "Food, Microbiota, and Immunity: debating the evidence." This class teaches students to find and read science, to be critical, and to take responsibility for sharing science with the public.

VALENTINA BIAGIOLI

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MATTHIAS GOLDIGER

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NICOLE HOWALD

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GIOVANNI MARASTONI

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THIERRY MARTI

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VEGA PETERHANS

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LAVANJA SELVAKUMAR

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ANNA WINTERBERG

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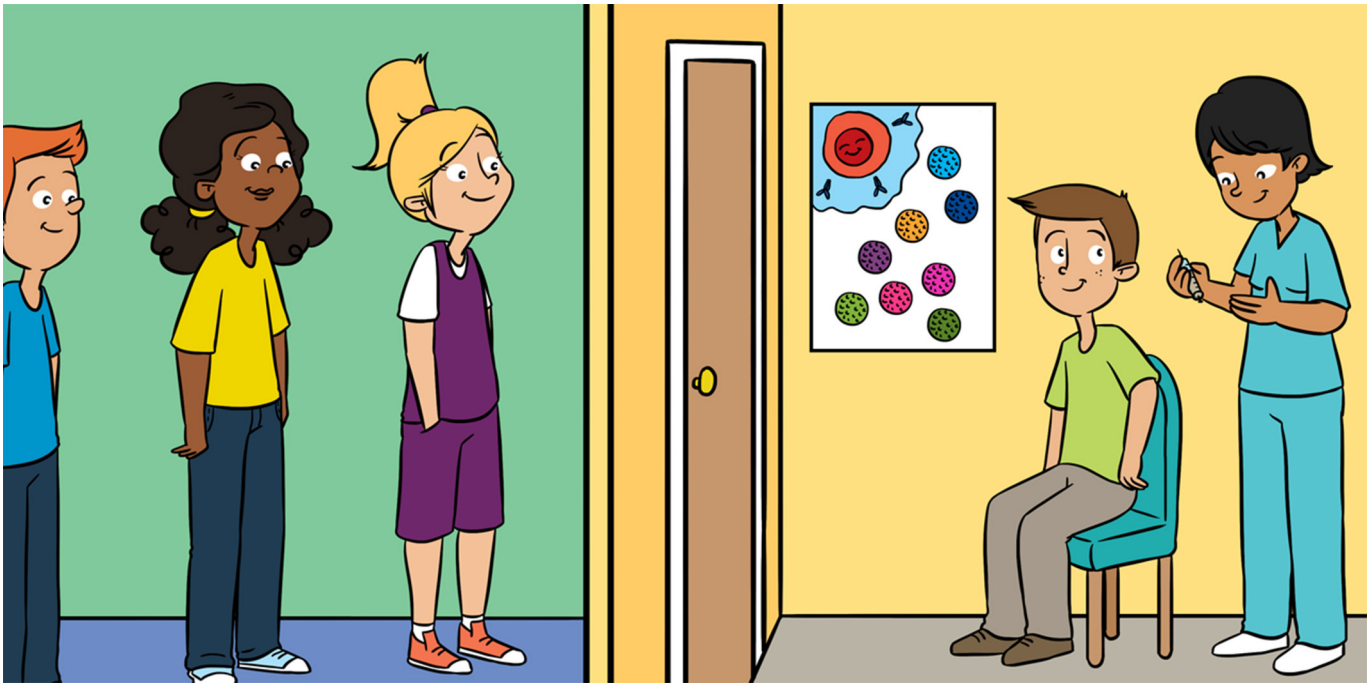

HUMAN PAPILLOMAVIRUS IS DANGEROUS—BUT A VACCINE CAN SAVE YOU!

Marie Neunez [1,2*], ***Susan Nasif*** [3,4,5], ***Pierre R. Smeesters*** [6,7,8,9] ***and Hilde Stevens*** [1]

[1] *Institute for Interdisciplinary Innovation in healthcare (I3h), Université Libre de Bruxelles, Brussels, Belgium*
[2] *The Belgian Kids' Fund for Pediatric Research, Brussels, Belgium*
[3] *Doctoral School of Biomedical Sciences, KU Leuven, Leuven, Belgium*
[4] *Cimaza Virology Comics, Brussels, Belgium*
[5] *The Neyts-Lab of Virology, Antiviral Drug and Vaccine research, Katholieke Universiteit Leuven, Leuven, Belgium*
[6] *Molecular Bacteriology Laboratory, Université Libre de Bruxelles, Brussels, Belgium*
[7] *Tropical Diseases Research Group, Murdoch Children's Research Institute, Melbourne, VIC, Australia*
[8] *Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*
[9] *Academic Children Hospital Queen Fabiola, Université Libre de Bruxelles, Brussels, Belgium*

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AGES: 13–15

Human papilloma virus (HPV) is a virus that can cause disease in the skin and mucus membranes of both women and men. There are more than 100 types of HPV. While most of them cause harmless infections, some types of HPV are more harmful and can lead to cancers. HPV infection cannot be cured. The only solution is to prevent infection by vaccinating girls and boys at the age of 9–15. HPV vaccination prevents the infection and also stops the spread of the virus from one person to another. This article will help you to understand the basics about HPV, the diseases it causes, and why the HPV vaccine is an important solution.

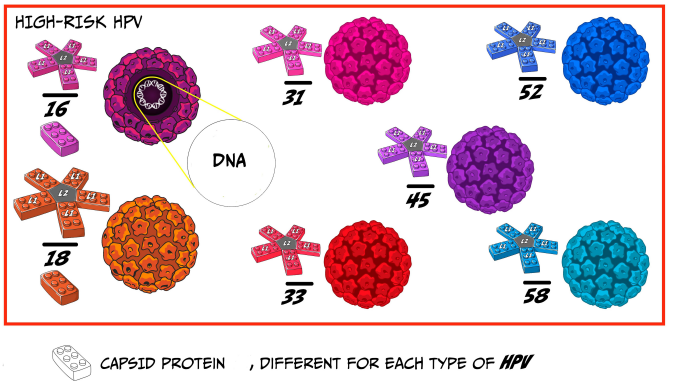

Figure 1

Figure 1

The structure of HPV. HPV is composed of proteins that assemble themselves into starry shield shapes. Seventy-two Starry shields assemble to create the capsid, which encloses the viral DNA (illustrated by Susan Nasif).

WHAT IS HUMAN PAPILLOMAVIRUS?

The human papillomavirus, also known as HPV, is a virus that infects humans and causes "*papilloma*." The word papilloma is composed of "*papilla*," which means pimple, and "*oma*," which refers to an abnormal growth of cells, otherwise known as a tumor. HPV preferably infects cells of the skin and the **mucous membranes**. The skin is an organ, with several tissue layers, that forms the natural protective barrier of a person's body. Mucous membranes are the tissues that line the inside of numerous organs, such as the mouth, the throat, and the genitals.

Viruses are invisible to the naked eye, but they can be observed using a powerful microscope. HPV has a round shape, and its diameter is 55 nm (1 nm = 0.0000001 cm). This is a million times smaller than a tennis ball! Some of the proteins that make up HPV combine to form a star-shaped shield, kind of like a star built from Lego®. In total, 72 starry shields assemble to create the round shape of HPV, which is called the **capsid**. The capsid contains the viral DNA (Figure 1) [1, 2].

HPV COMES IN DIFFERENT FORMS AND SPREADS VIA DIFFERENT ROUTES

HPV is not just one virus. There are more than 100 kinds of HPV, but most of them are rare and not dangerous. Each kind of HPV has a slightly different looking starry shield and therefore has unique characteristics. Scientists have given each type of HPV a number to identify it. Some types of HPV, like 16 and 18, are very harmful for humans (called high-risk HPV) and can cause **malignant lesions**, leading to cancers in various parts of the body. Others, like 6 and 11, are less dangerous (called low-risk HPV) and might create wounds, such as **warts** or **condyloma** (Figure 2) [2]. Condylomas are warts that are located in the mucous membrane of the body, for example in the

MUCOUS MEMBRANE

The tissue that lines the inside of numerous organs, including the oral cavity, the nasal cavity, and the genitals.

CAPSID

The protein structure that surrounds the genetic material of the virus, like a shell.

MALIGNANT LESION

An abnormal new growth of tissue/cells which usually develops rapidly and spreads to the whole body. It is life-threatening if it is not taken care of.

WART

An abnormal growth of cells, most frequently in the shape of a nipple or cauliflower.

CONDYLOMA

A wart located in the mucous membrane for example on the genitals or in the throat.

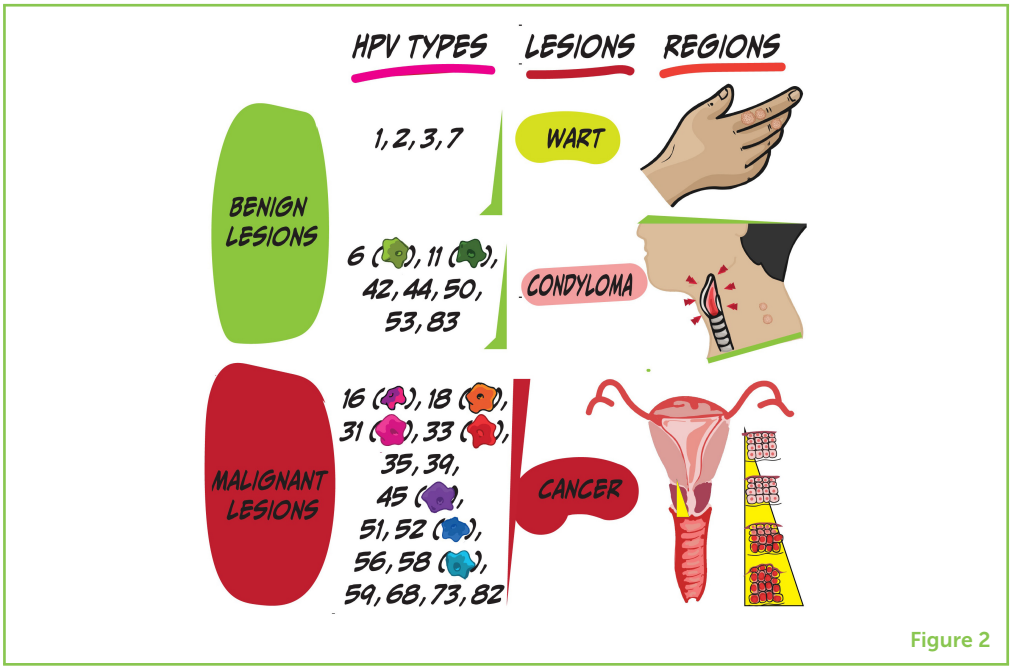

Figure 2

Lesions associated with HPV infection. Infection with some types of HPV can lead to benign conditions, such as warts or condylomas. Other HPV types are more dangerous and can cause malignant lesions, such as cancer of the uterus. The yellow triangle on the lower right image shows the evolution of the cervix cells from normal (top) to cancerous (bottom) cell formation (illustrated by Susan Nasif).

throat. Warts and condylomas are called **benign lesions** because they are not a threat to human lives.

BENIGN LESION

An abnormal new growth of tissue/cells which develops slowly and remains local where it initially originates. It is not life-threatening, but sometimes it evolves toward malignancy.

It is estimated that the majority of adults worldwide are or have been infected by HPV. Most people do not even notice the infection, but can still infect other people. Infections can happen in swimming pools or through skin-skin contact when you shake hands. When a mother is infected, she can transmit the virus to her baby during childbirth. HPV is also the most common sexually transmitted disease and can be passed on through close intimacy and sexual contact.

SYMPTOMS: FROM WARTS TO CANCER

More than half of the types of HPV (~60) cause warts on the skin of various body regions, like hands and feet. Those lesions are usually not dangerous for human health. The other HPV types (~40) enter the body during sexual contact and intimacy. Of these, types 6 and 11 cause condyloma. Condyloma is not life threatening. However, types 16 and 18 contribute to cervical cancer. The **cervix** is a part of the uterus, an essential female reproductive organ. Cervical cancer is one of the top killers of women in the world. The German physician-virologist Harald zur Hausen discovered the link between HPV and cervical cancer in 1983 [3]. In 2008, he won the Nobel Prize in Medicine for that discovery!

CERVIX

The narrow outer end of the uterus, which is the main female reproductive organ.

Although HPV infects women and men equally, women have the highest risk of developing cancer when they get infected by a high-risk type of HPV. Most cases of cervical cancer are caused by an HPV infection. Some oral and throat cancers can also be linked to HPV, and

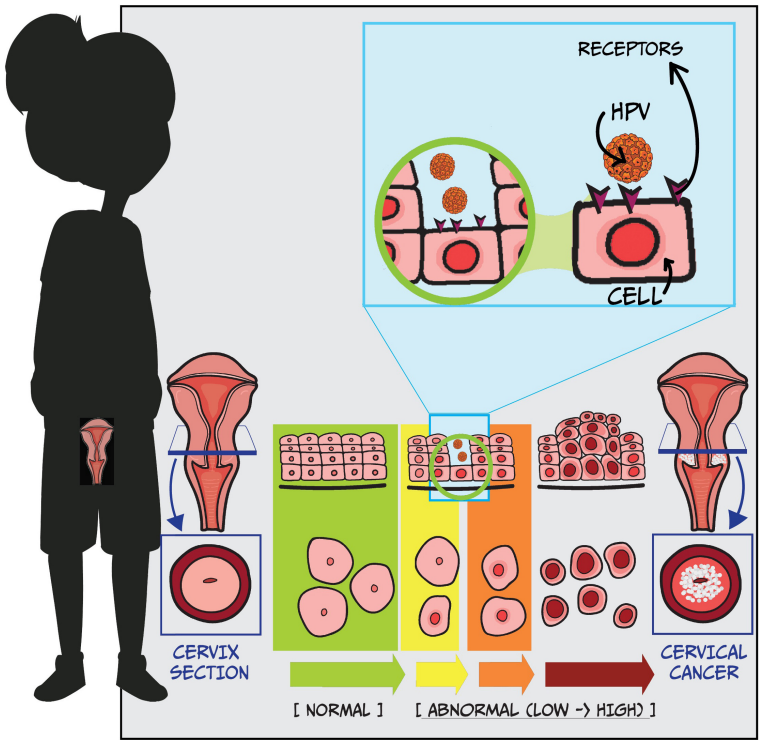

Figure 3

From HPV infection to cervical cancer. The blue square shows the infection of a cell by HPV. In the lower part of the drawing, you see the evolution of the cervix cells from normal (green) to cancerous (red) cell formation (illustrated by Susan Nasif).

although these are less common than cervical cancer, it is important to remember that men are also vulnerable to HPV infection and can also develop cancer.

Being infected by HPV does not mean that a person will definitely develop a tumor. This is good news, because HPV infection is the most common viral infection of the reproductive tract. To develop cancer, a person must be infected by a high-risk type of HPV and be infected for a long time, meaning that the person's body is not able to fight against the virus effectively. To better understand the risks linked to HPV infection, if 10 adolescents are infected, 9 will clear the virus from their bodies and only 1 will develop a serious disease, such as cervical cancer.

Sometimes, when a high-risk type of HPV infects human cells, the virus can mislead the immune system and maintain its infection. This long-standing infection is the first step in the potential development of cancer. The infection starts at the deepest layer of the skin or mucous membranes (see yellow triangle in Figure 2). HPV disrupts the functioning of the cells it infects [1]. After taking control of the cells, HPV can reproduce itself and invade more cells, from the deepest layers to the surface. Each infected cell displays an abnormal appearance that doctors and scientists can detect if they examine the cells using a microscope (Figure 3).

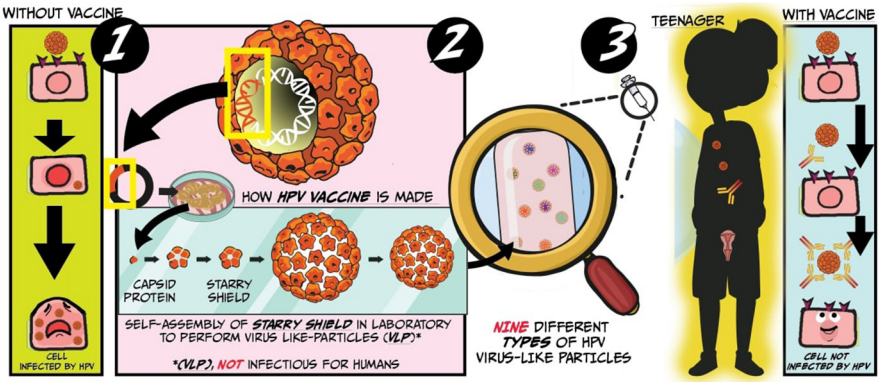

Figure 4

What is the HPV vaccine? Section 1 illustrates a cell being infected by HPV and turning sick. Section 2 illustrates the stages to create the vaccine against HPV, namely by using yeast cells to produce VLPs that mimic the appearance of HPV. Section 3 illustrates a cell being infected by HPV. The immune system of the cell fights efficiently the virus thanks to the vaccine previously received (illustrated by Susan Nasif).

VACCINATION KEEPS US PROTECTED FROM HPV

HPV infection cannot be cured. The only solution is to prevent HPV infection from happening in the first place, through vaccination. Currently, the HPV vaccine can protect us against nine high-risk types of HPV: 6, 11, 16, 18, 31, 33, 45, 52, and 58 [2]. Therefore, the vaccine prevents most cases of HPV infection that can lead to serious health problems.

The HPV vaccine is made of reconstructed starry shields of the viruses, which cannot cause any harm to humans. Those shields are called **virus-like particles** (VLPs) because they look like the HPV virus but do not actually come from it. VLPs are created in laboratories using yeast cells (Figure 4). When a person receives the vaccine, the immune system reacts against the VLPs and remembers them. If the person gets infected by HPV later, the immune system will remember the starry shield of the virus and immediately fight to eliminate the virus from the body.

VIRUS-LIKE PARTICLE

Small particle that appears like a certain virus since it contains proteins from the viral capsid. They do not contain viral genetic material and can therefore not cause an infection. They are usually synthesized in laboratories to mimic a virus, like in the HPV vaccine.

Girls and boys should be vaccinated against HPV between 9 and 15 years old. Why so early? It is important that you get your first HPV vaccine before you get intimate with somebody you like, because the virus is easily transmitted from one person to another. The sooner you get vaccinated, the fewer shots you need: between 9 and 14 years old, you only receive two shots, whereas if you are between 15 and 45 years old, you need three shots to be protected. The pinch of the shot is worth it, do not you think? Although the vaccine is very safe and effective, you might experience some mild side effects, such as a sore spot, swelling, and redness where the shot was given. Headaches and nausea can also occur, but less frequently.

TESTING FOR HPV INFECTION

HPV types not included in the vaccine can still cause infections in vaccinated people. Also, if people are infected before they get

vaccinated, the virus can stay dormant in the body and develop into an infection later on. Therefore, it is important to regularly check for potential HPV infections.

Girls and women can be checked for HPV infection during a visit to the gynecologist, which is a type of doctor specializing in the health status of a woman's reproductive organs. The Pap test is used to check for changes in cervical cells. It is named after Dr. George Papanicolaou, the Greek physician who developed the test. The gynecologist uses a swab to lightly brush over the tissue of the cervix, to collect a sample of cells. These cells are then analyzed under a microscope to see whether they look healthy or abnormal. If cells have a strange appearance, it means that they might be infected by HPV and could potentially lead to a cancer. Through the Pap test, we can detect at least 8 out of 10 girls who are infected by HPV, and help them so they do not develop cancer nor spread the infection. HPV cannot be cured, but if a doctor detects the infection early enough, he can remove the infected tissue of the cervix. Because some types of HPV can hide and re-appear later, it is important that girls get the Pap test every 3 years.

Boys usually get tested when something strange appears on their genitals or if they find out their partner is infected. There is no Pap test for boys, but HPV can be detected using a laboratory technique that looks for the DNA of the HPV virus. When a wart is observed on the genitals of a girl or a boy, the doctor can collect the wart cells, which can then be tested in the lab to see if they contain HPV.

WHAT DID I LEARN? VACCINATION TO PROTECT MYSELF AND OTHERS!

HPV is very common. It is considered to be the most common sexually transmitted disease and men are equally infected than women. In most cases, infected people clear the virus from their bodies, but sometimes the immune system is not strong enough to fight it. Hence, some people develop serious health problem, such as cancer. Currently, no cure exist to get rid of this viral enemy, but we can protect ourselves with a vaccine.

The more people are vaccinated, the lower the risk of HPV infection will be. Spread the news to your friends, classmates, and family to create a chain of solidarity against HPV and decrease the transmission of the virus. Widespread immunization against HPV could reduce, and eventually even eliminate, cervical cancers and other diseases caused by HPV worldwide.

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A. Y. Jackson Science Club promotes fun and challenging science initiatives through monthly events.

AUTHORS

MARIE NEUNEZ
Marie Neunez, Ir, is a Ph.D. student at the Faculty of Medicine and a Master student in medicine at the Université Libre de Bruxelles (ULB). Previously she was a part-time research assistant for 3 years at the Institute for Interdisciplinary Innovation in healthcare (I3h). She was a Clinical Research Coordinator for 2 years in the

departments of Nuclear Medicine & Radiotherapy at the Institut Jules Bordet (IJB). She also performed a 5-months internship at BASF SE (Mannheim, Germany) in the Human Health & Nutrition department. Marie holds a Bachelor's degree in medicine (ULB, Belgium), a M.Sc. degree in bioengineering with a specialization in Science, Technology and Quality of Food (UCL, Belgium), a Post-graduate degree in Management (ICHEC Business Management School, Belgium), and a certificate in Clinical Studies (Cefochim, Belgium). *mneunez@i3health.eu

SUSAN NASIF

Susan Nasif, Founder of Cimaza Science for Public Health Education and Science/Medical Communication, uses science and art to spread awareness on science-information deficits and vaccines myths. Susan's company uses the scientific method to find the most effective form and languages to appeal to different audiences. Combining her talent and research Susan's comics are fun and informative in many EU languages and in Arabic. She has received three global recognitions, winning the 2015 Science Hero Award, 2017 Innovation in Science Literacy Award, and 2018 Europe (Silver) Vaccines Communication Challenge Award. Susan's LinkedIn url is: `https://www.linkedin.com/in/susannasifphd/`.

PIERRE R. SMEESTERS

Pierre Smeesters is a pediatrician working as the head of the pediatric department from the Academic Children's Hospital Queen Fabiola at the Free University of Brussels (ULB) in Belgium. He is also leading a research group in Microbiology and Infectious Disease at the Free University of Brussels. His research interests include translational research in Strep A, vaccination, new diagnostic tests, and societal issues related to childhood.

HILDE STEVENS

I am an Associate Professor at the Université Libre de Bruxelles. My research focuses on how people with various cultures and ways of working (e.g., academics or people in the pharmaceutical industry) could optimally collaborate to bring inventions from the lab to the patient much faster, and how patients in low- and middle-income countries also could get access to innovative therapies. I love telling stories to my children about bad bugs and how to fight them, and then we make paintings about it!

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MENINGOCOCCAL VACCINES: A TECHNOLOGICAL REVOLUTION

Simone Pecetta, Vega Masignani, Mariagrazia Pizza and Rino Rappuoli *

Research and Development Centre, GlaxoSmithKline (GSK), Siena, Italy

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The sneaky meningococcus is a bacterium that can cause terrible disease. Development of an effective vaccine has been extremely difficult. Meningococcal vaccines developed in the 1990s are based on the bacterial capsule, a shield that protects the bacteria and that is used to instruct our body to combat this terrible disease. These vaccines work against four types of meningococcus: A, C, W, and Y. However, they do not work against meningococcus B. Scientists had to invent a completely new way to make vaccines, reading the bacterial DNA to search for new protective components. With this new approach, named reverse vaccinology, three new bacterial components were discovered: NadA, NHBA, and fHbp. When combined with a fourth component (PorA), they form the 4CMenB vaccine. This vaccine has reduced meningococcal disease in infants by 75% in the UK. Today, 4CMenB protects children all around the world.

Figure 1

How meningococcus invades the body. Meningococcus enters the nose, contacts the cells inside the nostrils, and moves into the blood. There, covered by its capsule and disguised by coating itself with human proteins, (like fH) it evades the body's defenses and starts dividing. When meningococcus reaches the organs and the brain, it causes great damage.

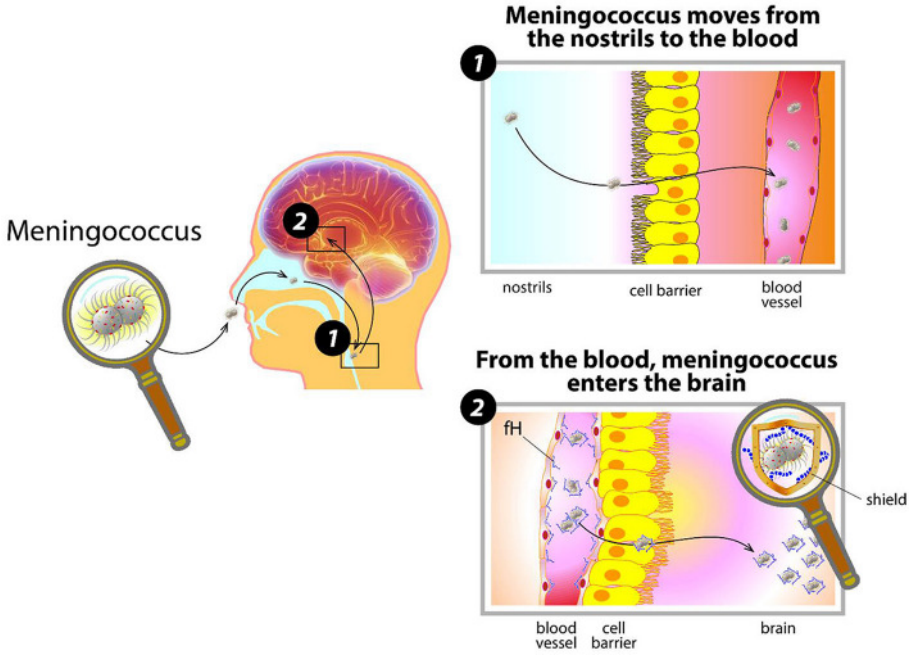

Figure 1

MUCH WORSE THAN A HEADACHE

You may not have heard of it, but there is dangerous microscopic organism called *Neisseria meningitidis*, also known as meningococcus. It is a bacterium, made of one single cell. Usually, meningococcus lives quietly in our noses or throats for some months. Sometimes, when we are sick or weak, it can move from the nose to the blood and cause sickness.

Meningococcus is the cause of a severe disease called meningitis that can initially cause fever, vomiting, and headache, like a simple flu. Then, the bacteria begin to travel through the body and grow very quickly, reaching the blood, nerves, and brain (Figure 1). Meningococcal meningitis can cause death in few hours. For those who survive, it can unfortunately lead to physical and mental disabilities, amputation of arms, legs, fingers, and toes. Infants and children are particularly vulnerable to meningococcal disease, and disabilities can occur in up to half of the cases. So why have not you heard of such a scary bacterium before? Because it is not very common. The disease is most present in Africa, south of the Sahara Desert, where 30,000 people get sick every year. But meningococcus sometimes spreads all over the world, often appearing in small outbreaks (it is common in gatherings of young adults in colleges and discos, for example) or in big epidemics. So, how do we avoid getting this bad disease? Well, with **vaccines**!

VACCINE

A purified component injected to train the body to remember an infectious organism, so that when we get infected for real, we do not get sick.

FINDING THE WEAK SPOT

ANTIGEN

A component of an organism that can cause protection. A vaccine uses one or more antigens to teach the body how to defend against disease.

CAPSULE

A shield that surrounds a bacterium and protects it from the environment and our immune cells.

ANTIBODY

Molecules that bind to foreign components like bacterial capsules or antigens. The body's defenses recognize the antibody "tag" and act to stop infection.

What does meningococcus look like? Like all other cells, it is surrounded by a membrane on which many structures, called **antigens**, are located. These antigens help the bacterium to attach to our noses and survive in our bodies. Covering the membrane, meningococci have a shield, called the **capsule**, which protects them from the environment, and most importantly, from the body's defenses. It takes the human body some time to prepare to fight meningococcus, and when the body is ready to destroy the bacteria, it is already too late: meningococcus multiplies rapidly in the blood, enters the organs and the brain, and causes great damage.

The capsule, the main defense mechanism of this bacterium, can also be our best weapon against it. Scientists have discovered that we can inject part of this capsule into a healthy person to teach the body how to defeat meningococcus. It is like showing the identification of a thief to the police, so that they can stop him before he steals. This teaching lesson is called vaccination.

Cells called B cells are part of the police force of our bodies, required to protect us from meningococcus. B cells produce molecules called **antibodies**. Antibodies are released into the blood and stick to the nasty bacteria, like a tag. After being tagged, the body can destroy the bacteria before they cause any damage.

HISTORY OF MENINGOCOCCAL VACCINES

CARRIER PROTEIN

A molecule obtained from bacteria which is highly attractive for T cells. It is used in conjugate vaccines.

CONJUGATE VACCINE

A vaccine composed of the bacterial capsule attached to a carrier protein. It can activate both B and T cells, and to protect children from meningococcus type A, C, W, and Y.

The first meningococcal vaccines made of the bacterial capsule only protected adults, and only for a short period of time. In children, the population most vulnerable to meningococcal disease, these vaccines were not useful. The reason is that the capsule alone can only recruit B cells, but it does not call into action other defense cells, called T cells, which are extremely important to protect children. T cells do not produce antibodies but instruct the B cells on how to make better, more precise antibodies and for longer periods of time—kind of like coaches. Thanks to our T cells, our bodies can remember an infection for years and be ready to fight more rapidly if the same infection-causing organism comes back. So how do we protect children if the capsule is not enough?

Scientists solved this problem in the 1990s: using chemistry, they linked the capsule to another molecule that is highly attractive for T cells [1]. This molecule comes from other nasty bacteria, such as diphtheria or tetanus, and it is called a **carrier protein** because it delivers the capsule to the T cells. In this way, the vaccine can stimulate both B and T cells. This brilliant idea led to the creation of what are called **conjugate vaccines**, which are commonly used worldwide today.

However, meningococcus is a master of disguise: the capsule can be of different types: A, B, C, W, and Y. If the body creates antibodies specific for one type, they are not protective against the others. To be protected against all types, we should teach our bodies to recognize all five variants of the capsule. Conjugate vaccines are highly protective against types A, C, W, and Y. But what about type B? Well, meningococcus had one more trick up its sleeve...

MENINGOCOCCUS B: THE LAST FRONTIER

The development of a vaccine against meningococcus B represents one of the milestones of modern medicine [2, 3]. Meningococcus B is a major cause of disease in the Americas, Canada, Europe, Asia, and many other countries. The stumbling block was that the B capsule does not cause antibodies to be produced, not even with the conjugation technology. The sneaky meningococcus B uses a sophisticated strategy: its capsule mimics the sugars presents on our cells, so that it can go under-cover as a harmless human cell. As a result, by attacking the meningococcus B capsule, the body could also damage its own cells, and that is why the immune system does not react to it. Many scientists concluded that using the capsule to fight meningococcus B could be too risky. A new technology was needed to overcome this challenge.

AN INSIDE-OUT REVOLUTION

If a problem cannot be solved using well-known methods, you must invent something new! Instead of looking for something clearly visible outside the bacterium, like its capsule, scientists decided to study the bacterium more deeply, looking at its DNA. The DNA is like a catalog of all the bacterial components that perform the functions of the bacterium. Using modern lab equipment, the DNA can be read like a text, exactly as you are doing with this manuscript (more than 2 billion letters and more than 2,000 words are contained in the meningococcal DNA!). While reading, you may recognize words that you do not know, and search for their meaning using a dictionary. Well, this is exactly what happened for meningococcus B. Scientists read its DNA to find yet-unknown bacterial components that, like the capsule in the other types, could be good targets for the body's defenses. This approach, from outside to inside, was called **reverse vaccinology**, and represented a revolution in the world of vaccines (Figure 2).

REVERSE VACCINOLOGY

The study of the DNA of an organism to identify new components for vaccines.

Sophisticated computer algorithms were used to screen the entire DNA of type B meningococcus and several months of work were necessary to go from 2,000, down to 600 potential antigens, and finally to the three best ones [4]. The top three components were called NadA, fHbp, and NHBA.

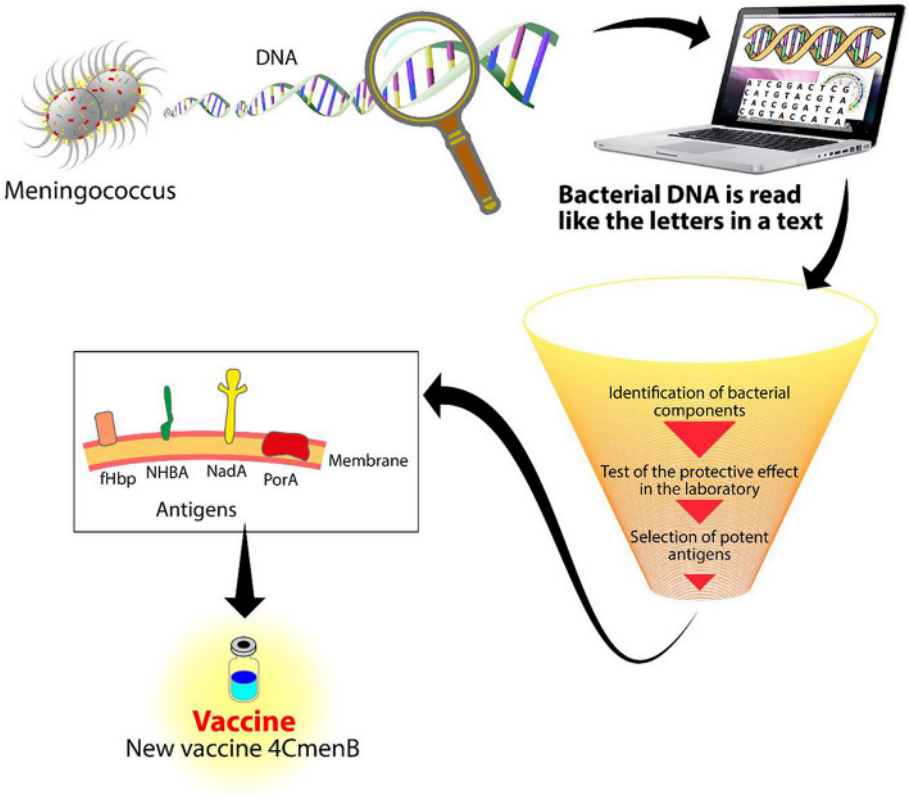

Figure 2

Reverse vaccinology. DNA from meningococcus is read by a machine called a sequencer. With the use of sophisticated computer programs, the DNA is analyzed to identify new components to be used for a vaccine. After many experiments, three antigens were identified with the potential of protecting against meningococcus B: NadA, NHBA, and fHbp. Combined with a fourth antigen, PorA, they form the 4CMenB vaccine.

Figure 2

These three antigens play an important role in the ability of meningococcus B to cause disease (Figure 3A). NadA is a sticky antigen that works as an anchor, allowing the bacteria to stick to the internal walls of human nostrils. When bacteria cross the nostril cells and enter the bloodstream, they start to multiply and reach all organs. To circulate in the blood without being attacked by antibodies, meningococcus have evolved several mechanisms to fool the body's defenses. Meningococcus uses fHbp and NHBA as glue to coat their surfaces with substances normally produced by the human body, making them "invisible." However, now that we know these tricks, we can instruct the immune system to produce antibodies against NadA, fHbp, and NHBA and we can block the meningococcus disguise mechanism. By combining these three meningococcal components with a fourth component, PorA, the first vaccine against meningococcus B, called 4CMenB, was born.

SAVING CHILDREN FROM MENINGOCOCCUS B

The UK was the first country that decided to protect its children with the novel 4CMenB vaccine, by introducing this vaccine in a national immunization program in 2015 [5]. In the 5 years since, about 5 million children in the UK have been vaccinated with the new vaccine. As shown in Figure 3B, the use of 4CMenB has prevented one case of

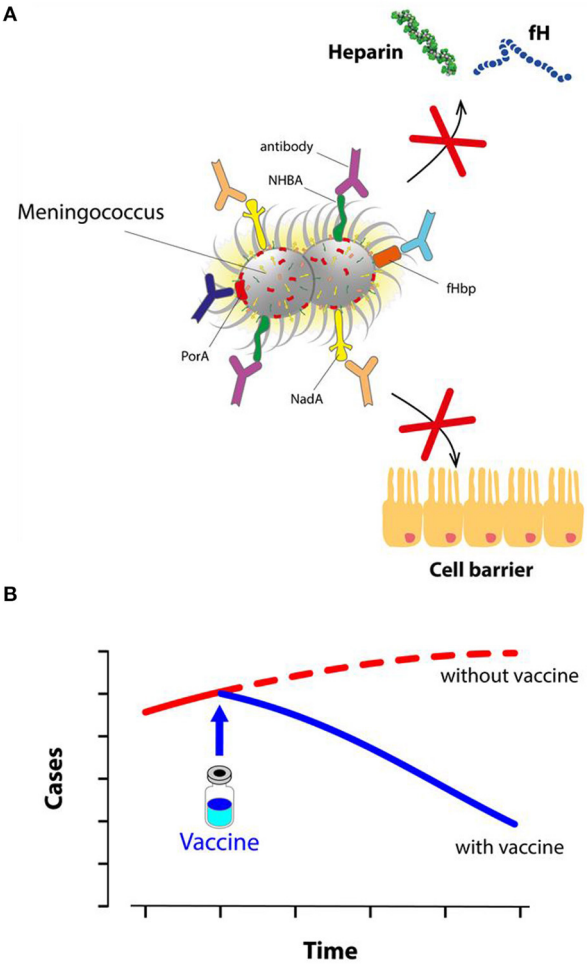

Figure 3

Vaccine protection against meningococcus B. **(A)** After 4CMenB vaccination, the body produces antibodies against meningococcus. Antibodies block NadA, limiting the ability of meningococcus to invade cells. Other antibodies block fHbp and NHBA, preventing them from sticking to human proteins (like fH and heparin) and thus stopping the bacterial disguise mechanism. Finally, other antibodies also block PorA and other components. Covered by antibodies, meningococcus B can do no harm and it is rapidly destroyed. **(B)** After its introduction in the UK in 2015, the use of 4CMenB greatly reduced the number of cases of meningococcal disease in young children.

meningococcal disease every 4 days! Today, the 4CMenB vaccine is available in 42 countries all around the world, helping to protect thousands of infants, children, and adolescents from dangerous meningococcal disease.

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YOUNG REVIEWERS

AMELIE, AGE: 12
I have been participating in Frontiers for Young Minds for the past 2 years. Reviewing papers is one of my passions as well as reading, painting, drawing, and writing. Through reading these scientific papers, I have learnt a lot about health and disease. I love to travel and my favorite animal is the pangolin.

ELLIOT, AGE: 10
My name is Elliot, and I am 10 years old. I live in a small town in Wisconsin out in the woods. I love almost all science, especially engineering and robotics/coding. I also love playing soccer, playing cello, and almost anything outside. I love to read, particularly the mythologies of many different cultures. I am currently reading the My Dark Materials series.

AUTHORS

SIMONE PECETTA

Simone Pecetta is a Senior Scientist in GSK Vaccines, with a long-term scientific interest in understanding the immunological mechanisms of vaccination. He has previously worked as post-doctoral scientist at the Francis Crick Institute in London (UK) and at the Ragon Institute of MGH, MIT and Harvard in Boston (USA), studying the biology of B cells, the antibodies they produce, and their role in the protection from HIV infection. His Ph.D. research, focused on the study of the effect of multiple vaccinations, was conducted at Novartis Vaccines R&D in collaboration with the University of Rome "Sapienza."

VEGA MASIGNANI

Vega Masignani holds a Ph.D. in Biotechnology and is currently Vaccine Development Leader at GSK Vaccines in Siena. She was first involved in the computational analysis of the *Neisseria meningitides* type B genome sequence and in the computer-based identification of novel candidates for the development of 4CMenB, the type B meningococcal vaccine, and contributed to the characterization of the main protein components of 4CMenB. During the past few years, she has also been involved in the research on the identification of novel antigen candidates for *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* vaccines.

MARIAGRAZIA PIZZA

Mariagrazia Pizza is currently Senior Scientific Director for Bacterial Vaccines at GSK Vaccines, in Siena. She contributed to the discovery of a pertussis vaccine based on a genetically detoxified toxin, and to the discovery of a new vaccine against meningococcus B, licensed in many countries worldwide. She has received several awards and is Honorary Visiting Professor at the University of Leicester. She has over 200 publications in international peer-reviewed journals and is co-inventor of many patents.

RINO RAPPUOLI

Rino Rappuoli is head of the vAMRes laboratory at TLS in Siena and Chief Scientist and Head External R&D at GSK Vaccines, Siena, Italy. He has received several awards including the Paul Ehrlich and Ludwig Darmstaedter Prize, the Gold Medal by the Italian President, the Albert B. Sabin Gold Medal, the Canada Gairdner International Award, and the European Inventor Award for Lifetime Achievement. He developed the pertussis and meningococcus B vaccines, among others, and was nominated third most influential person worldwide in the field of vaccines. Dr. Rappuoli is among the world's scientific leaders dedicated to the sustainability of global health. *rino.r.rappuoli@gsk.com

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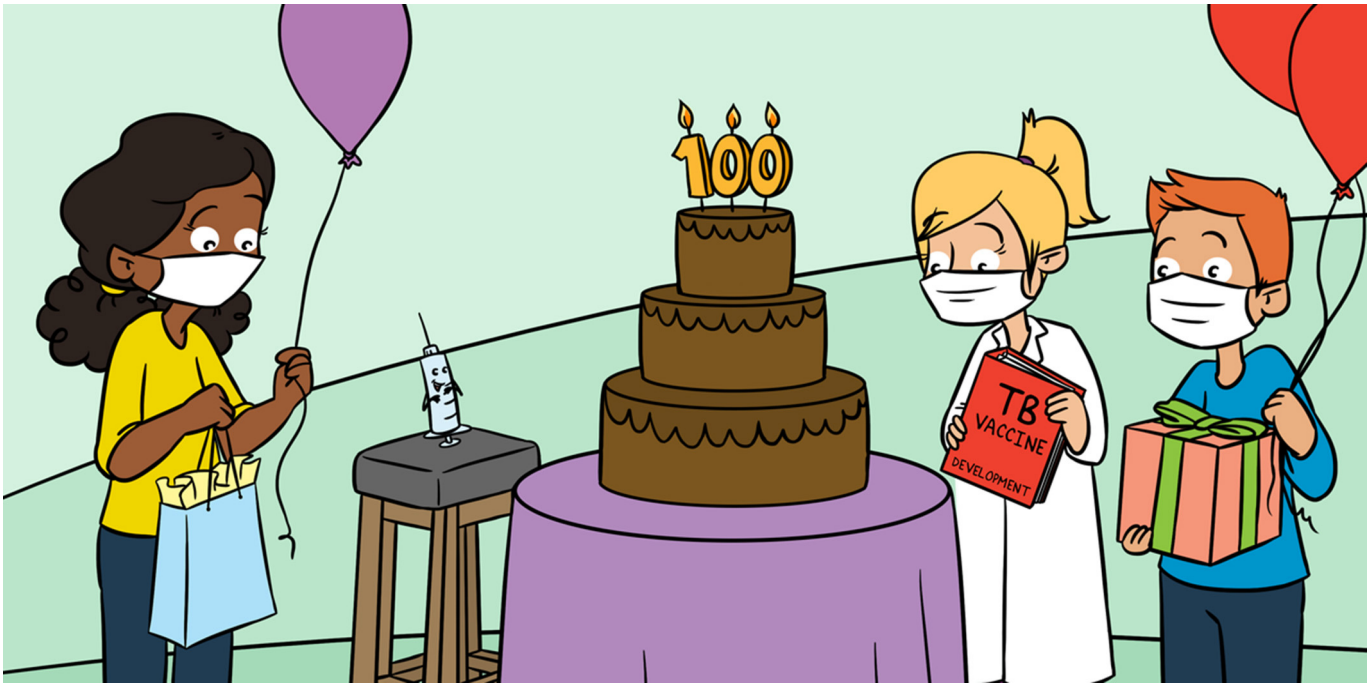

ONE HUNDRED YEARS OF BCG: THE WORLD'S MOST WIDELY USED VACCINE

Rachel Tanner * ***and Helen McShane***

The Jenner Institute, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

YOUNG REVIEWER:

APARNA

AGE: 12

2021 is the 100-year anniversary of the BCG vaccine, and there is a lot to celebrate! This vaccine has without doubt saved the lives of millions of people, by protecting them from the bacterial lung disease tuberculosis (TB) and possibly other illnesses too. However, there are some drawbacks to BCG—in particular, it does not work very well in some countries that have high rates of TB, so a new and improved vaccine is desperately needed. Scientists around the world are working hard to develop a new TB vaccine, but there are challenges. If we can better understand how BCG works and why it works in some populations and not others, it might help us to design a better vaccine to protect people against tuberculosis and to possibly one day eradicate this disease.

THE BCG VACCINE PROTECTS AGAINST TUBERCULOSIS

You might already know that a **vaccine** is a type of medicine, often given as an injection, that prevents infection or disease. The **BCG**

VACCINE

A product that stimulates a person's immune system to produce immunity to a specific disease, protecting them from that disease.

BCG

The only vaccine that currently exists against tuberculosis, named after its inventors Albert Calmette and Camille Guérin.

TUBERCULOSIS

A bacterial infection that usually affects the lungs, and is spread in the air through coughs and sneezes.

vaccine is designed to protect against **tuberculosis** (TB), which is a bacterial disease that usually affects the lungs and causes a serious cough. TB has existed for thousands of years—signs of TB have even been found in Egyptian mummies from around 3000 BCE! TB is also one of the most common infectious diseases in the world, with a quarter of the world's population infected. Almost 1.5 million people die from TB every year, and it can be particularly dangerous in babies [1].

One hundred years ago, two French scientists named Albert Calmette and Camille Guérin invented a vaccine against TB. They called it BCG, which is short for Bacillus Calmette-Guérin. It is made from the bacteria that causes the cow version of TB, and Calmette and Guérin altered the bacteria to make sure the vaccine would not cause disease in humans. Since then, BCG has been the most widely used vaccine ever, with around 100 million babies receiving it every year.

PROS OF THE BCG VACCINE

The BCG vaccine has been given to over 4 billion people and has been shown to be very safe. Some people get mild side effects, such as a headache or fever and a blister or sore arm where the injection went in. However, more serious side-effects are very rare.

When the BCG vaccine is given to new-born babies, it provides excellent protection against serious forms of TB—for example, TB that spreads to the brain (called TB meningitis) and TB that spreads throughout the body (called miliary TB). Because these forms of TB have a high risk of death, BCG is really effective in reducing the death rate from TB. The most common type of TB is disease of the lungs, and BCG is good at protecting against this in some countries, such as the U.K. [2].

ANTIBIOTICS

Medicines designed to treat infections caused by bacteria.

Although **antibiotics** have been developed to treat TB, prevention with a vaccine is better than treatment. If you can stop people from becoming sick in the first place, they will not suffer from the symptoms or risk dying. In addition, in countries that have high rates of TB, antibiotics are often too expensive or difficult to access. Some types of TB bacteria have evolved resistance against antibiotics, so these treatments are no longer effective.

BCG can protect against other diseases as well as TB. For example, it provides some protection against leprosy, which is a disease caused by bacteria that are related to the TB bacteria. Leprosy often causes patches or rashes on the skin and can lead to people being stigmatized. In the past, people with leprosy were even banished to "leper colonies," or islands away from everyone else. There is also some evidence that the BCG vaccine may protect babies against other illnesses that are not related to TB at all. A recent study in Uganda showed that babies

Figure 1

The BCG vaccine has many advantages.

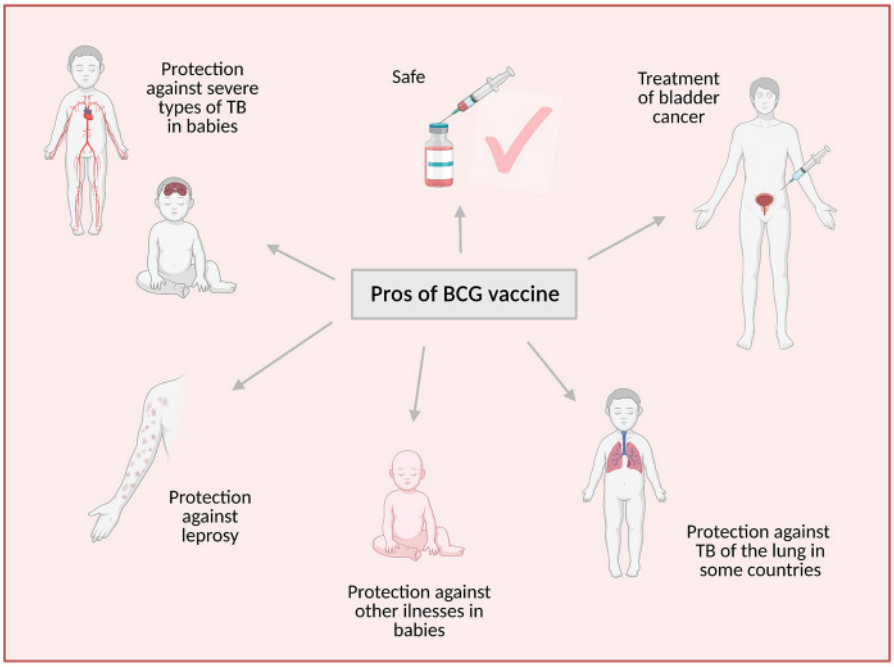

Figure 1

who received the BCG vaccine as soon as they were born were less likely to get ill in general than were babies who got their BCG vaccine at 6 weeks old [3].

BCG has another use you might find surprising—it can be given as a treatment for bladder cancer [4]. Scientists are still trying to figure out why BCG is effective at treating this disease, but it is thought that it might improve the ability of immune cells to kill cancer cells. The pros of BCG are summarized in Figure 1.

CONS OF THE BCG VACCINE

There are some situations in which the BCG vaccine should not be given. For example, BCG is not considered safe to give to babies or adults who are infected with HIV (a virus that attacks cells of the **immune system**), because the BCG vaccine is made from live bacteria. Although Calmette and Guérin tweaked the bacteria so that they would not cause disease, people with HIV or certain other disorders have weakened immune systems that BCG can overcome and make them sick.

IMMUNE SYSTEM

The organs and cells of the body that fight against infections and toxins to provide resistance against getting sick.

BCG is very effective at protecting children against TB in *some* countries, such as the UK, but not very effective in others. It provides low levels of protection, or even *no* protection, in places such as India and sub-Saharan Africa [2]. Unfortunately, these are the areas with high rates of TB, where a vaccine is needed the most (Figure 2). Scientists still do not fully understand why BCG works differently in

High efficacy (>75%)	Medium efficacy	Low efficacy (<25%)
UK	Israel	India
Norway	South Africa	Malawi
Sweden	Indonesia	Kenya
Denmark	Papua New Guinea	Georgia, USA

Figure 2

Figure 2

The BCG vaccine provides varying levels of protection against lung TB in different countries. While the vaccine protects over 75% of vaccinated people in areas like the UK, the efficacy (effectiveness) of the vaccine decreases in the regions close to the equator (shown in red) [2].

different countries, but most think it has to do with the presence of other bacteria that are related to TB. The closer you get to the equator, the more of these TB-related bacteria are found in the environment. If people are living with these bacteria around them, their bodies develop an immune response to the bacteria that might interfere with the BCG vaccine working properly.

Other reasons scientists have suggested for BCG working differently in different populations include differences in the specific version of the vaccine used, the ability to keep the vaccine refrigerated, differences in people's genetics or nutritional status, environmental influences such as the amount of sunlight exposure, or viral infections that are present when BCG is given (Figure 3).

NEW TB VACCINES

Because of these drawbacks of the BCG vaccine, a new and improved TB vaccine is desperately needed to bring TB under control. However, we need to make sure we do not lose the advantages of BCG. Scientists around the world are working hard to design and test new TB vaccines and there are several that look promising [5]. The main approaches are to try to improve on BCG through altering the genes of the bacteria, or to give a new vaccine as a **booster** to BCG. Researchers in Spain have been modifying human TB bacteria to make them as safe as BCG, and they are now testing this vaccine in human volunteers.

BOOSTER

A booster is a second vaccination given against the same infection or disease to try to "boost" protection provided by the first vaccination.

However, in the 100 years since BCG was developed, we still do not have a new TB vaccine approved for use. If you think about the new vaccines for COVID-19, it took less than a year to go from initial design to mass vaccination, so why is it so much harder for TB? One of the challenges is that we do not know which parts of the immune system are important to protect us from TB, which makes it difficult to design the vaccine and check whether it is working. We also do not have reliable ways to test the vaccine. It is not ethical to infect people with TB after giving them the vaccine, so testing needs to be done in animals instead. However, animals might not be a good representation of what happens in humans.

Figure 3

Scientists are still not sure why the BCG vaccine works better in some populations than others, but there are several possible reasons.

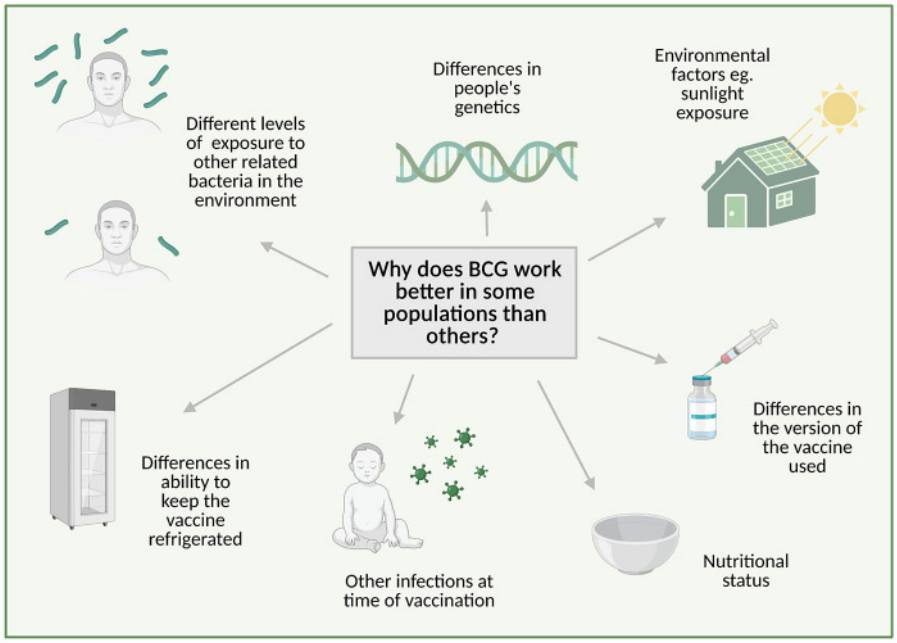

Figure 3

At the University of Oxford, our research aims to address some of these issues. For example, we are studying how the immune system reacts to BCG vaccination, to understand which types of immune responses protect people from TB and which parts of the bacteria the immune system targets. We are designing new vaccines based on these findings. We are also developing alternative ways to test TB vaccines: either by infecting people with safe bacteria that are related to TB, or by infecting cells in a test-tube as a model of what happens inside the body. If we can better understand how the BCG vaccine provides protection from TB, and why it works in some populations and not others, it might help us to design a better TB vaccine in the future.

CONCLUSION

2021 marks 100 years of the BCG vaccine, which is designed to protect against tuberculosis. This vaccine has been given to over 4 billion people. BCG is safe and offers many advantages, including protecting babies against serious forms of TB disease, protecting people in some countries against TB of the lungs, and reducing the risk of other related illnesses such as leprosy and maybe even unrelated illnesses like pneumonia. It is also used as a treatment for bladder cancer. However, BCG does not work very well in some of the countries that have high rates of TB and that are most in need of a vaccine. TB remains a major global health issue and scientists around the world are working to develop a new and improved TB vaccine, although there are many challenges involved. Better understanding of BCG might give

us the clues we need to design a vaccine that protects everybody and eventually eradicates TB once and for all.

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CONFLICT OF INTEREST: 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 REVIEWER

APARNA, AGE: 12

I am a 12 year old girl and my interests are science, music and art! I am also a sports enthusiast who loves any type of action. Other interests include playing violin, drawing and making new friends. I love the Harry Potter book series and the movies as well. My dream is to become a neurologist 1 day and help find cures to diseases.

AUTHORS

RACHEL TANNER

I am a post-doctoral research fellow and lecturer in human sciences at the University of Oxford. I became a medical scientist because I was shocked by how many people are still getting sick and dying every day from diseases like tuberculosis and HIV. I wanted to do something to help, and as everyone knows, prevention is better than cure—so I started working on vaccines. I now study the immune response to TB and try to develop new ways of testing vaccines instead of using animals for experiments. During my free time, I enjoy playing polo and have recently taken up beekeeping! *rachel.tanner@ndm.ox.ac.uk

HELEN MCSHANE

I am a professor of vaccinology, consultant physician, deputy head for the Medical Sciences Division and director of the Biomedical Research Center in Oxford. I have led a TB vaccine research group at the Jenner Institute, University of Oxford for the last 20 years. One important aspect of that has been the development of MVA85A—the first new TB vaccine candidate to enter efficacy testing. One of the current focusses of my work is developing TB vaccines that are inhaled rather than injected. I enjoy spending time with my three children and our dog Archie, and swim whenever I get the chance.

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VACCINES AND ANTIBODIES: WEAPONS IN THE FIGHT AGAINST EBOLA VIRUS

Patrice Debré [1*], ***Marie Neunez*** [2,3] ***and Michel Goldman*** [2]

[1] *Département d'immunologie, APHP, Sorbonne Université, CIMI (INSERM U1135) Hôpital Pitié Salpêtrière, Paris, France*

[2] *Institute for Interdisciplinary Innovation in Healthcare (I3h), Université libre de Bruxelles, Brussels, Belgium*

[3] *Grant of the Belgian Kids' Fund for Pediatric Research, Brussels, Belgium*

YOUNG REVIEWER:

MEHRANEH

AGE: 12

Ebola virus disease is one of the deadliest infections in the world today. The microbe to blame is the Ebola virus. It has already caused numerous outbreaks in Africa, in the regions located south of the Sahara. This article describes the main characteristics of this infectious disease as well as the currently available treatments, namely vaccines and antibodies. Antibodies are produced by the human body when it is infected by a microbe. Antibodies can be collected from the blood of infected humans or animals and purified or manufactured in a laboratory to produce drugs. While vaccines have demonstrated their effectiveness in preventing infectious diseases, antibodies are effective in stopping the progression of several infectious diseases. In this article, you will discover that the stimulation of the immune system, either by the vaccine or by antibodies, is essential to tackle Ebola virus disease.

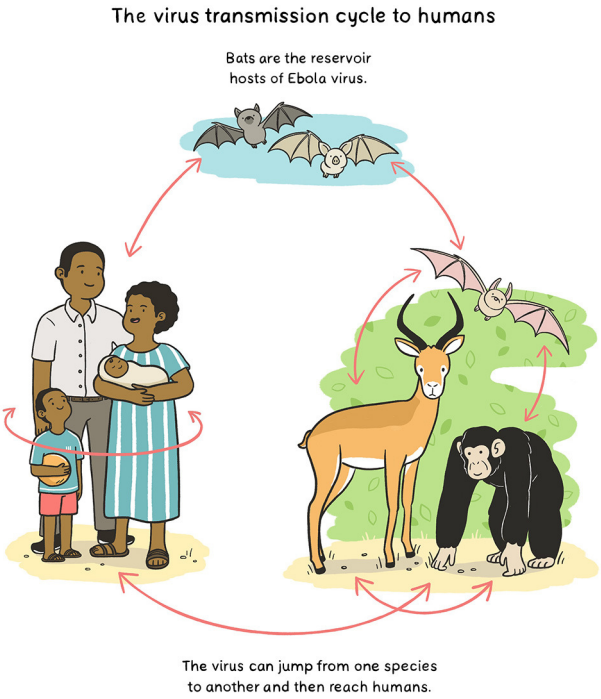

Figure 1

Transmission of Ebola virus to humans. Bats can be infected with Ebola virus without getting sick, and they can then spread the virus to other animals or directly to humans. Humans can also contract Ebola by handling sick or infected animals that were previously infected by bats. Infected humans can spread the virus to each other via bodily fluids, including blood, saliva, urine, and vomit.

EBOLA VIRUS ORIGIN AND TRANSMISSION TO HUMANS

Ebola virus was identified for the first time in 1976. Since its discovery, the virus has already caused more than 20 outbreaks in Africa. These outbreaks are quite deadly: it was estimated that if 10 people were infected by the Ebola virus, <4 people would survive [1–3]. Ebola virus infections appear in equatorial sub-Saharan Africa[1] , particularly in Sudan, Uganda, Gabon, and the Democratic Republic of Congo. Ebola virus disease originates from animals. Fruit bats naturally harbor Ebola virus, which means that the virus lives inside the bats without harming them. Hence, bats are the natural reservoirs of the Ebola virus. The Ebola virus can jump from bats to other species such as humans and apes (Figure 1).

Ebola virus infections occur when viral particles are absorbed through the mouth, the skin, or through skin wounds. Humans can become infected when handling sick or dead infected animals or by close contact with bats that have the virus. They can also be infected by other humans, for example by contact with blood, saliva, urine, breast milk, semen, sweat, stool, or vomit from infected people. Humans can also be infected through soiled clothing, bedding, gloves, protective equipment, and medical waste, such as syringes. You can see why people need to use extreme caution if they deal with infected patients in hospitals or dead people at funerals.

[1] https://en.m.wikipedia.org/wiki/Sub-Saharan_Africa

Figure 2

The appearance and machinery of Ebola virus. Ebola virus is a filamentous virus, which means it has a worm-like shape. Ebola virus is protected against the environment by its envelope. The viral envelope contains various proteins, including the spike glycoprotein that helps the virus to infect cells.

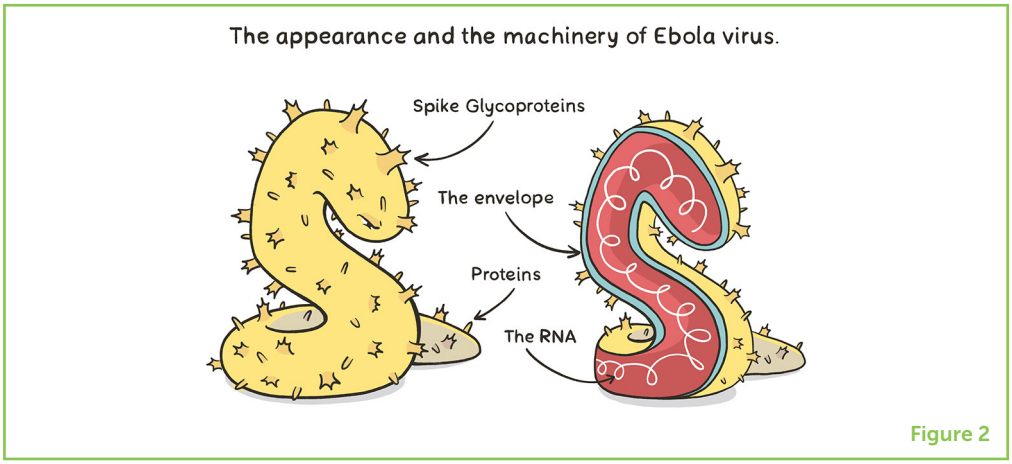

Figure 2

EBOLA VIRUS INFECTION

Ebola virus has been extensively studied by scientists. Ebola virus is a member of a family of viruses called Filoviridae. Filovirus are filamentous viruses, so named because there are fin and elongated. While the human genome and that of other animals is made of DNA, the genome of Ebola virus is made a related molecule called RNA. The RNA genome and various proteins that help the virus to replicate itself are enclosed within a protective layer called the **viral envelope**. The envelope has protruding molecules on its surface called **spike glycoproteins**. The spike glycoproteins help the virus to penetrate and infect cells (Figure 2). If an infection occurs, the immune system of an infected animal will spot these spike glycoproteins and will fight the virus, by calling its immune soldiers onto the field.

VIRAL ENVELOPE

A viral envelope is the outermost layer of many types of viruses. It protects the genetic material in their life-cycle when traveling between host cells.

SPIKE GLYCOPROTEIN

a glycoprotein that protrudes from the envelope of some viruses (such as a Ebola or also Coronavirus) and facilitates entry of the virion into a host cell by binding to a receptor on the surface of a host cell.

Ebola virus disease does not start right away after infection. There is a lag of 2–21 days, called the incubation period, before the replication of the virus causes the first symptoms appear. Ebola virus disease starts with high fever, malaise, fatigue, and body aches. Then gastrointestinal symptoms, such as vomiting and diarrhea, appear, which lead to drastic fluid losses of up to 10 l a day. While some patients recover, others suffer from bleeding and kidney damage, eventually leading to multiple organ failure and death. To diagnose Ebola virus disease, a blood sample is taken from the infected person and examined for the presence of viral particles.

LYMPHOCYTES: THE HEROES OF THE IMMUNE SYSTEM

Against microbes, and viruses in particular, there are two modes of protection. The first one is to avoid contact with infected people, by respecting a physical distance as proposed for Covid-19. Arthur Semmelweis was the first to promote hand washing back in the 1800s, making hand washing the oldest preventive measure. The French biologist Louis Pasteur, who was afraid of germ transmission, never shook hands. The second type of protection is provided by

the immune system. The immune system defends the body against all types of microbes, using cells and molecules that work together to prevent disease-causing organisms from causing infection. If a microbe succeeds in infecting the body, the immune system will kill the microbe or the infected cells, thanks to the action of its soldiers.

LYMPHOCYTE

White blood cells that belong to the immune system and protect against dangerous microbes.

ANTIBODY

A protein produced by B cells of the immune system that specifically detects and neutralizes pathogens.

ANTIGEN

A foreign substance which induces an immune response.

NEUTRALIZE

that prevents a virus from replicating.

VACCINATION

Giving a person or animal a preparation to stimulate the immune system, to protect against infection with a dangerous microbe.

There are two types of immune system soldiers: lymphocytes and antibodies. **Lymphocytes** are cells that travel through the blood and various tissues. They are activated by microbes and react against them. Some lymphocytes can directly kill infected cells: they are called cytotoxic T cells. Other lymphocytes, called B cells, produce **antibodies**, which are molecules that circulate in blood and other body fluids. Antibodies recognize specific targets on the surfaces of microorganisms, like the spike glycoproteins of the Ebola virus. Those microbial targets are called **antigens**. Antibodies **neutralize** viruses by targeting their antigens. Neutralizing antibodies are very efficient in preventing the spread of viruses from one cell to another.

THE EBOLA VACCINE FOR PREVENTION OF DISEASE

The best way to prevent people from getting infected with Ebola virus is to vaccinate them against the virus. **Vaccination** consists of giving a person one or more antigens from the microorganism. These antigens are just *parts* of the virus and do not cause the disease. Still, the antigens stimulate B cells to make neutralizing antibodies that will circulate in the blood of the vaccinated individual and prepare the immune system to fight the virus more rapidly and efficiently if it is encountered later (Figure 3A). For the Ebola vaccine, the antigen selected is the spike glycoprotein. To produce a vaccine capable of stimulating the immune system and producing neutralizing antibodies, scientists attached the spike glycoprotein to a different, completely harmless virus. The harmless virus carrying the Ebola spike glycoprotein produces large amounts of the Ebola virus spike glycoprotein when it is injected into people. This leads the vaccinated person to produce of high levels of protective neutralizing antibodies against the spike glycoprotein [4].

This Ebola virus vaccine was proven effective in Guinea during an outbreak in west Africa. The vaccine worked well when given as a single shot, and the study indicated that the vaccine could help people to build immunity rapidly. This is good, because it means the vaccine could be used when an Ebola outbreak is first identified, to protect people before they are exposed to the virus. Other vaccine candidates have been proposed, and although they take longer to stimulate immunity, they may provide an immune response that lasts longer. To successfully vaccinate populations at risk of Ebola, some important issues must be addressed. For example, the Ebola virus vaccine must be kept in a cold environment until it is used, which can be difficult

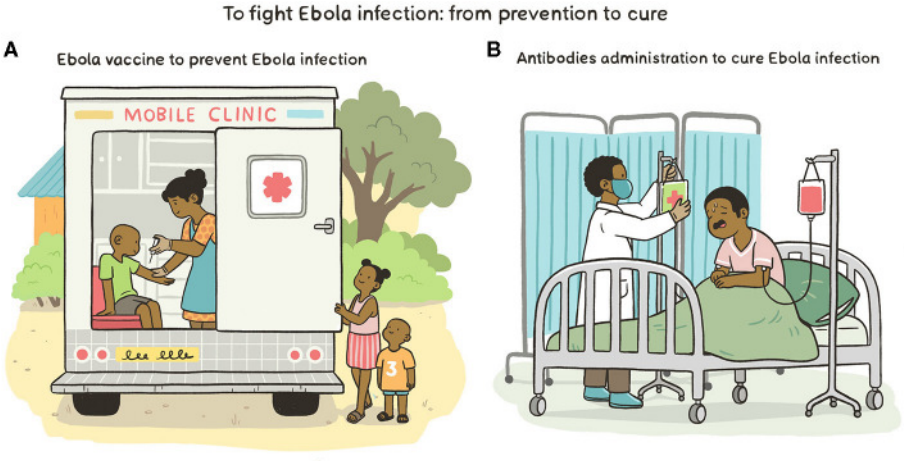

Figure 3

Fighting Ebola virus infection. **(A)** Vaccination can prevent healthy people from getting infected but cannot help when a person is already infected. **(B)** People who are already sick with an Ebola virus infection can be treated with monoclonal antibodies. When administered into the blood of a sick person, these antibodies can neutralize the virus that is already present and prevent it from spreading between cells.

in remote areas. Also, populations must agree to be vaccinated, which is often a huge challenge because a significant percentage of people are frightened by vaccination and do not understand that by vaccinating themselves not only are they protecting themselves but also protecting others from the transmission of the virus.

ADMINISTRATION OF ANTIBODIES FOR TREATMENT OF DISEASE

If a person is already infected with Ebola virus, there is no time for a vaccine to do its work stimulating the immune system. But neutralizing antibodies from other people or animals can still help! Such antibodies can be injected into an infected person, where they can directly neutralize the virus and decrease its spread from one cell to another (Figure 3B). In the past, these antibodies were obtained from the blood of infected animals or humans. Today, we use antibodies produced in laboratories, which are created to recognize a specific antigen from the virus. These are called **monoclonal antibodies** [4]. A single monoclonal antibody can be given, or patients might receive a mixture of monoclonal antibodies that recognize different viral antigens.

MONOCLONAL ANTIBODIES

antibodies produced by the same population of lymphocytes, specifically recognizing the same antigen.

CONCLUSIONS AND TAKE HOME MESSAGES

While simple measures, such as hand washing and reducing contact with infected people or animals, are effective in limiting the spread of a virus, stronger measures are often needed. Both the Ebola vaccine and treatment with monoclonal antibodies directed against Ebola virus have been shown to effectively defend humans against Ebola virus disease. This is important because Ebola virus is one of the deadliest infection of the world, through numerous outbreaks in Africa The effectiveness of vaccination and monoclonal antibody

treatment in fighting Ebola virus disease also shows us the importance of understanding how the immune system reacts to the Ebola virus—or any other dangerous virus. When scientists do laboratory research to understand how the immune system fights against a virus, they can then use this information to come up with treatments that will help to keep people healthy or, in the case of Ebola virus, even save many lives. It remembers us that vaccine does not only protect yourself from infection but also protect others by diminishing the virus spreading.

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YOUNG REVIEWER

MEHRANEH, AGE: 12

Hi, I am Mehraneh (Kinda hard to pronounce) ☺ I like to bake, read, shop, and bike. I REALLY like drawing and I am teaching myself using YouTube videos. My Mom is an editor. Then, MAGICALLY, we found this site! And now I get to Really work with mom. YAY ME (and mom)! I love this editing work even more than I thought I would! It is so cool, fun and challenging. I learn so many new things here!

AUTHORS

PATRICE DEBRÉ

Emeritus professor of Immunology at Paris Sorbonne University, full member of the French Academy of Medicine, Patrice Debré is former head of the Immunology department of the PITIE-SALPETRIERE Hospital, former director of CNRS and INSERM units and of an Institute of Cancer Immunity and Infection Research. He has held many national administrative responsibilities at Inserm, CNRS, Pierre and Marie Curie University, Assistance Publique Hôpitaux de Paris, Etablissement Français du Sang, Ministry of Research and Higher Education. He was ambassador in charge of the fight against HIV AIDS and communicable diseases at the Ministry for Europe and Foreign Affairs and has exercised many international responsibilities including the presidency of CIRAD (international research center in agronomy for development), and the French representation in many international multilateral organizations (Global Fund, EDCTP, UNITAID, Roll Back Malaria). He is currently an advisor to AVIESAN and to the International Relations Department of APHP. He is a member of the CNRS Ethics Committee and Chairman of the International Relations Committee and of the Biology Commission of the National Academy of Medicine. *patricedebre@yahoo.fr

MARIE NEUNEZ

I am a part-time research fellow at the I3h Institute and Student in Medicine at the Université Libre de Bruxelles (ULB). I was a Clinical Research Coordinator for 2 years in the Departments of Nuclear Medicine & Radiotherapy at the Institut Jules Bordet (IJB). I also performed a 5-month internship at BASF SE (Mannheim, Germany) in the Human Health & Nutrition department. I hold a MSc degree in Bioengineering with a specialization in Science, Technology and Quality of Food (UCL, Belgium), a Postgraduate degree in Management (ICHEC Business Management School, Belgium) and a certificate in Clinical Studies (Cefochim, Belgium).

MICHEL GOLDMAN

Michel Goldman graduated as a Medical Doctor (1978) from the Université libre de Bruxelles (ULB), Belgium, and received his PhD in medical sciences (1981) from the Université de Genève, Switzerland. From 1990 to 2008, he was the chairman of the Department of Immunology at Erasme Hospital in Brussels, and from 2004 to 2009 he served as the first Director of the Institute for Medical Immunology of ULB. From 2009 to 2014, Michel Goldman served as the first Executive Director of the Innovative Medicines Initiative (IMI) a joint undertaking between the European Commission and the European Federation of Pharmaceutical Industries and Associations. Managing a

budget of €2 billion, he was responsible for the launch of 59 public-private consortia in areas of major importance for public health.

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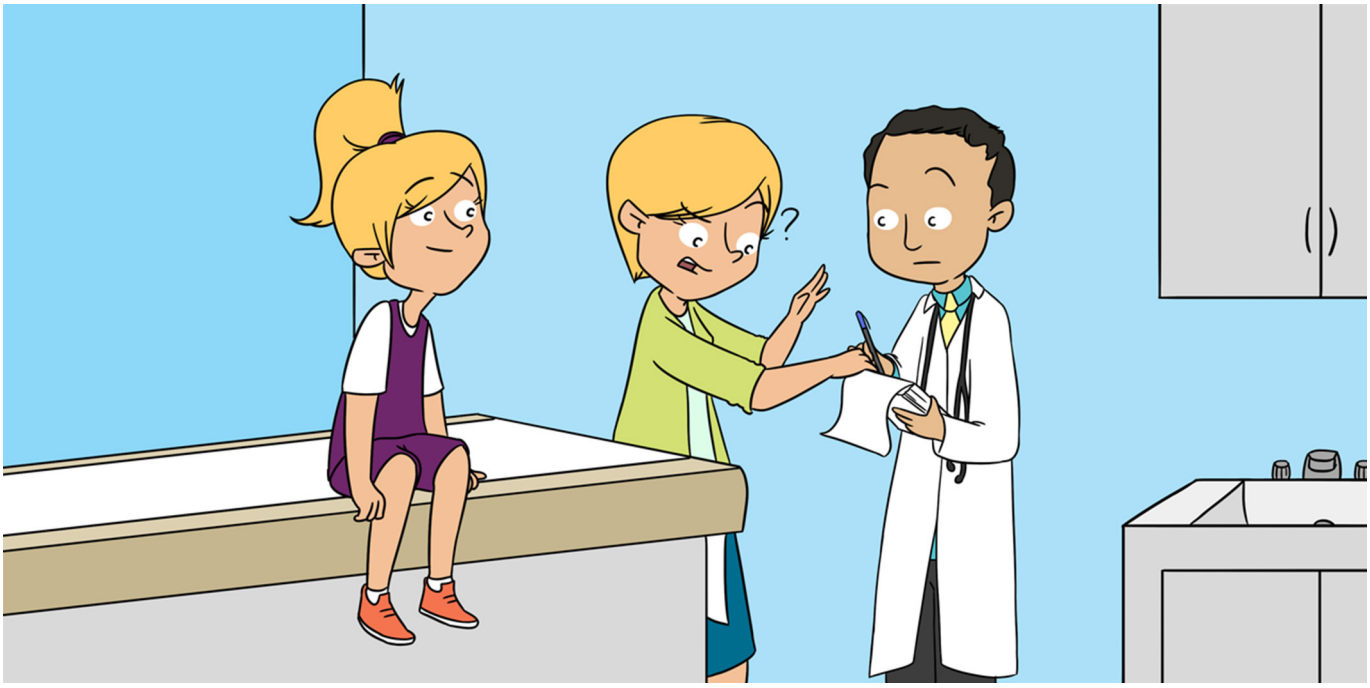

WHY VACCINES DO NOT WORK WITHOUT TRUST

Laura Spinney*

Science Journalist, Paris, France

YOUNG REVIEWER:

TALAL

AGE: 14

Vaccines protect you against diseases. They work by giving you a harmless version of the germ that causes the disease, so your immune system gets ready to fight the real thing. Getting a vaccine can hurt a bit, especially if it involves an injection, but a little pinch is nothing compared to getting sick with the disease itself. So why do some people refuse vaccines? Often it is because they do not trust the people who are offering them the vaccine. To keep society healthy we need doctors and scientists to build great vaccines, but we also need to build trust among ordinary people. One would not work without the other.

WHAT HAPPENS WHEN TRUST BREAKS DOWN?

There is one country where this lack of trust is happening right now. In August 2018, a dangerous disease called Ebola broke out in the Democratic Republic of Congo (DRC), in Africa. Teams of doctors and other experts flew in from abroad to help their Congolese colleagues fight the epidemic, or outbreak. At the moment, they are working with two vaccines. Because the vaccines are very new, one has only just received official approval and the other has yet to be approved, but

they have already saved lives. And yet the disease is still spreading. So far, around 1,800 people have died of Ebola—probably more by the time you read this. Why is the vaccine not stopping the disease?

One reason seems to be that people are avoiding the vaccine. The DRC is the second biggest country in Africa, and unfortunately for those who live there, this country has seen many wars and changes of government. That has left some Congolese people feeling suspicious of the authorities. Even though the government has put out a lot of information about Ebola, not everybody believes the disease is real. Others worry that the vaccines will poison them. In some cases, anti-government politicians have encouraged these rumors. The organizations fighting the Ebola epidemic say that mistrust and false information are their biggest obstacles [1].

IS THIS MISTRUST NEW?

Rumors and mistrust have always fuelled epidemics. A 100 years ago, the world saw its worst-ever flu pandemic. A pandemic is an epidemic that affects the whole globe, and this flu was much more dangerous than the type that comes around each winter. In 3 years, the pandemic is estimated to have killed between 50 and 100 million people. That is more than the First World War, probably more than the Second World War, and maybe even more than the two put together.

Flu is caused by a virus, but viruses had only just been discovered in 1918, and doctors did not know much about them. They thought, wrongly, that all infectious diseases were caused by bacteria. Today, we have a vaccine against flu and all kinds of drugs for treating it. One hundred years ago, doctors had nothing. Meanwhile, people were turning blue and dying in front of their eyes. To try to help their patients, the doctors started making vaccines against bacteria they knew infected the throat and breathing passages. Unsurprisingly, the vaccines did not work very well against the flu. What is interesting, though, is how people reacted to them.

In rich countries like America and France, where people tended to trust their governments, many people agreed to be vaccinated. But in other countries they did not. Many Indians steered clear of doctors, for example. India was ruled by the British at the time, and the British had invested far less in healthcare for Indian people than for British people living in India. The British had also dealt very harshly with a recent outbreak of plague in the country. Indian families were separated, supposedly to stop the infection spreading, and sometimes their houses were burned down. In South Africa, many black people also refused to be vaccinated. Rumors spread in the black community that white doctors armed with long needles were trying to kill them [2].

ARE GOVERNMENTS TO BLAME FOR CREATING MISTRUST?

Although governments are not always the reason people mistrust vaccines, they can make a big difference. When Thabo Mbeki was president of South Africa, between 1999 and 2008, AIDS was a serious problem in his country. AIDS is also caused by a virus, and by then treatments were available that attacked the virus and slowed the disease. So everyone was shocked when the president denied that AIDS was caused by a virus. He also appointed a health minister who said the best way to treat AIDS was with garlic, beetroot and lemon juice. The result was that many AIDS patients were unable to get the drugs they needed. Hundreds of thousands of them died, needlessly [3].

It seems impossible to understand Mbeki's attitude, until you remember the history of his country. He was only the second black president to rule South Africa after the end of apartheid, the cruel system of segregating black and white people that was put in place there soon after the 1918 flu pandemic. During the apartheid years, whites often blamed blacks unfairly for diseases that affected them both. Perhaps Mbeki was afraid that would happen again, with AIDS, and he preferred to believe the disease was something it was not. The point is, memories are long. It takes time to build up trust, or to rub out mistrust.

BUT CAN TRUST BE RESTORED?

Yes, trust in vaccines can be restored. Take an example from Nigeria. In July 2003, a rumor spread in that country that a polio vaccine was contaminated with toxins. Polio is an infection which, in rare cases, can cause children and adults to lose the ability to move their arms or legs, or even to breathe on their own. The rumor about the polio vaccine being contaminated was false, but five states in the north of the country decided to pull out of a polio vaccination campaign. Once again, the issue was trust. Religious and political leaders in the north feared what they saw as an American conspiracy to spread HIV and cause infertility. The rate of new polio cases rose by five times over the next 4 years in Nigeria, and the disease also spread beyond the country's borders.

The events in Nigeria were a major setback to the campaign to eradicate polio from the world. But the Nigerian government, supported by international health organizations, went to work to build trust in the north. They did so by listening to local leaders' worries and giving them accurate information. The five states rejoined the vaccination campaign, and by 2016 it was back on track. Though polio has not been eradicated entirely from the world, it

now occurs regularly in only three countries: Nigeria, Pakistan, and Afghanistan [4].

HOW IS TRUST BEING BUILT IN THE DRC?

One third of the workers fighting Ebola in the DRC are social scientists and community engagement workers. Their job is to understand why Congolese people are mistrustful and to reassure them. It is also to tell them the truth about the disease and the vaccines. One of the problems those workers face is that rumors spread really fast over social media—especially WhatsApp, which Congolese people use a lot. So communications experts keep an eye out for new rumors on social media. Whenever one appears they broadcast the facts instead, by the same channel.

WHAT ABOUT RICH, PEACEFUL COUNTRIES?

Rumors and mistrust can be a problem in rich, peaceful countries, too. Look at the current resurgence of measles worldwide, which is caused in part by people refusing to get their children vaccinated. Sometimes that is because these parents have less trust in experts than they used to. Some suspect, wrongly, that the vaccines are unsafe. Sometimes, the refusal happens because they have forgotten how horrible childhood diseases can be. Why have they forgotten? Because in rich, peaceful countries, vaccination campaigns do not get interrupted, and they have been very successful.

The lesson is that building trust is never finished. We have to keep building, otherwise old diseases will return and new ones will emerge. There will almost certainly be another flu pandemic, for example. We probably cannot stop it from happening, but we can protect ourselves to some extent. That means getting vaccinated at the right times, which means listening to the experts. Flu spreads quickly. If trust is not in place when a pandemic breaks out, it will be too late to build it. All the more reason to start building now.

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YOUNG REVIEWER

TALAL, AGE: 14

I am a 14 years old boy who lived in England and had all my education there. I have recently moved back to Belgium. I play a lot of sport including tennis, football, and hockey. I am also interested in sciences and would be inspired to be a doctor in the future.

AUTHOR

LAURA SPINNEY

Laura Spinney is a writer and science journalist. Her writing on science has appeared in *Nature*, *The Economist*, *The Guardian*, and *National Geographic*, among others. She is the author of two novels, *The Doctor* (2001) and *The Quick* (2007), and a collection of oral history, *Rue Centrale* (2013). Her critically acclaimed non-fiction account of the 1918 influenza pandemic, *Pale Rider: The Spanish Flu of 1918 and How it Changed the World* was published in 2017 and has since been translated into seven languages. *lfspinney@gmail.com.

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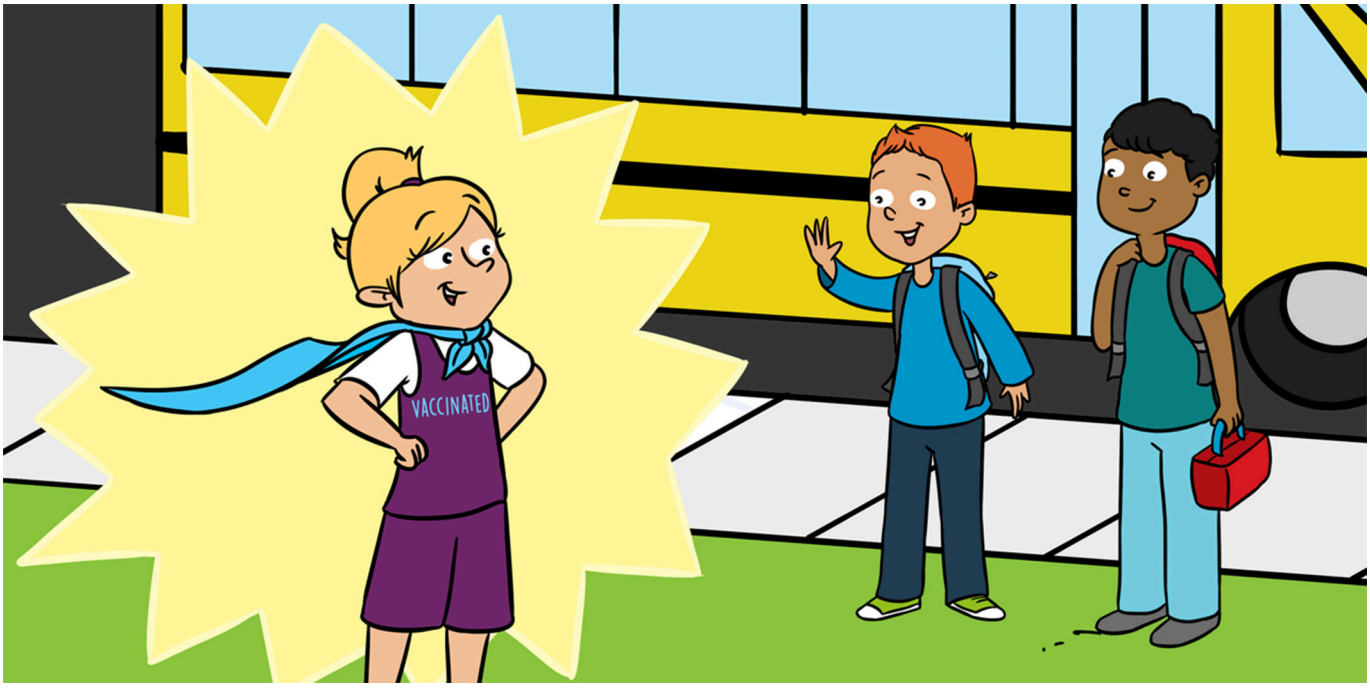

FLU FIGHTERS: HOW CHILDREN WHO GET THE NASAL INFLUENZA VACCINE PROTECT OTHERS FROM FLU

Alice Halliday[1], Mica Roan Tolosa-Wright[2], Aime Afua Boakye[2] and John S. Tregoning[3]*

[1] *Cellular and Molecular Medicine, University of Bristol, Bristol, United Kingdom*
[2] *National Heart and Lung Institute, Imperial College London, London, United Kingdom*
[3] *Department of Medicine, Imperial College London, London, United Kingdom*

YOUNG REVIEWER:

SANTIAGO
AGE: 10

Vaccines are a safe and effective way to protect people from infections. Vaccines train a system in your body -the immune system- to recognize the microbes that cause disease, so that the body can respond quickly when you encounter the real thing. There are many different types of vaccines available, and some include live microbes that have been weakened so that they cannot cause disease. In this article we focus on a nasal influenza vaccine that is given to children to prevent flu. Flu is a lung infection caused by the influenza virus. This vaccine is given as a nasal spray, and it trains the immune system to protect you in the place that matters—the nose. As well as protecting children who get vaccinated, this vaccine can reduce the likelihood of infection in others. Learn why kids who get the nasal spray flu vaccine are flu fighters!

VACCINES PROTECT US FROM INFECTIOUS DISEASES

There are many types of microbes (such as viruses and bacteria), but only a few of these cause diseases. Disease-causing microbes are called **pathogens** and when pathogens invade the body they can make you sick. We are studying flu, a disease caused by the **influenza virus**, which affects the respiratory system (the lungs). Flu is different from "stomach flu," which is a common term for diarrhea and vomiting. Catching flu makes you feel terrible—normal symptoms include a high temperature (called a fever), muscle weakness, and tiredness. However, some people can get very, very sick, ending up in hospital or even dying. Flu is particularly dangerous for the very young (<1 year old) and the elderly (more than 70 years old).

PATHOGENS

Microbes that can cause disease.

INFLUENZA VIRUS

The virus that causes influenza (flu).

THE FLU VIRUS: ALWAYS CHANGING

Flu is a very common, global disease. Each year there is a period of time (a flu season), during which most of the flu cases happen, usually during the winter, but this can vary depending on where you live. For example, in the tropics, the flu season tends to reach its highest point in the rainy season. Influenza viruses also change (or mutate) from 1 year to the next, so that your **immune system** does not recognize them anymore, and is less able to protect you against infection and disease. This means that, every year, scientists need to check which flu viruses are infecting people and design new vaccines to protect against these current virus strains [1]. Each year, flu vaccines are usually made up of a mixture 3 or 4 strains that match the main circulating strains.

IMMUNE SYSTEM

The cells and tissues in the body that help it to protect itself against infections.

Sometimes, new strains of virus emerge that are completely different from the circulating virus strains. Scientists are really worried about the threat the new influenza viruses could pose to human health. Some new flu virus strains could affect more people than seasonal flu and cause a global outbreak. We call such strains pandemic strains. One hundred years ago, in 1918, there was a flu pandemic (often called the Spanish flu) that killed millions of people worldwide—even more people than both world wars added together.

The immune system is a system of the body that helps to protect the body against pathogens. One way to prevent flu infections is to use vaccines to train the immune system to recognize specific parts of the virus, called **antigens**, without making you sick. After being vaccinated, your immune system remembers what the flu virus looks like and can quickly recognize and eliminate the real virus if you encounter it in the future.

ANTIGENS

The parts of a pathogen or vaccine that are seen by the immune system.

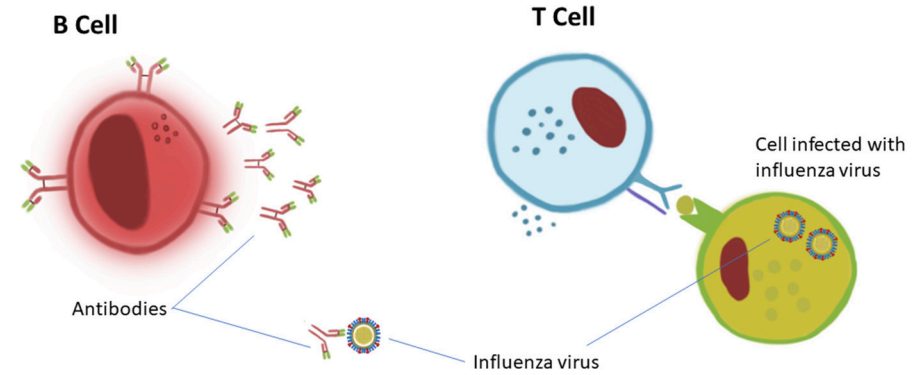

Figure 1

How lymphocytes protect against flu. There are two main types of lymphocyte: B cells and T cells. They act in different ways to help protect you against an infection with a flu virus. B cells produce antibodies, which are specific to a surface antigen on the influenza virus. Antibodies can block the virus from infecting other cells. T cells can recognize antigens from the flu virus on infected cells, and then kill the infected cells to prevent the virus from spreading to new cells.

LYMPHOCYTE

A type of immune cell. Each lymphocyte is specific to one antigen. The two main types of lymphocytes are B cells, which produce antibodies, and T cells, which kill infected cells.

ANTIBODIES

Molecules made by B cells that stick to antigens on a pathogen.

THE IMPORTANT ROLE OF THE IMMUNE SYSTEM

To protect us from flu infection, special cells of the immune system, which are called **lymphocytes**, need to be able to recognize the influenza virus. They do this by recognizing specific antigens from the influenza virus. In our bodies, we have a whole library of lymphocytes and each one is specific for a different antigen. So, for example, your body has influenza-specific lymphocytes, and after they "see" influenza antigen they multiply and help the body fight the influenza virus. We can group the lymphocytes by the way in which they prevent infections: B lymphocytes (B cells) produce **antibodies** (molecules that stick to the virus), and T lymphocytes (T cells) kill virus-infected cells [2] (Figure 1).

However, the process of activating lymphocytes can take several days, and in that time the flu virus can do a lot of damage. To avoid this delay in response each time we are infected by a virus, the immune system has a clever process of remembering viruses it has seen before, so that it can act more quickly the next time. This response is called immune memory [2].

VACCINES TRAIN THE IMMUNE SYSTEM

Flu vaccines are like a training session for your immune system. They contain antigens from influenza and they train immune memory without the body being exposed to the real virus. If the body encounters influenza virus after vaccination, the antigen-specific memory cells will be ready to respond quickly. So, with vaccines, we get immune memory without the pathogen causing any damage—a safe and effective way to protect against disease.

LIVE ATTENUATED INFLUENZA VACCINE (LAIV)

A type of influenza vaccine given as a nasal spray. This vaccine contains live, weakened influenza viruses.

Currently, there are many different vaccines available to help protect people against flu. One type, called the **live attenuated influenza vaccine (LAIV)** is now offered to school children in many countries worldwide. In this article we will explain how this vaccine is different from other flu vaccines, and how it can even protect unvaccinated people from getting sick.

WHAT IS A LIVE ATTENUATED VACCINE?

ATTENUATED

Weakened.

There are many different types of flu vaccines. Some contain a killed preparation of the whole virus, while others contain just one or a few pieces (antigens). Other vaccines contain live pathogens that have been weakened (or **attenuated**), so that they do not cause disease: these are called live attenuated vaccines. The good thing about live vaccines is that they usually work much better than other vaccines. This is because a living microbe is able to reproduce in the body, leading to more activated immune cells and stronger immune memory.

ARE LIVE VACCINES SAFE?

You might be wondering why live microbes are given to people in vaccines—is this safe? It is a good question! Luckily, live attenuated vaccines do not cause disease in most people, because they have been scientifically weakened to be safe. In the case of LAIV, the flu viruses have been modified so that they can only grow at cooler temperatures. This means that they are able to grow in your nose, which is cooler than the rest of your body because you are breathing in air (~30°C), but not in your lungs, which are at the same temperature as the rest of your body (37°C). The warmer temperatures in the lung kill the virus in the vaccine by cooking it. But the vaccine can replicate for a short period in the nose, enough to start an immune response that is similar to a natural infection with the real flu virus. The main differences between LAIV and other flu vaccines are described in Table 1.

Table 1

Differences between LAIV and other flu vaccines.

	LAIV	Other flu vaccines
How is it given?	Spray	Injection
Where is it given?	Up the nose	Into the arm
Antigen/s	Live attenuated viruses	Killed viruses
Does it hurt	No	Sometimes
Known side effects	Runny nose	Pain at injection site
	Headache	Muscle aching
	Muscle aching (rare)	Fever (rare)
	Vomiting (very rare)	Feeling unwell (very rare)
Which age group/s is it given to?	Children only	All ages from 6 months

Table 1

So, why should you get vaccinated with LAIV? We think there are several benefits:

It Does Not Hurt

Most vaccines currently available for flu are given by injection into the arm. The LAIV is different—it is given as a nasal spray, not an injection. Many people think this is much better, because it does not hurt! However, some people who receive LAIV do report some side effects, including a runny or blocked nose, a headache, muscle aches and a cough [3]. These side effects are rare and usually mild and do not last long.

A Nasal Spray—Gets the Vaccine to the Right Place

Flu is a disease of the respiratory system, meaning it mostly infects the nose, throat, and lungs. Therefore, for your immune system to have the best chance of fighting off a new infection quickly, the flu-specific immune cells will work best if they are in the respiratory system, too. That is why we give LAIV as a nasal spray—so that the vaccine reaches the part of the body that needs to be protected from the flu virus [4].

Good for Granny

Interestingly, it is not just the vaccinated children who are protected against infections. Unvaccinated children are really good at spreading viruses around, because they wash their hands less and tend to mix with more people regularly. Vaccinating children stops them from spreading the virus to other people, including babies and older family members who can get much sicker if they get the flu (Figure 2). This protection of people who are not vaccinated is called herd immunity.

LAIV Gives a Different Kind of Protection

The injectable flu vaccines are good at creating antibody responses, but not T cell responses. Because LAIV can stimulate strong T cell responses AND strong antibody responses, it is believed that LAIV can help the immune system to protect you from infections, even infections with strains of flu that were not included in the vaccine [4]. It would be helpful if LAIV can protect against new strains, because at any time a new flu virus could come along that causes more severe disease.

FUTURE SCIENTIFIC QUESTIONS

We are still not sure if LAIV can protect against flu strains other than the circulating ones, which is why more work on how LAIV protects children from flu is needed. By researching how LAIV works and figuring out how it is able to stimulate the immune system, we may be

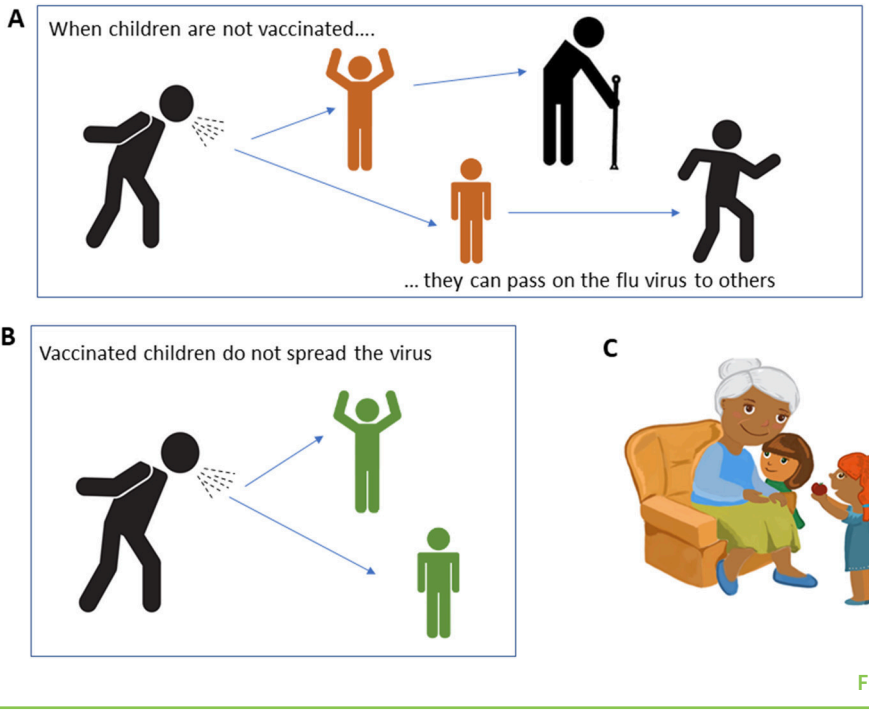

Figure 2

How children vaccinated with LAIV protect others from flu. **(A)** Children who do not receive the flu vaccination (in orange) can get sick if they are in contact with someone who has the flu virus. They can also spread the virus to others, including family members who might be more likely to get very sick, such as older people. **(B)** However, children who receive LAIV (in green) are better protected against catching the flu virus. As well as preventing the children from getting sick, vaccination also protects others around them, because the children would not spread the virus to others. **(C)** So, getting the LAIV vaccine is good for Granny, since she will be less likely to get the flu.

able to develop an even better vaccine, which could protect us against new pandemic strains of flu virus.

THANKS, FLU FIGHTERS!

So, finally, if you have been given LAIV this flu season, here is a big THANK YOU! You have done your part in protecting everyone against flu.

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YOUNG REVIEWER

SANTIAGO, AGE: 10

Hello my name is Santiago, and I am 10 years old (almost 11). You can call me Santi. My favorite sport is soccer. I play for a team and my position is midfield. I like to play with my friends. I am in fifth grade. I like History and Science, especially chemistry or lab experiments.

AUTHORS

ALICE HALLIDAY

I am an early career researcher at the University of Bristol with an interest in infectious diseases—particularly those in disadvantaged areas of the world. I am fascinated by the ongoing battles that take place between the microbes that can cause disease and our immune cells, which are designed to fight them. I currently work on group A streptococcus, a bacterium that causes a range of different diseases. However, I have an interest in many different other infections and in the development of improved vaccines. I also enjoy talking about science with children and the wider community. *alice.halliday@bristol.ac.uk

MICA ROAN TOLOSA-WRIGHT

I studied Forensic Science (B.Sc.Hons.) and have since moved to using the skills I gained to understand the perpetrators of disease, rather than perpetrators of crime. I am currently a Genomic Medicine Master's student as well as a research technician in Prof. Ajit Lalvani's laboratory. I am currently investigating the immune response to tuberculosis infection, and influenza vaccines.

AIME AFUA BOAKYE

I am a Junior Study Coordinator and the Patient and Public Involvement (PPI) and Public Engagement (PE) Lead within the Health Protection Research Unit in Respiratory Infections at Imperial College London. I support a range of clinical studies in the areas of tuberculosis, flu and pneumonia, liaising between Imperial

College London and Public Health England. I have a long-standing interest in clinical research with the aim of making a difference in the lives of patients and those around them. I gained my undergraduate degree in Biomedical Science (B.Sc.) at the University of Warwick and an M.Sc. in Immunology from Imperial College London.

JOHN S. TREGONING

I work at Imperial College London, in the UK. I find a broad range of biological sciences fascinating—especially anything to do with infection: how microbes make us sick, how the body gets us well again, and how we can stop the microbes and help the body. I spend most of my time researching and teaching about viral infections in the lungs. In addition to developing new vaccines for influenza (flu) and respiratory syncytial virus (RSV), I am investigating how the immune system protects us against these infections.

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SUPERBUGS AMONG US: WHO THEY ARE AND WHAT CAN YOU DO TO HELP WIN THE FIGHT?

Maria Letícia Bonatelli[1], *Laura Maria Andrade Oliveira*[2] *and Tatiana Castro Abreu Pinto*[2*]

[1] *Escola Superior de Agricultura Luiz de Queiroz, Universidade de São Paulo, Sáo Paulo, Brazil*

[2] *Instituto de Microbiologia Paulo de Goes, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*

YOUNG REVIEWER:

FELIX

AGE: 16

Antibiotics are essential medicines used to treat diseases caused by bacteria. Bacteria are tiny organisms (microbes or "bugs") that can be found in our bodies, in animals, and in the environment. Most bacteria are helpful, so antibiotics are used to kill only some bacteria–those that can cause disease. However, since the discovery of the first antibiotic, disease-causing bacteria have been finding ways to survive, acquiring resistance to antibiotics and even turning into superbugs. Superbugs are one of the most important threats to human health today, so they should be prevented and controlled. In this article, we will tell you about the history of antibiotics, the rise of superbugs, and what you can do to join the fight against superbugs.

SUPERBUGS? BUT I DO NOT EVEN KNOW WHAT A REGULAR "BUG" IS...

SUPERBUGS

Bacteria that have many weapons to fight against antibiotics and are therefore resistant to them.

MICROBES

Tiny living organisms that can only be seen with a microscope and can be found in us, animals, and the environment.

BACTERIA

One type of microbes. Bacteria with antibiotic resistance have become dangerous superbugs.

ANTIBIOTICS

Medicines used to treat diseases caused by bacteria.

In order to understand what **superbugs** are, we need to first understand what a regular microbe, or "bug," is. **Microbes** are tiny organisms that can only be seen with a microscope and can be found almost everywhere. **Bacteria**, viruses, fungi, and protozoa are different types of microbes. If you look around your house, the plants, animals, food, and even you are full of them. But do not panic! Most microbes actually help us. For example, some microbes that live in our intestines have an essential role in helping us digest the food we eat. Other microbes that live in the environment are essential for manufacturing certain kinds of foods. Cheese and yogurt, for example, are formed when microbes grow in milk [1, 2].

However, there are also bad microbes in the world. These can make us sick and even put our lives at risk. If you investigate the history of human civilizations, there were many diseases caused by different microbes that led to the death of millions of people. Some remarkable examples are the Spanish Flu (caused by a virus) in the early twentieth century and the Black Death (caused by a bacterium) in the mid-fourteenth century. It is estimated that, together, these two diseases killed around 300 million people [3].

Because they can potentially kill so many people, we need to figure out ways to control the spread of these bad microbes. The most effective way to do that depends on the type of microbe causing the disease. In this article, we focus on bacteria, and one of the most efficient ways to treat diseases caused by bacteria is by using medicines called **antibiotics**. Breaking down the word antibiotic can help us understand its meaning: anti—meaning opposed to or against; and biotic—meaning related to life or living things. In this case, the living thing refers to bacteria, since antibiotics are usually ineffective against other types of microbes (viruses, fungi, or protozoa). But do you know how antibiotics were first discovered?

THE DISCOVERY OF PENICILLIN AND THE ANTIBIOTIC REVOLUTION

Alexander Fleming was a British physician/scientist who became interested in studying bacteria after he returned from World War I, where he witnessed several soldiers dying from bacterial infections. After the war, he became a Professor of Bacteriology (the science that studies bacteria) at St. Mary's Hospital in London, United Kingdom. He studied a bacterium named *Staphylococcus*, which can cause a variety of infections. To study *Staphylococcus*, Fleming needed to grow them in the laboratory. He used a plate (a circular, flat dish made of glass or plastic) filled with a nutritional medium that enables the growth of microbes [4].

Figure 1

Representation of the culture plates observed by Alexander Fleming that helped him to discover the first antibiotic, penicillin. Penicillin is produced by the fungus *Penicillium*.

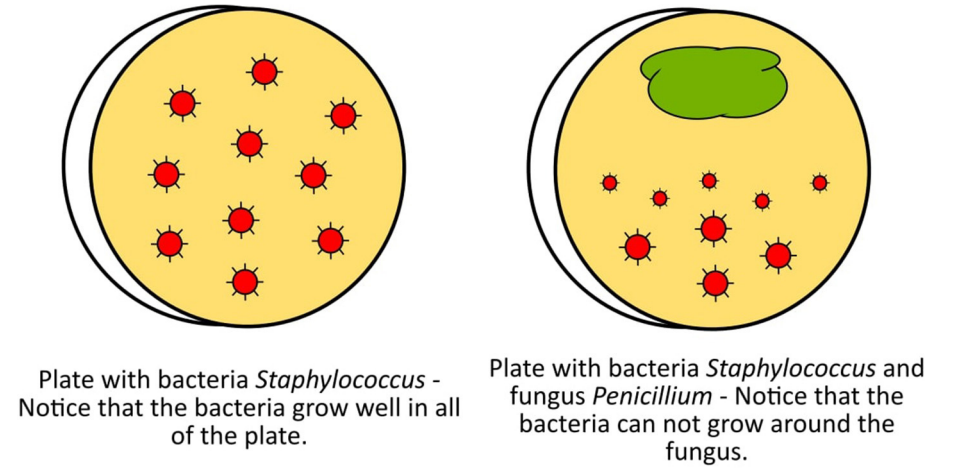

Figure 1

One day in 1928, Fleming noticed another microbe growing on his plates–a fungus called *Penicillium*. This fungus is harmless to humans and is frequently found in soil and on spoiled food. Fleming observed that where the fungus grew, bacteria did not. Somehow, the fungus was producing something that killed *Staphylococcus* (see Figure 1). This accidental finding led to the discovery of the first antibiotic, **penicillin**, which was named after the microbe producing it.

PENICILLIN

The first antibiotic to be discovered, in 1928, by Alexander Fleming. The antibiotic was named after the microbe that produces it, a fungus called *Penicillium*.

In 1941, penicillin was used for the first time to treat a bacterial infection in a human being. Penicillin became an essential medicine during World War II, helping to prevent many soldiers' deaths. This was the beginning of the "antibiotic revolution." After the discovery of penicillin, scientists found that many other microbes are able to produce other types of antibiotics. Most of these microbes live in the soil and are harmless to humans, and they produce antibiotics to protect themselves against other soil microbes or to compete for space in the environment.

Between 1940 and 1970, several new antibiotics were discovered, and bacterial diseases were easily treated using these medicines. People even thought that a day would come when humans would destroy bad bacteria for good! But it did not happen like that...

THE RISE OF SUPERBUGS

Bacteria are living organisms. As human beings evolved during the last 3 million years and fought to survive through the changes that happened in the world, bacteria did the same. As antibiotics began to be widely used to treat infections, bacteria started to find ways to survive, by acquiring resistance to antibiotics.

Figure 2

How bacteria can become resistant to an antibiotic and turn into superbugs. In the presence of the antibiotic, only the bacteria that have the antidote (antibiotic resistance) will survive. Then, those antibiotic-resistant bacteria will reproduce to create more resistant bacteria.

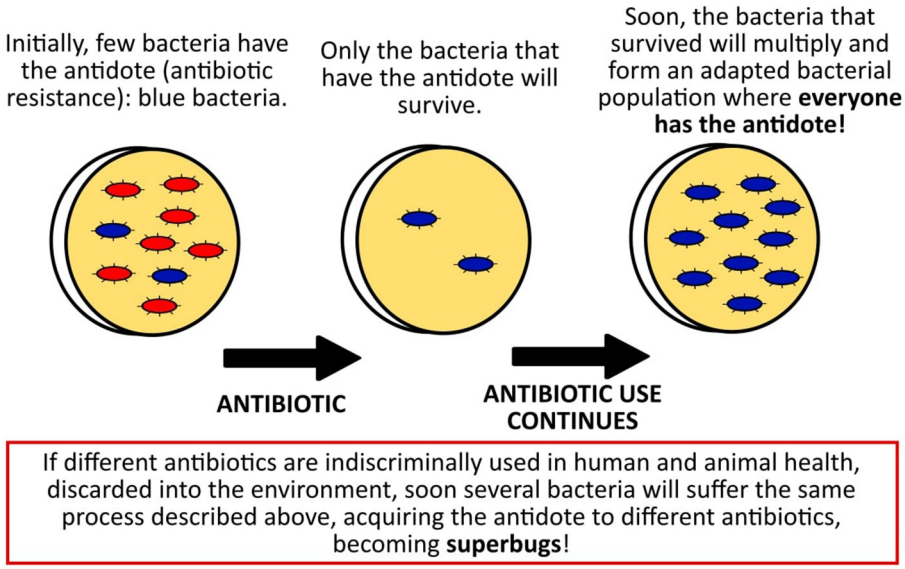

Figure 2

But how can bacteria become resistant to antibiotics? Let us remember that antibiotics are natural products of some microbes. Thus, it makes sense that microbes that naturally produce antibiotics are also naturally resistant to them. This means that resistance to antibiotics is as old as antibiotics themselves and has always existed in nature.

So, when antibiotics are used too much and too frequently and whole populations of bacteria are being exterminated by them, only those bacteria that have the "antidote," called **antibiotic resistance**, will survive. Some bacteria acquire antibiotic resistance from nature, and those resistant bacteria then survive to start a new generation of bacteria. The new generation will then all be resistant to that particular antibiotic (see Figure 2). That means that this antibiotic will no longer work for treating infections caused by these bacteria. But that would be okay, since we have discovered several different antibiotics, right?

ANTIBIOTIC RESISTANCE

When bacteria are not killed by antibiotics; the weapon used by bacteria to survive antibiotics.

Wrong! Some bacteria can simultaneously have resistance against many antibiotics, turning them into superbugs for which we may not have any antibiotic options soon. Interestingly, one of the first superbugs that spread among humans was *Staphylococcus*, the very same microbe that led to the discovery of penicillin decades before.

Initially, superbugs were only a threat in hospitals. Because there are so many patients in hospitals, and different types of antibiotics are used to treat different infections, superbugs can easily survive and be transmitted from one person to another in the hospital setting. However, superbugs are everywhere now. They have been found in

healthy people outside of hospitals, in animals, and in the environment. No matter where they have been found, the appearance of superbugs happened because of the widespread use of antibiotics. In farm animals, for example, antibiotics are administered to prevent and treat infections and to promote faster growth. Superbugs from animals and the environment can be transmitted to humans, either through contact or by eating contaminated food [5–7].

HOW CAN WE BEAT SUPERBUGS AND WHY YOU SHOULD HELP?

If superbugs are resistant to the antibiotics that are currently available, why do not scientists just discover new antibiotics? Unfortunately, it is not so simple. The process of discovering a new antibiotic in nature, and producing lots of it so it can be used by people, is complex, time-consuming, and very expensive.

So, we are currently facing a challenging and disturbing scenario. People infected with superbugs usually require an expensive treatment, using medicine that is more toxic than antibiotics, and they stay in the hospital a long time. Unfortunately, these people often end up dying. The World Health Organization estimates that, by 2050, infections caused by superbugs will cost approximately USD 84 trillion and will be responsible for nearly 10 million deaths in the world each year, which is a burden greater than cancer [5–7].

Since discovering new antibiotics is a difficult and slow task, the most important action that we can take to control superbugs is to reduce the inappropriate use of antibiotics in order to stop resistant bacteria from spreading. It is well-known today that controlling the spread of superbugs in humans depends on the control of superbugs in animals, food, and the whole environment. This means that everyone should get involved in this fight: medical doctors, veterinary doctors, environmental scientists, food specialists, and you!

One important action that all of us can do is to use antibiotics correctly and only when needed. We should stick to antibiotics that are prescribed by a physician; taking antibiotics without a prescription is highly discouraged. In addition, other simple public health strategies can help controlling superbugs. These include vaccination, access to clean water, basic sanitation, good hygiene, correct food preparation, and appropriate hand washing.

As far as treating people who have been infected by superbugs, scientists have been searching for and evaluating non-antibiotic alternatives, including some very cool and different medicines. These include the use of certain viruses (called bacteriophages) that can kill bacteria. Although promising, many of these alternative therapies are still being researched and are not yet available as real treatment

options. The path may still be long, but we all should do what we can now if we want to win the fight against superbugs.

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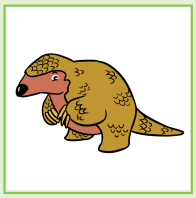
YOUNG REVIEWER



FELIX, AGE: 16

I am a high-school student at Ecole Decroly in Brussels. I have a variety of interests and enjoy studying sciences and the humanities. My hobbies include playing rugby, rock climbing, watching documentaries, hanging out with my friends. Also, I enjoy being a member of the Boy Scout movement. I was pleased to contribute to this interesting article.

AUTHORS

MARIA LETÍCIA BONATELLI

I am a biologist who is passionate about microbes. During my graduate studies, I focused on studying the microbes that live in industrial environments, and I tried to understand what they were doing there. I was always fascinated by the idea that microbes are everywhere and that they can shape our world. Now, I am a researcher at the University of São Paulo (USP) in Brazil, and I am trying to understand how different bacteria can help us improve crop production, that is, help us grow more and better food to eat.

LAURA MARIA ANDRADE OLIVEIRA

I am a Pharmacist, M.Sc. in Biological Sciences, with emphasis in Immunology and Infectious Diseases. I studied at the Federal University of Juiz de Fora (UFJF) and got a Ph.D. in Microbiology at the Federal University of Rio de Janeiro (UFRJ), both in Brazil. I am enthusiastic about the microbial world and I am interested in understanding how microbes are connected to our health and how they can cause disease. I believe that sharing the knowledge generated by the academic community with everyone is important for science to keep advancing.

TATIANA CASTRO ABREU PINTO

I got my Ph.D. in Microbiology from the Federal University of Rio de Janeiro (UFRJ) in Brazil, and have been an Associate Professor at Instituto de Microbiologia Paulo de Goes (IMPPG) of UFRJ since 2014. I coordinate a research group focused on understanding the virulence and antimicrobial-resistant aspects of certain disease-causing bacteria. I am also a mother, wife, daughter, and Brazilian citizen. I have been passionate about science since elementary school and have dedicated the last few years to enhancing the enthusiasm for science among the general population and encouraging and inspiring the next generation of scientists in my country. *tcap@micro.ufrj.br

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ANTIMICROBIAL RESISTANCE: A TALE OF NASTY ENEMIES AND POWERFUL WEAPONS

Fabiola Vacca[1,2†], *Dario Cardamone*[1,3†], *Marco Troisi*[1,2†], *Claudia Sala*[1*] *and Rino Rappuoli*[1]

[1] *Monoclonal Antibody Discovery Laboratory, Fondazione Toscana Life Sciences, Siena, Italy*
[2] *Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Siena, Italy*
[3] *University of Turin, Turin, Italy*

YOUNG REVIEWERS:


AARAV
AGE: 8


SINHA
AGE: 8

Have you ever had a sore throat, cough, or fever? All of us have felt badly at least once in our lives! A doctor may have helped you by prescribing antibiotics to kill the microbes responsible for the infection, thus eliminating pain, cough, and fever. Thanks to medicines like antibiotics, we can recover quickly from diseases. Unfortunately, the extraordinary power of antibiotics is threatened by a phenomenon called antimicrobial resistance. What is antimicrobial resistance and is there anything we can do to stop it? In this article, we describe antimicrobial resistance, how it may arise, and how we can help to prevent it by vaccination.

Let us clarify an important point before we get started: most microbes, especially bacteria, are our friends and live with and within us, for instance in our guts or on our skin. Though small, these microbes do an incredible job helping us digest food and protecting us from external

enemies that cause disease. However, there are some bad microbes that we should keep at bay because they are dangerous. Keep reading to see how we can fight and defeat them.

IS IT POSSIBLE FOR AN ANTIBIOTIC TO BECOME USELESS?

ANTIBIOTICS

Drugs used to treat diseases caused by bacteria.

In many cases, we fall sick because invisible living microbes have invaded our bodies, causing an infection that makes us feel sick. Fortunately, there are medicines, called **antibiotics**, to help us get better. The word "antibiotic" comes from Greek and means "opposing life." This explains what antibiotics do: they kill our enemies, the bad bacteria. Antibiotics can be produced by friendly bacteria, by molds or plants, or they can be synthetic molecules produced in laboratories. Antibiotics interfere with processes essential for bacterial life. For example penicillin, discovered by Alexander Fleming in 1928, is produced by the mold *Penicillium notatum* and blocks bacterial multiplication by preventing the outer wall of the bacterial cell from developing. Without the cell wall, bacteria burst and die. Many antibiotics have been discovered since penicillin, and all of them are powerful weapons against invading microbes. In addition, thanks to the progress of science, it is now possible to mass-produce synthetic antibiotics and use them to successfully treat bacterial infections.

It may seem that, once discovered, antibiotics should remain effective against bacteria forever. Unfortunately, this is not the case. Bacteria are smart and they try to survive in the presence of antibiotics by becoming resistant to these drugs, meaning the antibiotics cannot harm them anymore. This bacterial ability is known as **anti-microbial resistance (AMR)**. Because of AMR, even the most potent antibiotic can become useless in a short period of time [1].

ANTIMICROBIAL RESISTANCE (AMR):

The ability of bacteria to survive treatment with antibiotics. AMR is due to bacterial genes that provide the bacteria with protection from the antibiotic.

HOW DO BACTERIA ACQUIRE RESISTANCE TO ANTIBIOTICS?

To test whether an antibiotic is useful against a certain type of bacterium, scientists can put bacteria in contact with the antibiotic and check whether the bacteria die (sensitive bacteria) or survive (resistant bacteria). This is a direct measurement of the potency of the antibiotic and the sensitivity of the bacteria to the drug. Alternatively, we can read the bacterium's "blueprint," which is called the genome or the DNA. The DNA contains the information that regulates the life of the bacterium and provides the instructions to make proteins, which are the building blocks of most organisms. In the case of bacteria, we can find and read the particular portions of their genomes that explain how they became resistant to an antibiotic.

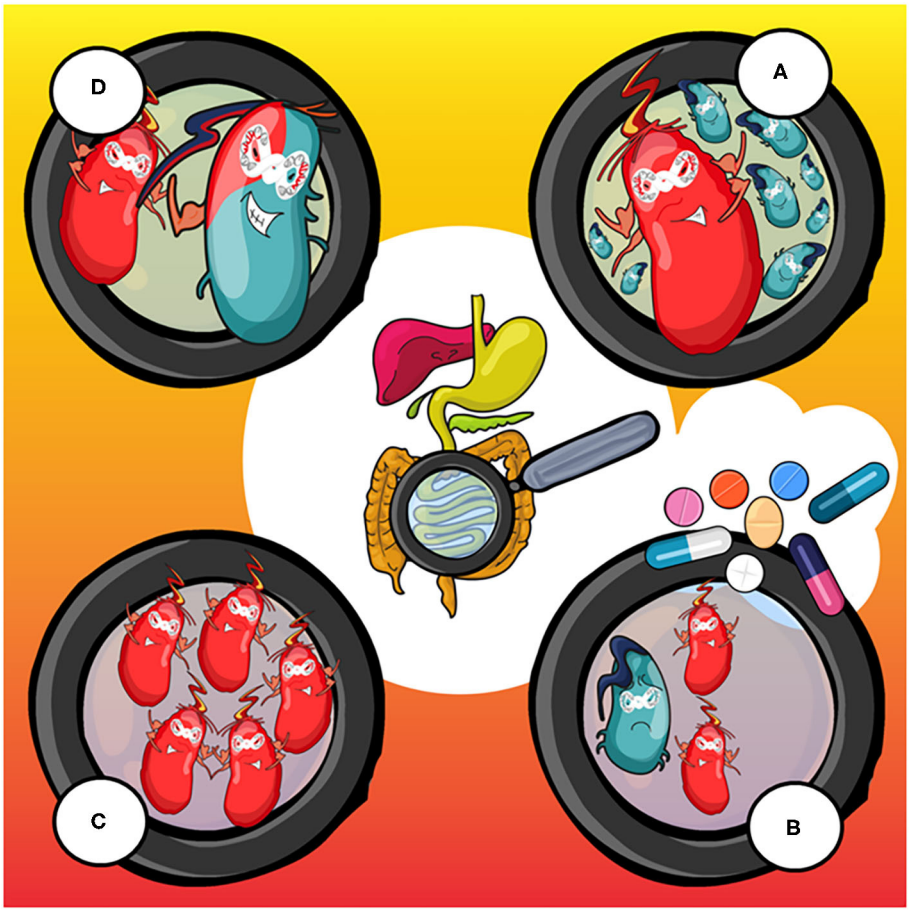

Figure 1

How antimicrobial resistant (AMR) bacteria arise and spread. **(A)** Bacteria that cause an infection in the body, for instance in the gut, are mostly antibiotic-sensitive (blue). One of them may develop AMR (red) because of a mutation in its DNA. **(B)** Antibiotics, here shown as pills, cure the infection and kill almost all of the blue bacteria, but the red ones survive and multiply, until they reach a very high number (see panel **C**). This is dangerous because antibiotic-resistant bacteria are difficult to kill and can cause a severe infection to the body. **(D)** The red bacterium can then transfer a piece of DNA to a sensitive bacterium (the blue one), transforming it into a resistant bacterium also.

The bacterium's "blueprint" undergoes changes, known as mutations, that sometimes help a bacterium to survive in the presence of antibiotics. So, bacteria that are sensitive to antibiotics today could develop AMR tomorrow through mutations in their genomes. Bacteria can also transfer portions of their DNA to other bacteria, so they can basically "learn" from the bacteria that are already antibiotic resistant (Figure 1).

What happens if we use antibiotics too frequently? We put so much pressure on bacteria to survive that they become increasingly resistant. In other words, AMR bacteria will spread more and more and throughout the human population [2]. By limiting the use of antibiotics as much as possible, we reduce this pressure. This is why we need alternatives to antibiotics, and ways to reduce our risk of developing diseases that need to be treated with these drugs.

OUR ARMY: THE IMMUNE SYSTEM

The human immune system is composed of cells and molecules that specifically protect us against external invaders, such as bacteria and

viruses. When the body is infected with a bacteria or virus, that microbe is recognized by the immune system as "foreign," because it is usually not present in the body. The parts of the infecting organism that the immune system "sees" are called **antigens**, and these antigens are usually present on the surface of the bacteria or virus. To block antigens, the immune system produces substances called **antibodies**. Antibodies bind to the antigens, acting like specific arrows capable of recognizing the microbes and killing them.

During this battle between the immune system and microbes, our immune cells memorize the features of the microbes they fight against, thus making it harder for the same type of microbe to invade the body again. So, if the same type of microbe ever thinks of coming back, it would be knocked out with no second thoughts. This is called **immunological memory** and it is the basis of how vaccines work.

ANTIGENS

Proteins or sugars from a microbe that are recognized as foreign by the immune system. Antigens can be included in vaccines to teach the immune system what the microbe is made of.

ANTIBODIES

Substances produced by the immune system that help in the fight against our enemies, the bacteria and the viruses.

IMMUNOLOGICAL MEMORY

The ability of the immune system to rapidly and specifically recognize a microbe that it has already encountered. It is the basis of vaccination.

THE VACCINE: TRAINING THE IMMUNE SYSTEM

Now that you have an idea of how the immune system works, it will be easier to understand how important vaccines are for all of us, and how they help to prevent AMR. Vaccines are composed of dead, or sometimes weakened, microbes, which can cause no harm to us. Vaccines can also be made of bacterial antigens, such as proteins and sugars. When a vaccine is injected into the body, the dead or weakened microbe (or its parts) is seen as foreign by the immune system, in much the same way that an infectious microbe would be. The antigens contained in the vaccine stimulate the immune system to produce antibodies against them. Antibodies are highly specific and effective, but need some time to develop, which is why vaccines must generally be administered early in life [3]. Antibodies will hang around in the body, so that if the vaccinated person encounters the actual nasty microbe later, the antibodies will already be there to fight it.

Vaccination also allows the immune system to develop immunological memory, so that the body will respond quickly when it sees the microbe again. This is exactly what a vaccine is made to do: it teaches the immune cells what a bacterium or virus is made of, so that the immune system can prepare its weapons in advance and be ready when the real microbe comes (Figure 2). In the case of a bacterial infection, if the immune system of a vaccinated person is ready to tackle the bacteria, that person might not need external help from antibiotics.

WHAT ARE THE DIFFERENCES BETWEEN ANTIBIOTICS AND VACCINES?

So, you can see that antibiotics and vaccines are both used to fight microbes. But it is important to understand that they work in different

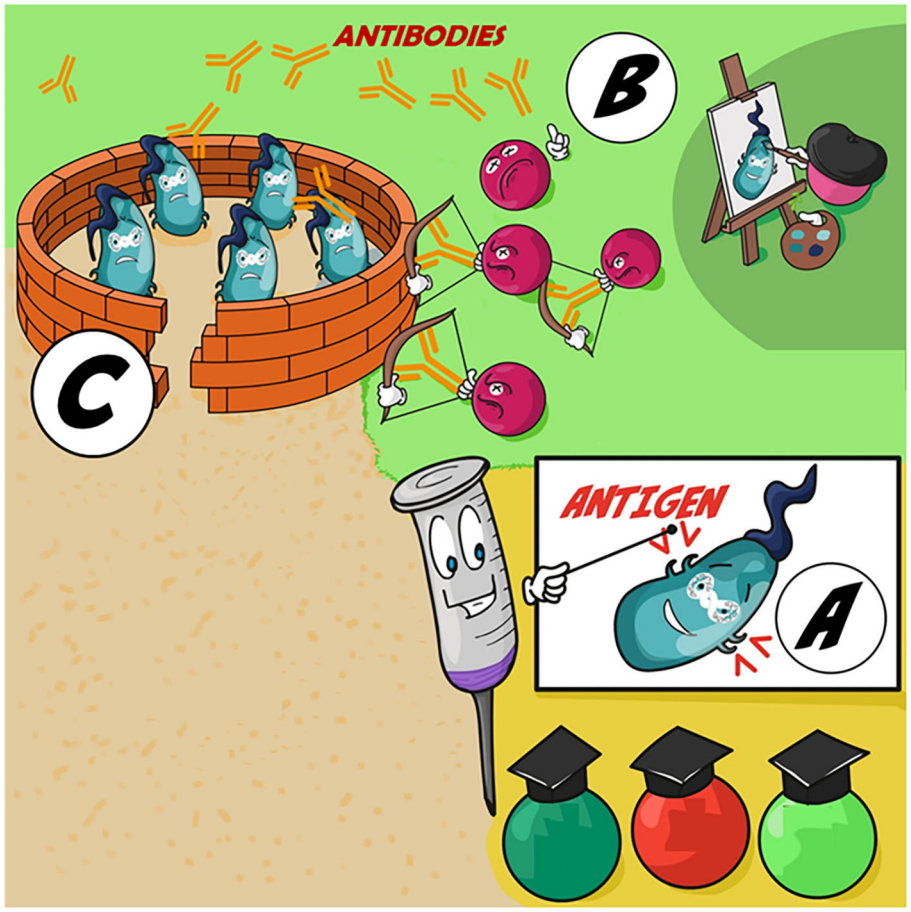

Figure 2

Vaccines and the immune system. **(A)** The vaccine (syringe) teaches cells of the immune system what a certain type of bacteria is made of. **(B)** Immunological memory keeps a record of the bacterium, so that the body is ready to fight again if the same type of bacterium comes back. **(C)** When the body later encounters the actual bacterium, the trained immune cells can quickly produce antibodies (Y-shaped arrows) to fight the bacterial invaders, which try to defend themselves from the attack.

ways. First, while antibiotics are used to treat diseases that are already happening, vaccines are administered before we get infected, as a means of prevention. As you just learned, the role of vaccines is to guide the immune system to fight future infections. Second, antibiotics usually have one single mode of action, meaning that they attack bacteria in a specific way. In contrast, vaccines can expose our immune system to multiple bacterial antigens that are usually found on the bacterial surface. This exposure helps the immune system to attack the bacteria using multiple strategies at once. Last, vaccines can provide life-long protection from infections, which means that, if you are vaccinated against a specific type of bacteria, you will never be infected by them during your entire life. Antibiotics cannot do this.

HOW CAN VACCINES DEFEND US AGAINST AMR?

Reducing misuse of antibiotics is key for fighting AMR, and vaccines can help us reach this goal. Since vaccination prevents infections, it reduces the need for antibiotics. Less antibiotic use means less chance that bacteria will develop nasty antibiotic resistance.

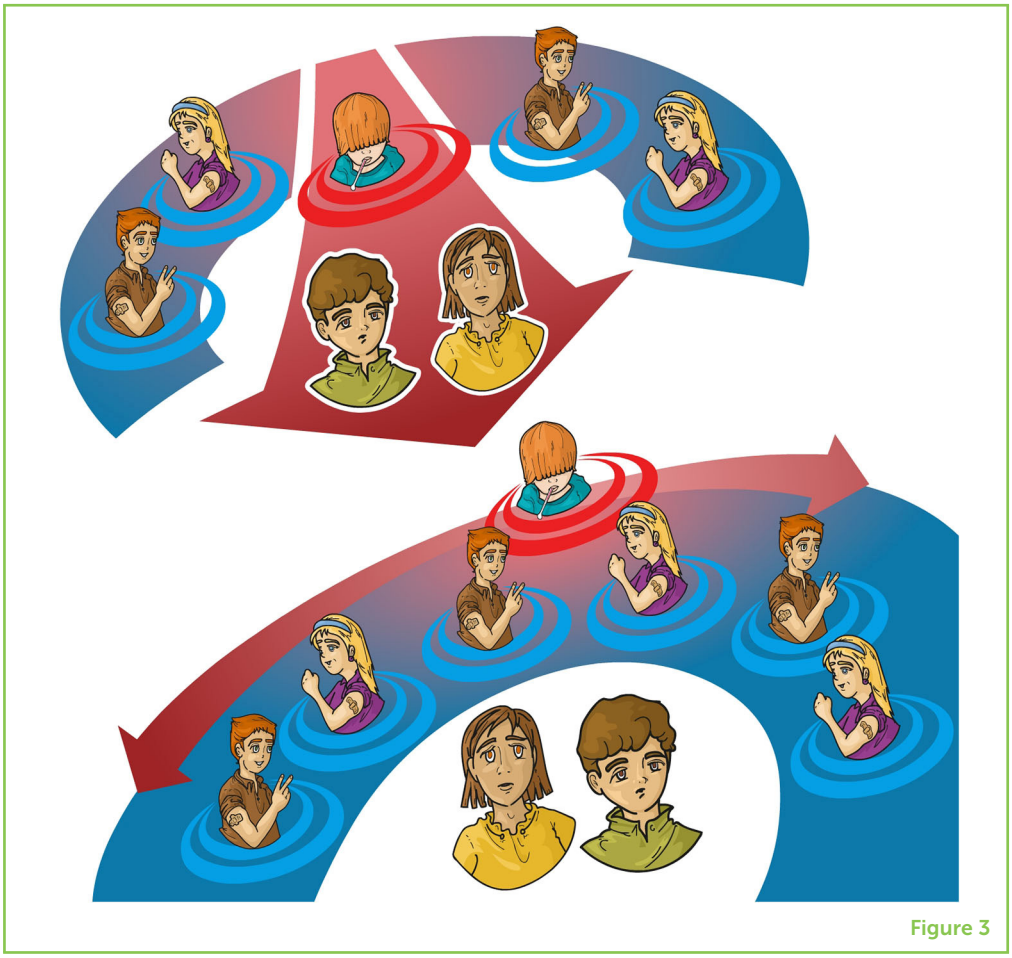

Figure 3

Figure 3

The importance of vaccination for herd immunity. In the top panel, there are very few vaccinated people (those with a bandage on their arms). There are not enough vaccinated people to protect the ones with the green and yellow shirts, who have not been vaccinated, from catching the virus from someone who is infected (the guy surrounded by red circles). In the bottom panel, there are enough vaccinated people to basically create a shield against the infection for people who, for medical reasons, cannot be vaccinated. This is herd immunity: after enough people are vaccinated, an infection cannot easily spread in the population, so all people, including those who are unvaccinated, are protected. Herd immunity helps with AMR because, if fewer people are infected, less antibiotics will need to be used.

Today, vaccines are already helping us manage the problem of AMR. Let us look at influenza as an example. Influenza is the virus that causes "the flu." Although antibiotics are effective for stopping the multiplication of bacteria, they do not have any effect on viruses. However, influenza infection is often inappropriately treated with antibiotics. So, if people get vaccinated against influenza, we will reduce the number of influenza infections and therefore reduce the amount of antibiotics used inappropriately. We also reduce the pressure on bacteria to develop AMR. Other examples of how vaccines help to reduce AMR worldwide include bacterial diseases like diphtheria and pertussis, against which all of us were vaccinated as young children. Due to vaccination, these diseases are less frequent nowadays, which has greatly diminished the need for antibiotics to treat them. Again, this lowers the risk that the bacteria causing diphtheria and pertussis will develop AMR.

Finally, there is another important aspect of vaccination that you may have heard about, called **herd immunity** (Figure 3). Herd immunity is an indirect form of protection that is generally achievable only by vaccination. Basically, the more people that are vaccinated, the harder it is for microbes to spread in the population, because there are so few people left to infect. Herd immunity is crucial for protecting people

HERD IMMUNITY

Vaccinated people create a shield against the infection for people who, for medical reasons, cannot be vaccinated. In this way an infection cannot easily spread in the population, so all people, including those who are unvaccinated, are protected. Please see Figure 3.

who cannot be vaccinated, like infants, who are too young, and those who are too ill to receive vaccines [4, 5]. The sum of all these effects of vaccines makes them an important line of defense against microbes and an effective weapon in combatting AMR.

Overall, we hope that this article has helped you understand what AMR is and why it is important that we use antibiotics according to the doctor's recommendations. Also, you should now know what a vaccine is and why it helps in our fight against AMR microbes.

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YOUNG REVIEWERS

AARAV, AGE: 8

I am an eight-years-old in grade 3, who loves anything related to buildings and space. When I grow up, I want to be an architect. My favorite pastime is building things with Lego, Kapla, and Jenga. I love riding bike and playing with my friends. I also have lots of questions about everything, many that I have still not found answers for.

SINHA, AGE: 8

I like to play with friends, play video games, and science.

AUTHORS

FABIOLA VACCA

Fabiola Vacca is a Ph.D. student of the Biochemistry and Molecular Biology Doctoral Programme at the University of Siena. She works at TLS in the Monoclonal Antibody Discovery research group led by Dr. Rino Rappuoli. She earned a Master's degree in Medical Biotechnologies at the University of Siena. Through her Master's research, which focused on the development of a peptide as a new potential drug against antibiotic-resistant bacteria, she became interested in translational research and in drug resistance. Currently, she is working on setting up tools (genetically modified bacteria) that help understand how monoclonal antibodies work.

DARIO CARDAMONE

Dario Cardamone is a researcher in the Monoclonal Antibody Discovery laboratory led by Dr. Rino Rappuoli at TLS in Siena (Italy), and a Ph.D. fellow in Complex Systems for Life Science at the University of Turin. His research is focused on analyzing photos of bacteria obtained by potent microscopes in order to understand how antibodies kill the bacteria. He received his Master of Science in Mathematics from the University of Bologna. During his studies, he visited the Humboldt University of Berlin, working as a research assistant at the Zuse Institute Berlin (ZIB), an interdisciplinary research institute for applied mathematics and data-intensive high-performance computing.

MARCO TROISI

Marco Troisi is a Ph.D. student at the University of Siena and a member of the Monoclonal Antibody Discovery research group coordinated by Dr. Rino Rappuoli in TLS. His research project aims to develop new vaccines against bacteria resistant to antibiotics. Marco has a Bachelor's degree in Biology and a Master's degree in Medical Biotechnologies. His Master's research focused on the analysis of cancer cell signaling involved in cellular migration. During his studies, Marco became passionate about immunology and microbiology, with great interest in vaccinology.

CLAUDIA SALA

Claudia Sala is a molecular microbiologist. She obtained her degree in Biological Sciences and her Ph.D. in Genetics and Molecular Biology at the University of Milan (Italy). She worked as a post-doctoral fellow in the laboratories of Prof. Stewart Cole, at the Pasteur Institute in Paris, and then at the Ecole Polytechnique Fédérale de Lausanne, where she was subsequently promoted to senior scientist. Her research was mainly focused on *Mycobacterium tuberculosis*. She moved to TLS in Siena in 2019 and joined the Monoclonal Antibody Discovery group led by Dr. Rino Rappuoli, where she performs research on monoclonal antibodies and vaccine development. *c.sala@toscanalifesciences.org

RINO RAPPUOLI

Rino Rappuoli is head of the vAMRes laboratory at TLS in Siena and Chief Scientist and Head External R&D at GSK Vaccines, Siena, Italy. He has received several awards including the Paul Ehrlich and Ludwig Darmstaedter Prize, the Gold Medal by the Italian President, the Albert B. Sabin Gold Medal, the Canada Gairdner International Award, and the European Inventor Award for Lifetime Achievement. He developed the pertussis and meningococcus B vaccines, among others, and was nominated third most influential person worldwide in the field of vaccines. Dr. Rappuoli is among the world's scientific leaders dedicated to sustaining global health.

†These authors have contributed equally to this work

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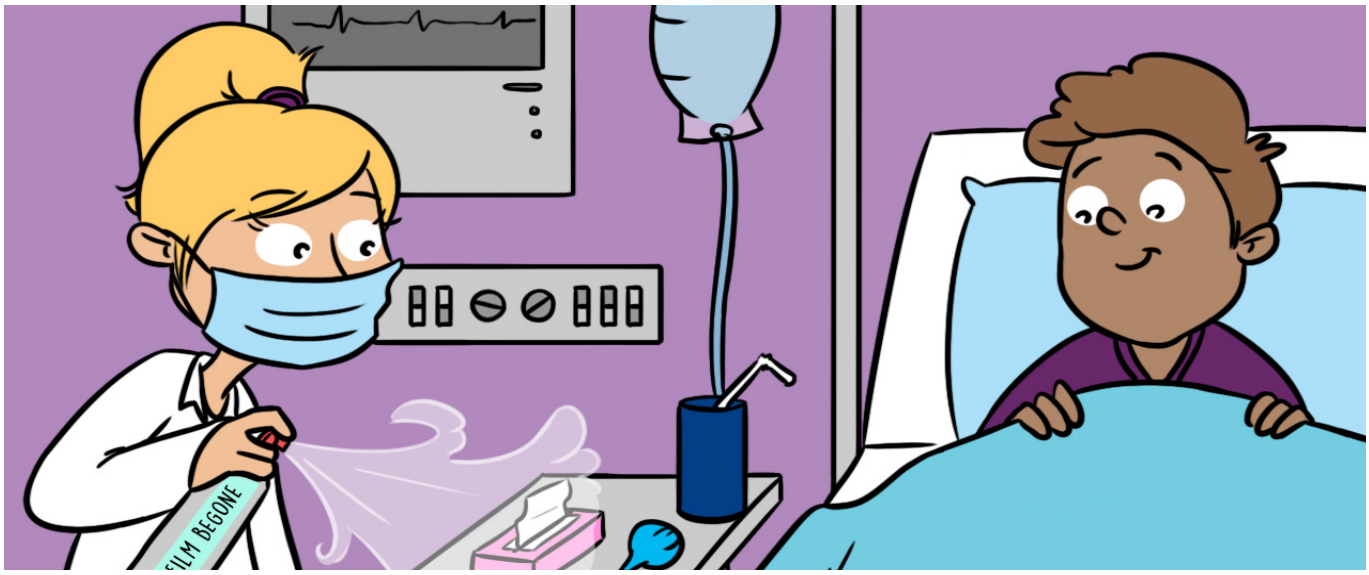

FIGHTING BACTERIA: HOW CAN WE PREVENT HOSPITAL-ACQUIRED INFECTIONS?

*Meital Reches**

Institute of Chemistry, Center for Nanoscience and Nanotechnology, The Hebrew University of Jerusalem, Jerusalem, Israel

REVIEWED BY:

GIFTED CLASS, EIN GANIM, PETACH TIKVA
AGE: 11–12

Bacteria live with each other in an organized network called a biofilm. The biofilm allows the bacteria to communicate with each other and transfer nutrients and signals from one bacterium to another. This communication provides the bacteria with new properties that allow them to survive, even when they are exposed to harmful compounds that usually kill them (for example, antibiotics). These persistent bacteria can now cause what are called hospital-acquired infections because patients often get them while in a healthcare facility, like a hospital. Hospital-acquired infections obviously endanger the health of patients and may lead to death. So, it is important to find solutions that prevent bacteria from forming biofilms. My research group designed and synthesized a compound that forms a coating on different materials and does not allow bacteria to form biofilm. This compound may be useful in the future as a coating for medical devices, water desalination facilities, and food preparation surfaces.

CELL WALL

A rigid layer made of proteins and sugars that defines the borders of the cell, provides it with physical support, and protects it from the environment.

WHAT ARE BACTERIA AND HOW DO THEY LIKE TO LIVE?

Bacteria are small organisms that cannot be seen with the naked eye. To detect them, one must use a microscope. A bacterium is made up of a **cell wall** that

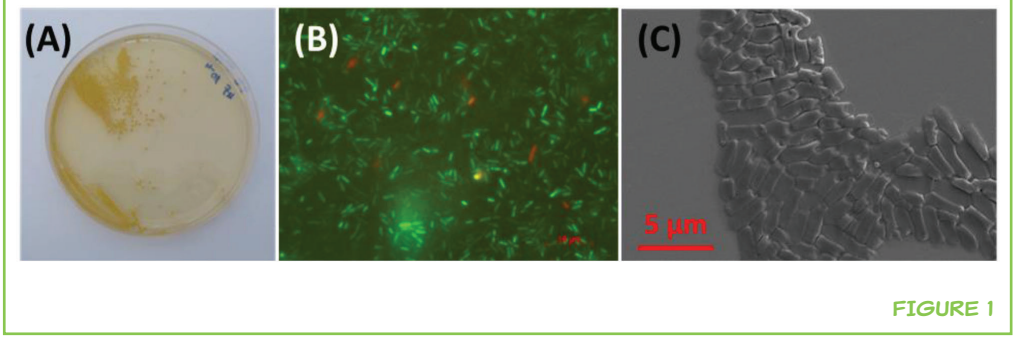

FIGURE 1

FIGURE 1

What do bacteria look like? **A.** Bacteria live together and form colonies on the surface of the laboratory dish. In the picture, the colonies are the round yellow dots. Each dot contains thousands of bacteria. **B.** It is possible to dye the bacteria with a fluorescent dye that colors the live cells green. This staining method allows us to test materials for their antimicrobial activity. **C.** Each colony is made up of many micron-size bacteria. A micron, also called a micrometer (µ) is 10^{-6} m.

CELL

The most basic living unit that has all the characteristics of life—respiration, motion, and reproduction.

surrounds the genetic material and other structures that are needed for the bacterial **cell**. Bacteria are the most abundant form of life on our planet. They exist in multiple sizes, shapes, and colors. Bacteria reproduce by division, where each cell divides into two new cells, called daughter cells. Within half an hour or so, bacteria can double in number. Many bacteria are not harmful to humans and are considered "good" bacteria. These good bacteria are beneficial to humans. For example, "good" bacteria can take up the space of harmful bacteria and by doing so protect us from infections. Other bacteria help us to digest our food [1]. Harmful bacteria, also called pathogenic bacteria, cause various illnesses.

Bacteria live in colonies, in which each bacterium is surrounded by many other bacteria that protect it from the external environment. Within the colony, the bacteria communicate with each other using chemicals. These chemical signals help the bacteria to form a network called a biofilm (Figure 1). Another name for a biofilm is a plaque. The term plaque is often used by dentists to describe the bacterial layer on teeth. This layer is well attached to the teeth and secretes materials that destroy the teeth. A biofilm can provide bacteria with resistance to antibiotics, which can usually kill individual bacteria (Figure 1). As a biofilm, some bacteria can still live, multiply, and cause infections—even in the presence of antibiotics. These infections are a major problem in hospitals, where they harm and even kill the patients. To prevent these infections, hospitals and the healthcare system invest much effort to clean hospital facilities and medical devices [2].

HOW DO ANTIBIOTICS WORK?

An antibiotic is a compound that kills bacteria. Antibiotics stop essential cell activities that allow the bacteria to live. For example, some antibiotics harm the cell wall and some prevent the bacteria from reproducing. The first antibiotic, penicillin, was discovered over 90 years ago. Since then, many other antibiotics have been found. Since the discovery and use of antibiotics, bacteria have evolved that resist antibiotics and multiply even when antibiotics are present. These are called "antibiotic-resistant

bacteria." Antibiotic resistance evolves by mutations (genetic changes) in the bacterial DNA that allow the bacteria to survive in the presence of antibiotics. A year ago, the World Health Organization published a report on 12 different bacterial strains that are resistant to antibiotics [3]. For these antibiotic-resistant bacterial strains, solutions other than antibiotics must be found to kill the bacteria. My research group believes that, if we can prevent biofilm formation, we will be able to successfully fight the antibiotic-resistant bacteria.

HOW DO WE FIGHT BACTERIA?

Many research groups around the world are trying to find compounds that will prevent biofilm formation. Some of that research focuses on finding compounds that will prevent the first step of biofilm formation. In the first step of biofilm formation, large **molecules** such as proteins and polysaccharides (large sugars) are produced by the bacteria and stick to the surface that the bacteria are growing on. These substances provide a "glue" for bacteria, and that is how biofilm formation starts.

MOLECULE

A substance that is made up of more than two atoms that are connected by a chemical bond.

Over a decade ago, several research groups showed that small particles of silver can kill bacteria and the groups suggested that these particles might be able to act as a new antibiotic. However, it was later found that these particles can also kill human cells and are dangerous to humans. So, silver particles were banned from use. Another material that was suggested to possibly prevent biofilm formation was polyethylene glycol (PEG). This compound can bind up many water molecules, which prevents the bacteria from sticking to the surface. However, PEG breaks down over time, and so it is not possible to use it for long-term applications. Other researches tried to mimic natural surfaces that prevent bacteria from sticking to them. For example, lotus leaves are always clean, even though this plant usually grows in swamps and shallow water. The lotus leaves stay clean because there are many bumps on the leaves that are covered with wax. The combination of bumps and wax helps a water drop to slip from the leaf, dragging all the dirt with it, like a mop. This phenomenon is called "the lotus effect." Many research groups are trying and even succeeding in mimicking this effect. However, mimicking the lotus effect often requires expensive and complicated production processes that are limited to small surfaces. Therefore, this solution cannot yet be used in hospitals or other places where we want to prevent biofilm formation.

Interrupting the communication among bacteria is another possible way to prevent biofilm formation. Bacteria communicate with each other using various chemicals. One bacterium produces a certain molecule and another receives it and produces a different molecule as a response. Synthesizing molecules that harm this communication, by blocking the signals, is another option to fight biofilm formation [4].

OUR PROPOSED SOLUTION

My research group developed a small molecule that prevents the sticky biological molecules (proteins, sugars, etc.) from adhering to surfaces, and therefore reduces biofilm formation [5]. To form this "non-stick" coating that will prevent the attachment of biological molecules to a surface, we mimicked the chemistry of Teflon®. Teflon® is a non-stick material used in the production of frying pans. This molecule we developed is made up of **amino acids**. Amino acids are the building blocks of proteins. We chose amino acids because they are not toxic to humans, they are easy to synthesize in large quantities, they can be stored in the refrigerator for years, and, most interestingly, because they can self-assemble. Self-assembly is a process by which molecules spontaneously form an ordered structure, without any need for external energy. In other words, these amino acids can interact with each other and connect like Lego building blocks.

AMINO ACIDS

The molecules that make up proteins.

To adhere our self-assembling non-stick molecules to the surface, we used another amino acid, one that serves as the main component of mussel's adhesive proteins (MAPs). Mussels can attach strongly to rocks in the sea and hang on during high and low tide. Mussels adhere using strings made of MAPs that are rich in the amino acid L-3,4-dihydroxyphenylalanine (DOPA). This amino acid enables MAPs to adhere to any surface—metal, glass, and plastic.

We synthesized our non-stick molecule in the lab, in the form of a powder that looked like powdered sugar. We dissolved this powder in a liquid and sprayed it on different surfaces. We then performed several measurements to prove that the molecules indeed self-assembled on the surface. To test if the coating prevented bacterial adhesion, we incubated the coated surface in a solution that contained a million bacterial cells and their required nutrients. We always tested two types of surfaces: one with the coating (the experiment) and the other without the coating (the control). The surface without the coating served as a control, because it showed us the number of bacteria that would adhere to a surface without a coating. According to our previous experiments, the strain of bacteria that we used produced a biofilm on the surface within 9 h. Therefore, we waited 9 h before we took the surfaces out of the solution of bacteria. To determine how many bacteria we had on the surface, we scratched the surface with a toothbrush and transferred the bacteria from the toothbrush to a plate that contained food for the bacteria. This plate is called a Petri dish (Figure 2). Bacteria grew on the Petri dish and formed colonies. Each colony resulted from one bacterium that came off the surface. We counted the number of colonies and found that the number of bacteria on the coated surface was significantly smaller than the number of bacteria on the non-coated surface.

To make this coating useful in real life applications, we still need to prove that the coating can reduce the number of bacteria under normal conditions in

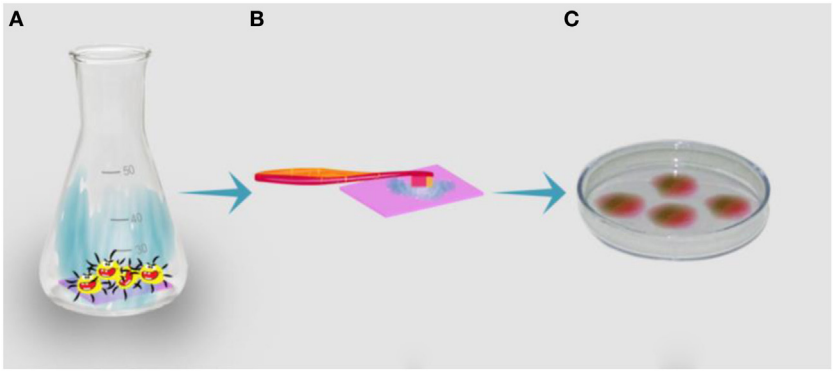

FIGURE 2

FIGURE 2

Determining the number of bacteria on a surface. **A.** In the first step, the surface (the colored rectangle at the bottom of the container) is placed in a container that holds the bacteria and their nutrients. **B.** In the second step, the surface is taken out of the container and the bacteria are scraped from the surface using a toothbrush. **C.** During the third step, the bacteria are plated on a dish that contains all the necessary food for the bacteria. On this solid surface, the bacteria grow into colonies. The colonies appear as rounded spots or dots on the plate (see Figure 1A). Each colony originates from one bacterium, and therefore, the number of colonies reflects the number of bacteria on the original surface.

the outside environment. This means that the coating should survive sunlight, scratches, and exposure to high and low temperatures. In addition, it is necessary to prove that the material is not toxic to humans. These tests are called regulation assays, and they are required for any new material. The material we developed is currently being tested in regulation assays.

WHAT ABOUT THE FUTURE?

Unfortunately, an ultimate solution that completely prevents biofilm formation does not exist. Biofilms not only cause hospital-acquired infections but they also harm the quality of food and water. Research groups that try to solve the problem of biofilms have come up with several different solutions, but there is still a need for a coating that will be stable enough, will not come off from the surface, will not be toxic to cells, and will be easy to apply and inexpensive. We hope that the solution we proposed, made up of amino acids, will provide a good solution to the problem. Do you have your own idea for a solution to this problem?

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REVIEWED BY

GIFTED CLASS, EIN GANIM, PETACH TIKVA, AGE: 11–12

We are in six grade, in the gifted track in Petah Tikva. There are 27 kids in the class: 17 boys and 10 girls. The kids come from all over the city. The class is very social and we meet a lot after school. We are very curious and autodidacts and we love to explore various topics. Most of us like to read and develop our minds. Some of the kids excel in bridge, chess, play musical instruments, and play football and basketball.

AUTHOR

MEITAL RECHES

I am an associate professor of chemistry at the Hebrew University of Jerusalem. I teach chemistry of materials and physical chemistry and I also lead a group of scientists researching the interactions between biological entities (such as cells, bacteria, and proteins) and surfaces. Our goal is to control the interface between these entities and the surface in such a manner that we can design responsive and functional surfaces. *meital.reches@mail.huji.ac.il

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HEALTH
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DANGEROUS SLIMES: HOW BACTERIAL BIOFILMS MAKE YOU SICK AND HOW TO COMBAT THEM

Hervé Poilvache [1,2] ***and Françoise Van Bambeke*** [1*]

[1] *Pharmacologie Cellulaire et Moléculaire, Louvain Drug Research Institute, Brussels, Belgium*

[2] *Neuromusculoskeletal Lab, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium*

YOUNG REVIEWERS:

NAVIN
AGE: 13

RANJANA
AGE: 14

TALAL
AGE: 14

Yes, we can house dangerous slimes called biofilms in our bodies. They can cause severe infections anywhere in our bodies. They contain bacteria hidden and hibernating in a protective matrix. This makes them really difficult to treat. They like to stick on implanted material like prostheses or catheter. They can also persist on your teeth, in your ears, even sometimes in your lungs. Luckily, researchers are very aware of this problem. They are experimenting with diverse solutions to try to destroy these biofilms. Are you curious about their brilliant ideas? Then follow us to learn more about how biofilms make you sick and how we try to combat them.

Bacteria are small living organisms. They are much more numerous than humans on our planet. There are more bacteria in 1 ml of water than humans on Earth! They can inhabit the environment, but also the human body. Facing such a big world, they need to find strategies to survive. Do you know the saying "Together, we are stronger"? Microbes know it! To better survive, most bacterial species are able

Figure 1

A few examples of biofilm-related infections. In red, those developing on tissues in our body. In purple, those developing on implanted material.

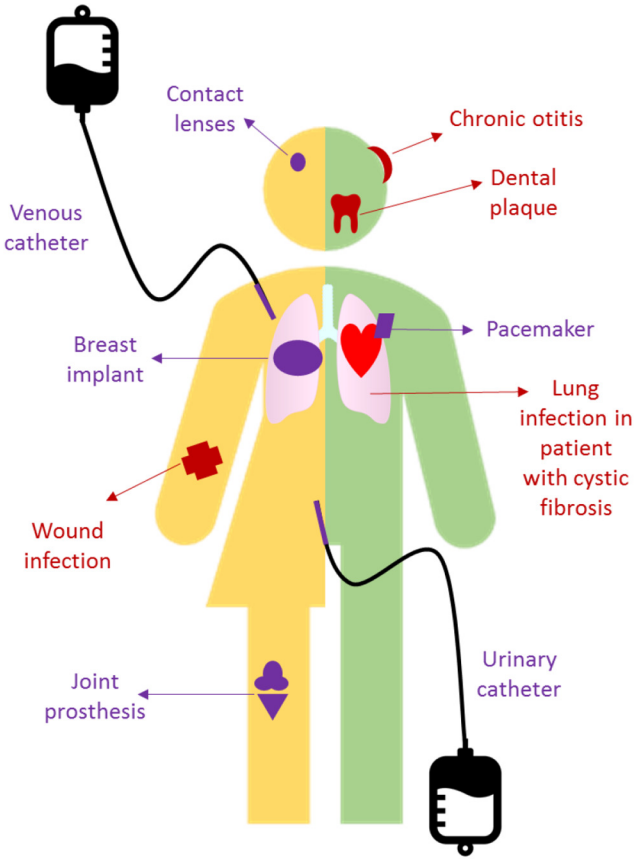

Figure 1

to gather in communities called biofilms[1] . In biofilms, bacteria play hide-and-seek. They produce a protective blanket called a **matrix**. It contains sugars, proteins, and nucleic acids [1]. Biofilms are thus very different from what we call "planktonic cultures." These consist of isolated bacteria freely swimming in a liquid, like plankton in the sea. In the environment, biofilms form everywhere: on pipelines, boat hulls, rocks, or even in hot water springs. In the human body, they can attach to organs and, more easily, on implanted material. If they contain pathogenic bacteria, they are a major cause of chronic infections.

MATRIX

A mixture of substances in which bacteria are embedded and support the global architecture of the biofilm.

[1] https://kids.frontiersin.org/article/10.3389/frym.2016.00014

WHY ARE BIOFILMS IMPORTANT IN HUMAN PATHOLOGIES?

Bacteria love to attach everywhere in our bodies [2] (Figure 1). Do you know about dental plaque? This slimy substance forms on your teeth between visits to the dentist. It contains a mix of bacteria and proteins from your saliva. You can remove it by regularly brushing your teeth. Otherwise, the bacteria inside the plaque will consolidate the biofilm. In the end, you will suffer from inflammation of the gums and dental cavities. Good hygiene and frequent care by a dentist help you keep your teeth in good health! Biofilms can also form in many other places and cause chronic infections. These infections may improve

when you take an **antibiotic**. But they restart soon after you stop the treatment. A few examples of such infections? Chronic infections of the ear (otitis) if you often go to the swimming pool, or pulmonary infections in children with a genetic disease called cystic fibrosis[2] . Poor children! The mucus in their lungs is slimy and bacteria find it very comfortable. Such infections are difficult to get rid of. This is a big problem. The patient will undergo extended and frequent antibiotic treatments, but the bacteria will defend themselves and evolve. Eventually, they become resistant to the treatment and in the end, antibiotics will no longer work to fight off the infection at all.

Most devices used in medicine also offer perfect shelters for the development of biofilms. Think about your last visit to your grandparents at the hospital. They probably had intra-venous **catheters** to deliver medicine in their blood or other **drains**. Maybe they also had a joint prosthesis implanted in the hip or knee when their own joint was too painful. These artificial surfaces are easily colonized by bacteria. They strongly bind to them. Then, they quickly start to multiply and produce a matrix. On these devices, biofilms grow in very complex structures. Bacteria will gradually adapt to their new environment. They will no longer respond to antibiotics anymore. In the end, the only option for doctors will be to remove the device and replace it with a new one, if possible. Of course, it is easy when the device is a simple catheter. But removing an implant, such as a hip or a knee prosthesis, is a complex procedure. It often requires multiple surgeries and your grandparent will probably not like that very much!

WHY ARE BIOFILM-RELATED INFECTIONS TOLERANT TO ANTIBIOTICS?

A biofilm is like a well-protected burrow where bacteria hibernate. The matrix creates a barrier against antibiotics. But this defensive barrier also limits the penetration of oxygen and food. Bacteria located in the deepness of the biofilm will start starving. They slow down their **metabolism**[3] , as if they were sleeping (Figure 2, left panel). A sleeping soldier is easier to kill than a vigilant one. But this does not apply at all to bacteria! Many antibiotics only act on bacteria that are actively multiplying and this cannot happen when the bacteria are sleeping in the biofilm. This phenomenon is called "tolerance" to antibiotics. Contrary to **antibiotic resistance**, tolerance is reversed when bacteria leave the biofilm [3]. But tolerance also contributes to treatment failure. We need 1,000 times more antibiotics to kill bacteria in biofilms than in planktonic cultures. The antibiotic prescribed by your doctor will therefore not work! Except if you take 1,000 more pills ... but are you really willing to swallow that many pills? And even if you could, such high doses would make you very sick! Would you like to have a very bad stomach ache, diarrhea, or headache? Or even worse, would you like to destroy your kidneys, liver, or blood cells? No!

ANTIBIOTIC

A substance that is capable of preventing bacterial growth, or even more, to kill bacteria.

[2] https://kids.frontiersin.org/article/10.3389/frym.2019.00106

CATHETER

Thin tube that can be inserted in the body to inject drugs in the blood or to drain fluids (urine or pus, for example).

DRAIN

Tube implanted to remove fluid collections from the body (for example at the end of a surgical procedure).

METABOLISM

The whole chain of chemical reactions that occur in a cell and support life (production of energy, synthesis of molecules needed as building blocks for the cell).

[3] https://kids.frontiersin.org/article/10.3389/frym.2019.00045

ANTIBIOTIC RESISTANCE

Acquisition by bacteria of a mechanism making them insensitive to antibiotics (for example, destruction of the antibiotic, modification of the antibiotic target).

Figure 2

(Left) Why biofilms are tolerant to antibiotics. (Right) Strategies to combat biofilm-related infections.

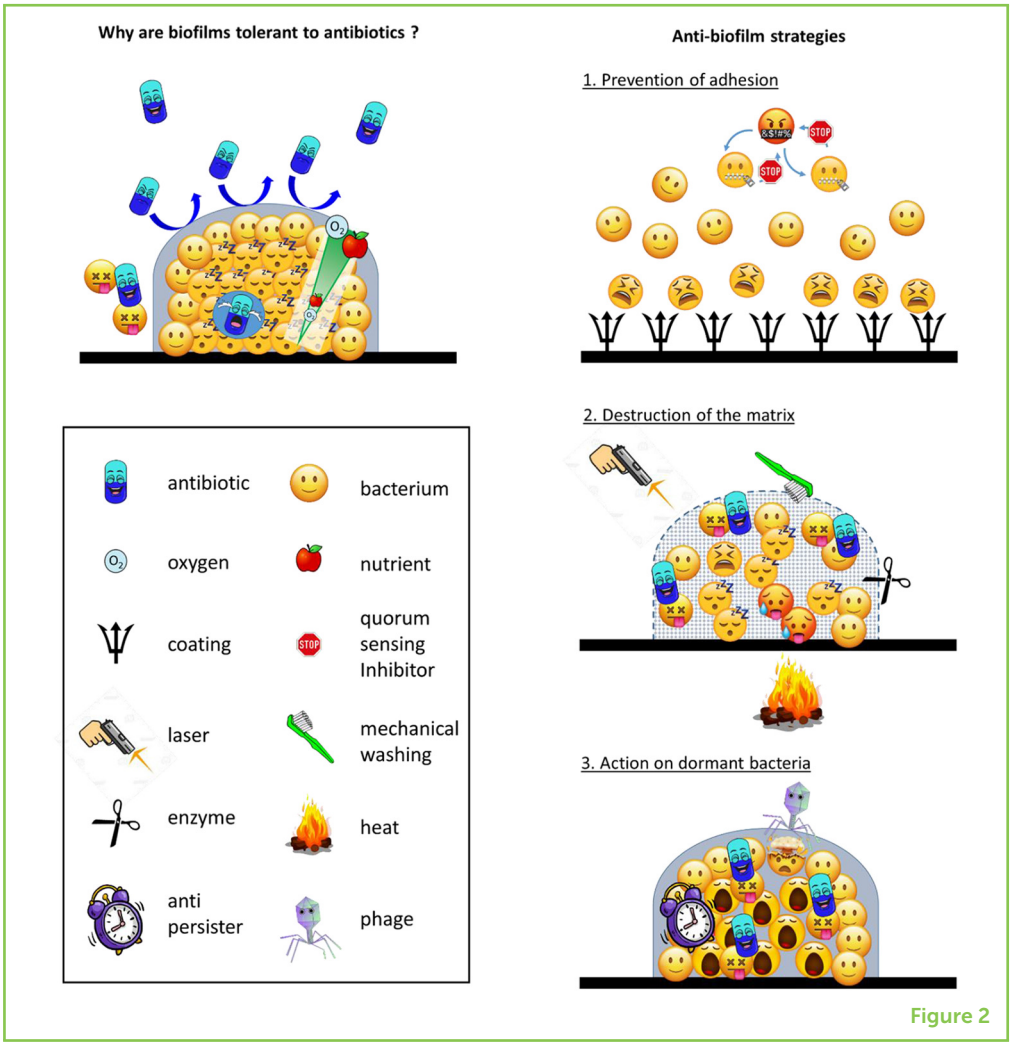

Figure 2

WHICH THERAPEUTIC STRATEGIES CAN WE USE AGAINST BIOFILMS?

You now understand that antibiotics do not work against biofilms. We need to imagine other strategies to fight biofilms. This is one of the main topics of intensive research at the moment [4]. You can think of three types of approaches (Figure 2, right panels).

First, prevention is better than a cure! We can try to prevent biofilm formation. This is a good idea for biofilms forming on implanted material. We can coat the surface of the implant with substances that prevent the attachment of bacteria. You can get this effect with silver coating, for example. With this noble metal in your body, you are now very precious! We can also fill the implanted device with high amounts of antibiotics. They are thus ready to act on bacteria before they start to sleep. For example, we can use a type of cement, loaded with antibiotic beads, to repair a bone fracture. We can also wash a catheter with a concentrated antibiotic solution. Most of these approaches are already used in clinics. Alternatively, we can interfere with the communication

system bacteria use. It is called quorum sensing [5]. It consists of molecules produced by bacteria and is sensed by their neighbors, as if they were smelling a nice perfume. Without your cell phone, you cannot call your friends. Without quorum sensing, bacteria cannot find each other to start building the biofilm.

Second, we can try to destroy the matrix. This should help the antibiotic to reach the hidden bacteria. This goal can be achieved with **enzymes**. They will cut the substances present in the matrix into small pieces, just like if you were to unknit your pullover—you are more exposed and fragile, are not you? We can also wash the biofilm with a high-pressure Karcher (a high pressured cleaning tool). Or we can try other impressive techniques, like laser shocks, electrical currents, or even heat. This may look like science-fiction! And somehow barbarous and painful! But be aware that some of these techniques are already used by your dentist or by your surgeon while you are sleeping in the operating room...

ENZYME

Protein capable of transforming one molecule in another one, for example in degradation products.

Third, we can try to wake the sleeping bacteria up. This is not an easy task. We need to discover "anti-persister" molecules. These will help antibiotics to kill sleeping bacteria. The first anti-persister molecule was discovered only a few years ago [6]. It activates an alarm system in bacteria. When the bell rings, it is time to wake up! Other anti-persisters make holes in the bacterial envelope. What will happen if you open all the windows in your home? On the one side, fresh air from outside will enter the room and wake you up. This means that bacteria are not sleeping anymore. On the other hand, pollens could enter and make your eyes itch if you are allergic to them. For bacteria, it means that antibiotics could enter the cell to harm them. These anti-persisters are still being tested in laboratories. They are not yet used to cure people. Another amazing approach uses biological weapons. Bacteriophages [7] are viruses of bacteria. They make bacteria sick but not humans. Some of them also produce enzymes that can destroy the matrix. That means that they can hit two targets with one shot!

WHAT ABOUT THE FUTURE?

Most of these new strategies are still under development. A lot of work is required to make sure that they are active and work right. Another concern is the risk that these strategies could be toxic. However, we are making progress at a steady pace. Some treatments have recently been tried in patients! For example, bacteriophages have been used, with success, to treat an infant with a severe liver infection.

Are you interested in joining a team of researchers to work on these topics? We are looking forward to seeing you in our laboratory in the near future!

You can find more information in this Young Minds Article [5, 7].

ACKNOWLEDGMENTS

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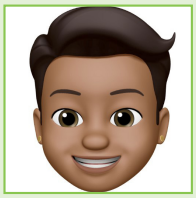
YOUNG REVIEWERS



NAVIN, AGE: 13

I am interested in the medical field and aspire to become an anesthesiologist in the future. I enjoy reading and drawing cartoons. I have been playing ice hockey and love being on the rink. Tennis, swimming, and cross-country is also my favorite sports. I love eating anything that is vegetarian. I want to contribute to my community in any way I can and make a positive change.

RANJANA, AGE: 14

I love science and am especially into medicine. I am passionate about health and wellness. I enjoy reading and watching heist movies. I love spending time in labs, researching, and learning. I would like to learn more languages; right now, I can speak three. I hope to travel to more countries in the future!

TALAL, AGE: 14

I am a 14 years old boy who lived in England and had all my education there. I have recently moved back to Belgium. I play a lot of sport including tennis, football, and hockey. I am also interested in sciences and would be inspired to be a doctor in the future.

AUTHORS

HERVÉ POILVACHE

I am a medical doctor from the Université Catholique de Louvain (Brussels, Belgium), I have begun a specialization in Orthopedic Surgery, and I am currently a Ph.D. student in Pharmaceutical and Biomedical Sciences at the same university. My main research interest is the development of new ways to treat biofilm-related infections in the orthopedic field.

FRANÇOISE VAN BAMBEKE

I am a pharmacist passionate about research on antibiotics and bacteria. After a doctoral thesis and a visit at the Pasteur Institute (Paris, France), I came back to the Université Catholique de Louvain (Brussels, Belgium) where I work for the Fonds de la Recherche Scientifique with a team of researchers. We are trying to understand why antibiotics are not always active on bacteria and to find solutions to restore their effectiveness. I also teach the proper use of medications to future pharmacists.
*francoise.vanbambeke@uclouvain.be

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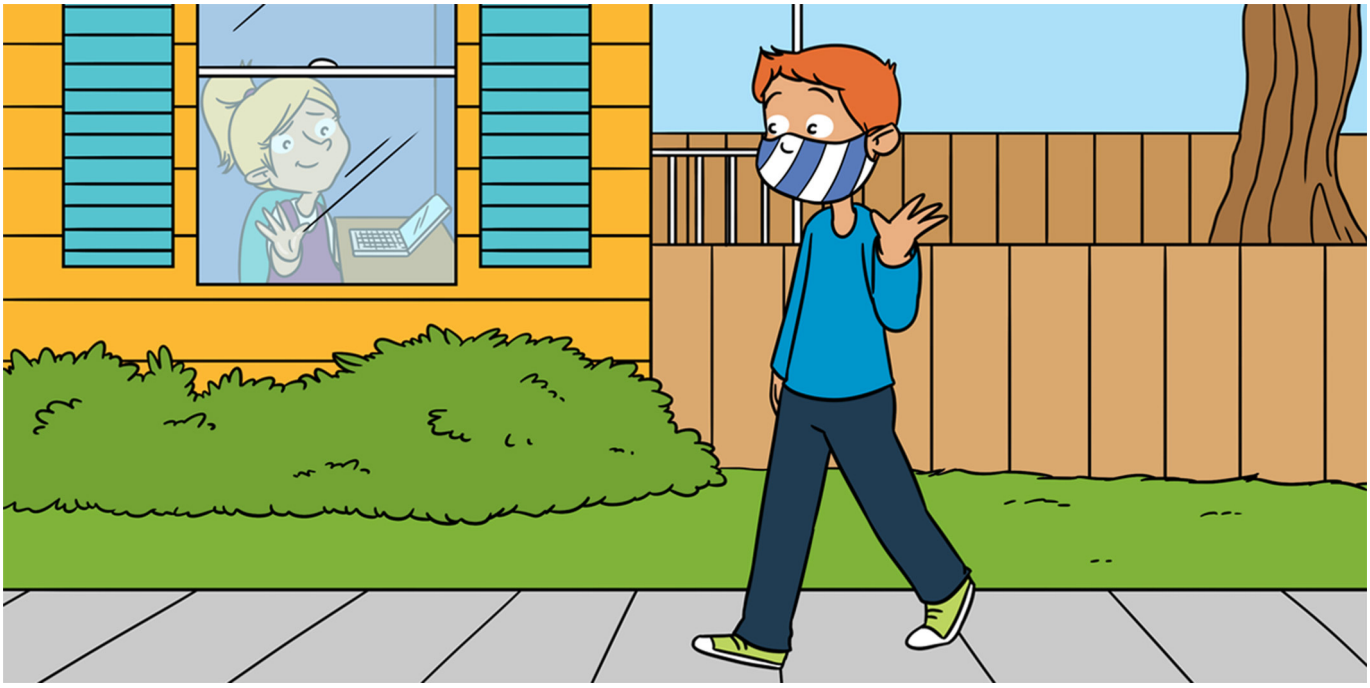

WHAT IS COVID-19?

Gabriela Gama Freire Alberca, Iara Grigoletto Fernandes, Maria Notomi Sato and Ricardo Wesley Alberca *

Laboratory of Dermatology and Immunodeficiencies, LIM-56, Department of Dermatology, School of Medicine and Institute of Tropical Medicine of São Paulo, University of São Paulo, São Paulo, Brazil

YOUNG REVIEWERS:

MARINA
AGE: 14

MIRIAM
AGE: 14

COVID-19, the abbreviation for coronavirus disease 2019, is the name of the disease caused by a virus named SARS-CoV-2, an abbreviation for severe acute respiratory syndrome coronavirus 2. The first report of this virus was in Wuhan, China, in November 2019 and now (Spring 2020) it has spread all over the world, so it is called a pandemic. This viral infection may cause fever, cough, tiredness, shortness of breath, and, in some cases, diarrhea. The infection usually causes mild symptoms in children and teenagers, but it can be lethal to the elderly. This virus can be spread between people very easily, so it is important to understand how to prevent its spread. The most effective ways to do this are by regularly washing hands with soap and water, maintaining a safe distance from other people, covering the mouth when coughing or sneezing, avoiding touching the face, eating a healthy diet, and staying home.

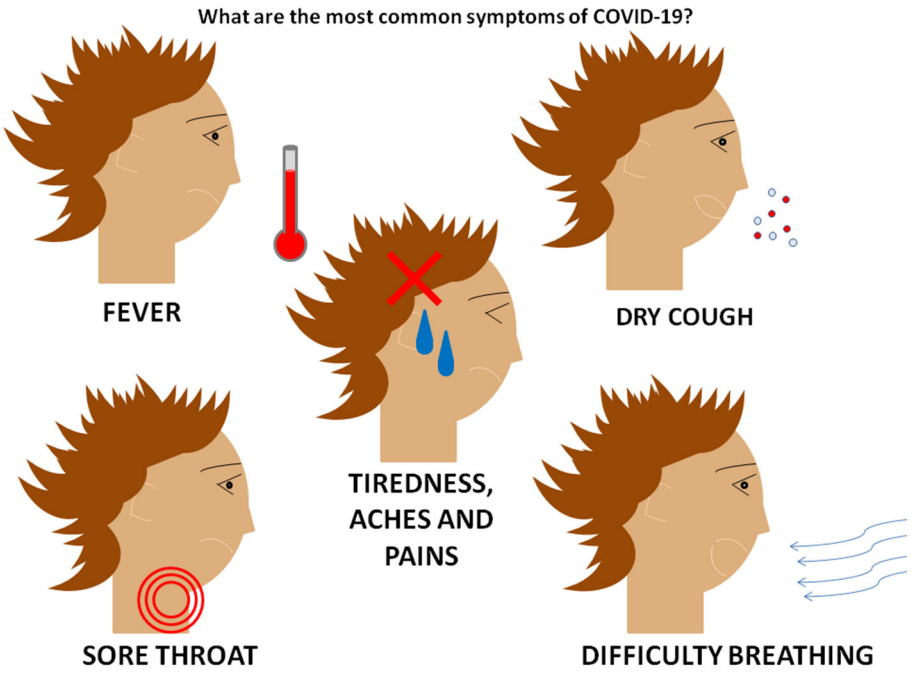

Figure 1

What are the most common symptoms of COVID-19? The most common symptoms are fever, dry cough, sore throat, tiredness, aches and pains, and difficulty breathing.

WHAT IS COVID-19?

COVID-19 is a new disease, caused by a type of virus named severe acute respiratory syndrome coronavirus-2 (**SARS-CoV-2**). It has now spread all over the world this is known as a **pandemic**. Coronaviruses are a family of viruses that can cause problems with the **respiratory system**. Previous infections by coronaviruses named SARS-CoV-1 (in 2002) and MERS-CoV (Middle East respiratory syndrome) (in 2012) have infected over 10,000 people.

The first report of SARS-CoV-2 was in November 2019, in Wuhan, China [1], but little is known about the exact origin. Currently, there is no specific treatment or vaccine for SARS-CoV-2. When someone is infected by this new virus, the person may or may not have any symptoms. If a person does have symptoms, those symptoms can range from mild to severe. The most common symptoms are fever, dry cough, tiredness, sore throat, and shortness of breath (Figure 1) [1]. These symptoms usually appear 2–14 days after the person is infected with the virus. It is estimated that every person infected will infect ~2 others. So, in this math problem, it is estimated that the number of infected people will double approximately every week during the initial outbreak.

WHO IS AT RISK OF DEVELOPING A SEVERE FORM OF COVID-19?

It is still not clear why some people develop severe symptoms and need intensive care and mechanical ventilation to help their lungs

COVID-19 (CORONAVIRUS DISEASE 2019)

A disease caused by a virus called SARS-CoV-2.

SARS-COV-2 (SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2)

A newly discovered coronavirus that causes the disease called COVID-19.

PANDEMIC

A disease that is spread all over the world.

RESPIRATORY SYSTEM

A system responsible for breathing in oxygen and breathing out carbon dioxide. The primary organs of the respiratory system are the lungs, responsible for the exchange of gases as we breathe.

Figure 2

SARS-CoV-2 life cycle. **(A)** When SARS-CoV-2 gets into the body, it binds to the ACE-2 receptor on cells in the lungs. **(B)** The virus is then taken up by the cell. **(C)** Once inside, the virus releases its genetic material and hijacks the cell's replication machinery to produce new viruses. **(D)** The newly created SARS-CoV-2 are released from the cell to start the process over again.

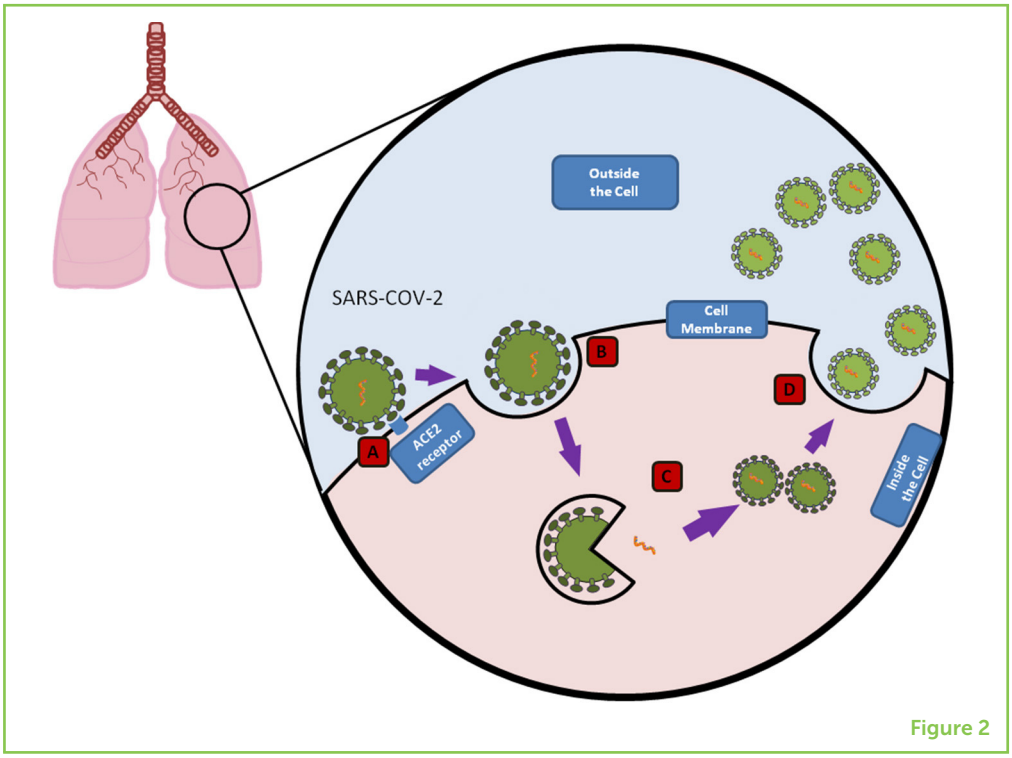

Figure 2

to function properly. It is known that people with some pre-existing conditions, such as diabetes and high blood pressure, as well as older people (people aged 60 years or older) have a higher risk of developing severe complications and being hospitalized. While children, teenagers, and young adults are not immune to SARS-CoV-2, they do not develop severe symptoms as often. Investigations are still ongoing to identify other possible factors that may cause people to have a severe form of COVID-19. Factors such as chronic respiratory disease and cancer [2] may play a role in the development of severe symptoms. It is also unclear if there are any long-term effects associated with COVID-19.

HOW DO PEOPLE GET INFECTED?

SARS-CoV-2 is a respiratory virus, so it is spread mainly from person to person when an infected person sneezes, coughs, or talks. Very small droplets of saliva can be expelled by an infected person during these actions, and the droplets can carry the virus into direct contact with another person's nose, eyes, or mouth.

Interestingly, the virus can still be found on materials like stainless steel or plastic, even several days after the material has become contaminated [3]. So, if you put your hand on a surface contaminated with SARS-CoV-2 and then touch your mouth, eye, or nose, you could possibly become infected.

WHY DOES THE VIRUS ATTACK THE LUNGS?

Even through SARS-CoV-2 can enter the body by many routes, it can only infect a cell if that cell has a molecule on its surface called ACE-2. This molecule is called the receptor (**ACE2 receptor**), and it is present in high amounts on the cells of the lungs. This is the reason SARS-CoV-2 primarily attacks the lungs and reproduces inside lung cells (Figure 2). As the virus enters the lungs, the infected person's immune system tries to eliminate the virus, generating a huge amount of **inflammation** in the lungs. The inflammation can end up damaging the tissues of the lungs, causing shortness of breath.

ACE2 RECEPTOR

The molecule on the cell surface that is used by SARS-CoV-2 to invade host cells.

INFLAMMATION

The protective reaction of the body against an infection or an injury, resulting in heat, redness, and swelling. If inflammation is not controlled, it can be harmful to the body.

HOW DO WE KNOW IF A PERSON HAS BEEN INFECTED?

If a person has been experiencing the common symptoms of COVID-19 for more than a few days, a doctor may order a test to determine if the person has been infected with SARS-CoV-2. There are two ways to know if a person is infected or has been infected recently.

One test can determine whether the sick person currently has SARS-CoV-2 in his or her body. For this test, the medical team usually collects a sample of fluid from the nose with a swab. Since the quantity of virus collected this way is very small, a technique called **polymerase chain reaction (PCR)** is used to make lots of copies of the genetic material of the virus, so that lab workers will be able to see whether the virus is present in the sample (Figure 3A).

POLYMERASE CHAIN REACTION (PCR)

A method that enables us to make copies of the genetic material in a sample. Therefore, this method helps in a rapid detection if there is SARS-CoV-2 genetic material in the sample, even if the quantity is very small.

Another way to test if a person has been infected with SARS-CoV-2 is to analyze whether the person has antibodies to the virus. Antibodies are only created after a person has been exposed to a virus, and they help to protect the person from getting infected again. Depending on the type of antibodies, it is possible to know if the infection is recent (the test will show the presence of a type of **antibody** called IgM) or if the person was infected in the past (the test will show the presence of another kind of antibody, called IgG) (Figures 3B–G) [4].

ANTIBODY

A protein produced by the immune system in response to a virus or other microorganism that helps to protect the body from reinfection with that same organism. Antibodies called IgM are produced early during infection and others called IgG are produced later.

If a person is infected, it is very important for the person to isolate themselves and minimize contact with others, to avoid spreading the infection. The medical team that diagnoses the person will provide all the necessary information to help the sick person self-isolate effectively.

HOW CAN WE PREVENT COVID-19?

To protect ourselves and to protect others who may be more vulnerable to severe COVID-19, we can take some simple actions. According to the World Health Organization, it is essential to maintain

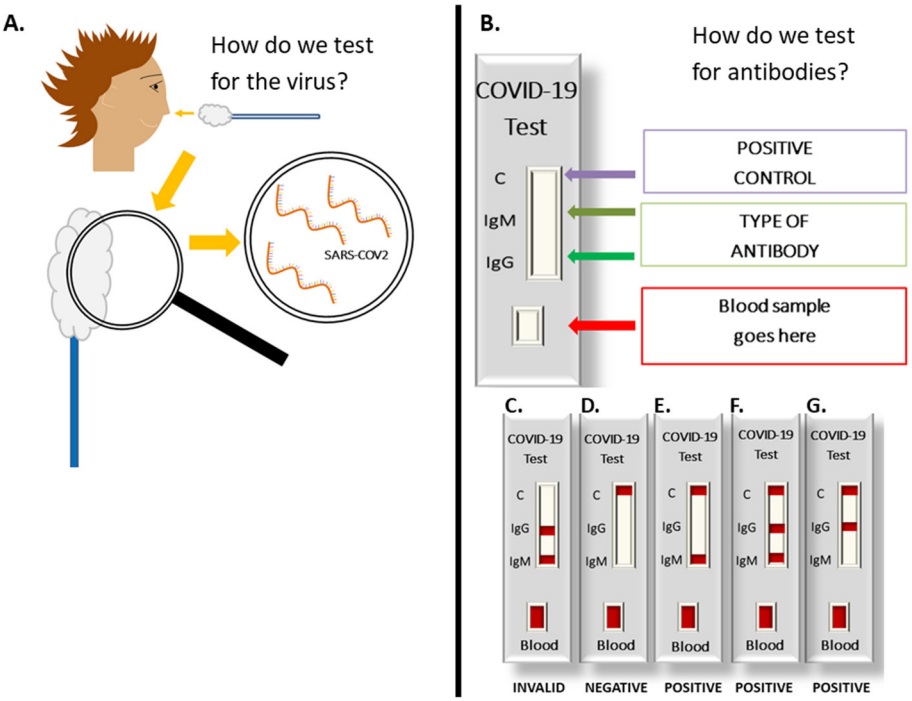

Figure 3

Figure 3

How does a coronavirus test work? **(A)** How do we test for the virus?: A small sample of fluid is collected from the nose with a swab, and then the medical team looks for the genetic sequence of SARS-CoV-2 in the sample. **(B)** How do we test for antibodies?: A blood sample is collected and placed in the correct spot on the test kit, and the results will then appear in the window, showing 5 possible outcomes. **(C)** If the positive control does not light up, the test is not valid. **(D)** If the positive control light up, but there is no IgM or IgG, the person does not have antibodies against SARS-CoV-2 and was therefore not infected. **(E–G)** If the positive control and IgM and/or IgG light up, the person has been infected and is producing antibodies against SARS-CoV-2.

some distance (1–2 m) when talking to other people. We should also avoid crowded places, wash our hands with soap and water frequently or use hand sanitizers that contain 70% alcohol. It is also very important to avoid touching our faces and to cover our mouths with our arms when we cough or sneeze. We may also be asked to wear face masks in public places (Figure 4) [5]. These procedures can help reduce the spread of the virus and help us make sure that hospitals do not get overcrowded, so that everyone who needs medical help can get it.

All over the world, different treatments are being tested in individuals infected with SARS-CoV-2, but it will take some time to identify which drugs are effective and safe. Many drugs aim to prevent the virus from infecting other cells or from replicating to produce more viruses. Vaccines are also being developed. Vaccines are given to people before they get sick, to prevent the disease from happening. It is important to remember that safe and effective vaccines can take a long time to develop. Because many scientists and doctors around the world are working hard to help people with SARS-CoV-2, it is possible that treatments and a vaccine may emerge within the near future.

SUMMARY

In conclusion, SARS-CoV-2 is a new coronavirus that can cause a severe disease named COVID-19. There is currently no specific treatment or vaccine available for this virus. Although some people

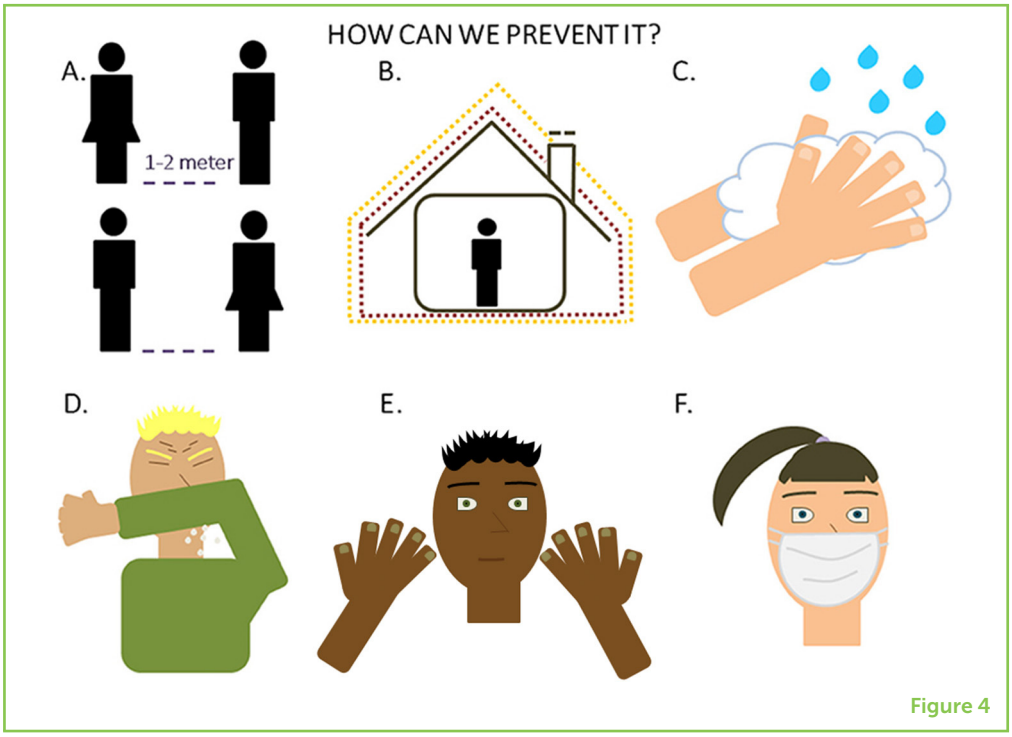

Figure 4

How to prevent SARS-CoV-2 infection. **(A)** Maintain some distance (1–2 m) when talking to other people. **(B)** Stay at home or avoid crowded places. **(C)** Wash hands with soap and water frequently, or use alcohol-based hand sanitizers. **(D)** Cover your mouth with your arm when you cough or sneeze. **(E)** Avoid touching your face. **(F)** Wear a protective mask.

may not have symptoms, they may still be infected and able to infect other people, some of whom may go on to develop severe COVID-19. To protect ourselves and others, many actions can be of great value, such as maintaining distance between yourself and others, avoiding crowded places, washing your hands frequently with soap and water, and covering your mouth when you cough or sneeze. These simple steps will help people all over the world to stay safe from COVID-19.

AUTHOR CONTRIBUTIONS

GA contributed to the conception, drafting, and review of the manuscript. IF contributed to review and illustration. MS contributed to review. RA contributed to the conception, illustration, drafting, and review of the manuscript.

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CONFLICT OF INTEREST: 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

MARINA, AGE: 14
I decided to review this article because I think it is a really serious problem, since currently there is no vaccine against coronavirus. I think it is really important, not only for people my age, but for everyone, to know as much as possible about the coronavirus. Because if we all collaborate, we can stop this as soon as possible. I highly recommend reading these types of articles and staying safe from this misfortune.

MIRIAM, AGE: 14
I really like science and I was curious to learn more about COVID-19. I wanted to help improve this article by giving my opinion because this virus is a huge problem now, and we have never seen something similar to this worldwide pandemic. I watch and listen to the news a lot these days and reading this article gave me the feeling I understand what is happening.

AUTHORS

GABRIELA GAMA FREIRE ALBERCA
I am a Ph.D. student at the Institute of Biomedical Science at the University of São Paulo. My research focuses on understanding the influence of gastrointestinal bacteria on the development of diseases. In my free time, I enjoy cooking.

IARA GRIGOLETTO FERNANDES

I am a Ph.D. student at the Institute of tropical medicine at the University of São Paulo. My research is on oxidative stress and viral infections skin in the elderly. My hobbies are taking care of plants and playing with my cat.

MARIA NOTOMI SATO

I am a professor at the University of São Paulo. My research focuses on maternal-fetal interactions, allergy, and viral infection. I enjoy coffee and coconut desserts.

RICARDO WESLEY ALBERCA

I am a post-doctoral researcher at the University of Sao Paulo. My research focuses on the development of treatments for respiratory diseases, like asthma and other inflammatory syndromes. I enjoy books and movies. *ricardowesley@usp.br

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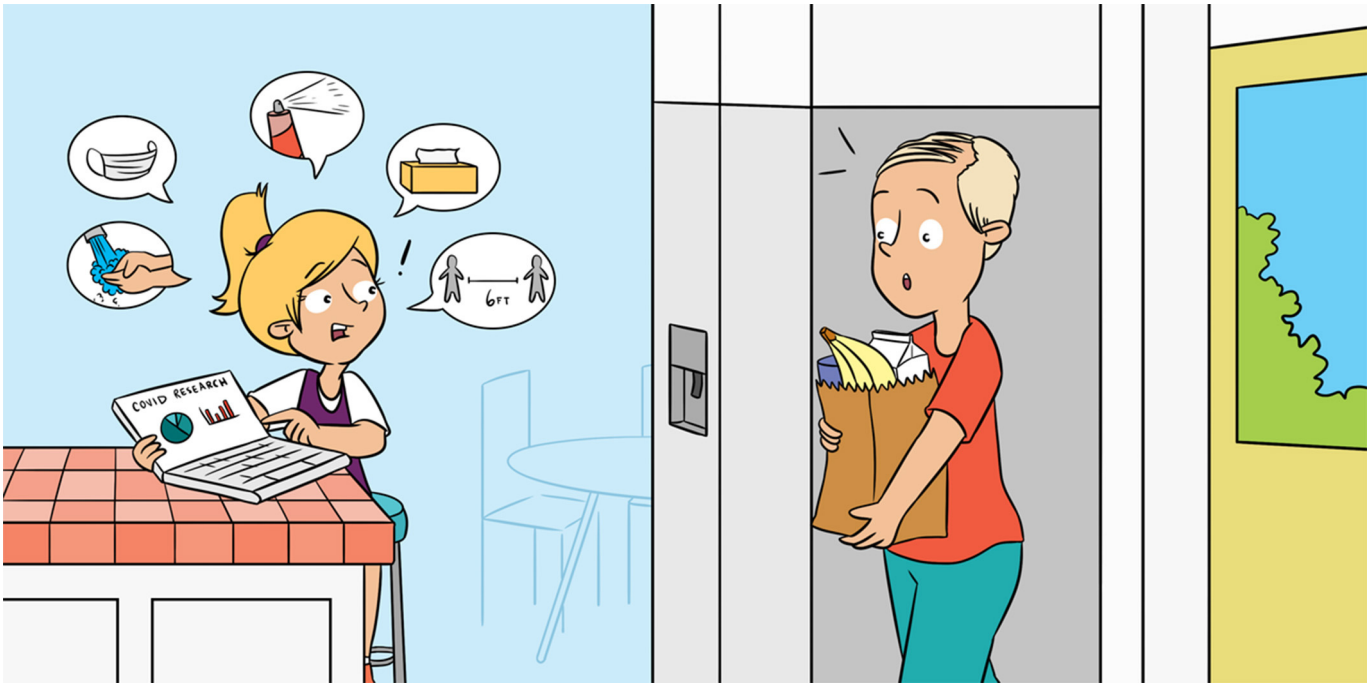

COVID-19, THE QUARANTINE-VIRUS DISEASE

Hilde Stevens * ***and Marie Neunez***

Institute for Interdisciplinary Innovation in Healthcare (I3h), Faculty of Medicine-Solvay Brussels School, Economics & Management, Université libre de Bruxelles, Brussels, Belgium

YOUNG REVIEWER:

CAROLINE

AGE: 15

Since December 2019, the world has been facing an outbreak of a new Coronavirus, called SARS-CoV-2, causing a disease called COVID-19. The virus spreads through close contact and droplets created when we sneeze, cough, or speak. Luckily, when children get infected, they seem to only have mild symptoms, like fever and cough. Mainly people over 65 years old and people with other health conditions are most seriously affected by COVID-19. The disease causes infection of the lungs, blood, and digestive system. Increased hygiene, good ventilation of rooms, keeping a "social" distance of at least 1.5 m from those who do not live in your house, and staying at home are our best protection against spreading the virus. Currently, the best way to contain SARS-CoV-2 is through thorough testing for infections and quarantining infected patients and others who were in contact with the infected person before he/she got sick. A COVID-19 vaccine is also being developed!

THE NEW CORONAVIRUS: THE BASICS

SARS-CoV-2 is the name of the youngest member of the Coronavirus family known to infect people (Figure 1). Its full name is **s**evere **a**cute **r**espiratory **s**yndrome-**co**rona**v**irus-**2**. The virus causes severe infections of the lungs, blood, and digestive system. The disease SARS-CoV-2 causes is called COVID-19 (**co**rona**vi**rus **d**isease 20**19**). SARS-CoV-1 (severe acute respiratory syndrome coronavirus-1) and MERS-CoV (Middle-East respiratory syndrome coronavirus), two other famous family members, also caused considerable human suffering and death—SARS in 2002 and MERS in 2012. Four other successful family members cause about a third of common colds [1, 2].

ZOONOTIC

Zoonotic is a term used to refer to a disease that can spread from animals to humans. A zoonosis is any disease or infection that is naturally transmissible from vertebrate animals to humans. Animals thus play an essential role in maintaining zoonotic infections in nature.

SARS-CoV-2 is a **zoonotic** virus, meaning that it jumped from an animal to a human. The virus' genetic similarity to bat coronaviruses explains why scientists believe that SARS-CoV-2 jumped from its original host, a bat, to a human. Since the first patient was diagnosed in Wuhan, China, this was thought to be the place of origin of the virus. However, scientists from different countries found traces of the virus in sewage water in early December, long before the first infected patient was diagnosed. This adds to evidence that the virus may have been circulating much earlier than thought. Coronavirus looks like a little ball (diameter 50–200 nm, so tiny it is only detectable with a very powerful microscope) with crown-like spikes ("corona" means crown). The virus' outer layer consists of fatty particles that are easily destroyed when the virus comes into contact with soap [1, 2].

HOW DID COVID-19 CAUSE A PANDEMIC?

PANDEMIC

A pandemic is an epidemic (a sudden outbreak) that becomes very widespread and affects a whole region, a continent, or the world due to a susceptible population. A true pandemic causes a high degree of mortality (death).

Zoonotic viruses have caused more and more outbreaks in the past few decades. A disease spreading over the whole world is called a **pandemic** [3]. But why did SARS-CoV-2 cause a pandemic like we have not seen in more than a century? Worldwide, almost 15 million people have been infected, and nearly 650,000 people have died from COVID-19 (as of 21/07/20) [4]. For a disease to become a pandemic, spreading around the world in just months and causing that much harm to people, it must be very contagious, but not too deadly.

ACE2 RECEPTOR

A molecule on the surface of cells in the lungs, arteries, heart, kidneys, and intestines that serves as an entry point into cells for some Coronaviruses.

All viruses need to hijack other cells to reproduce. That is their only goal: to survive and multiply themselves (Figure 2). SARS-CoV-2 spreads through close contact and the droplets we spread when we sneeze, cough, or speak. It can enter our bodies through our eyes, nose, or mouth. The virus can survive on various surfaces for hours, so people can get it on their hands and infect themselves by touching their faces, something we do on average 20 times per hour [1, 2].

Once inside the body, the crown-like spikes of SARS-CoV-2 attach to molecules called **ACE2 receptors**, which are found on many human cells. Using these receptors, the virus enters our cells and gives the cell

Figure 1

SARS-CoV-2 is the newest member of the family of coronaviruses; it particularly likes to infect older and weaker people, but does not really like to infect children.

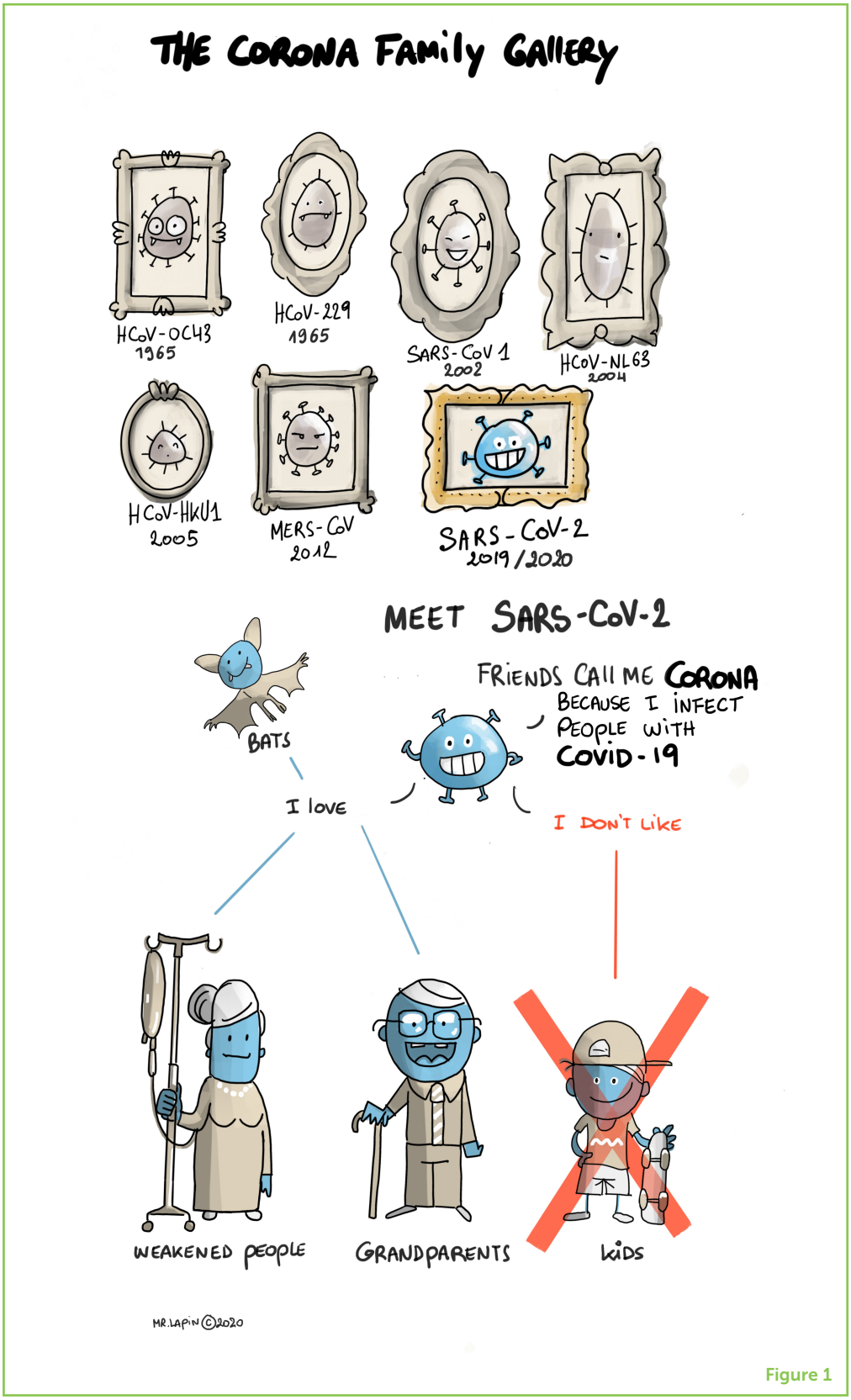

Figure 1

instructions to produce numerous copies of itself, which can go on to invade more and more cells. As more cells get infected, this can lead to flu-like symptoms, such as cough, fever, and fatigue. Other symptoms

Figure 2

Through attaching to the ACE 2 receptors, found on many human cells, the virus enters and gives the cell instructions to produce numerous copies of itself, so the virus can invade more and more cells.

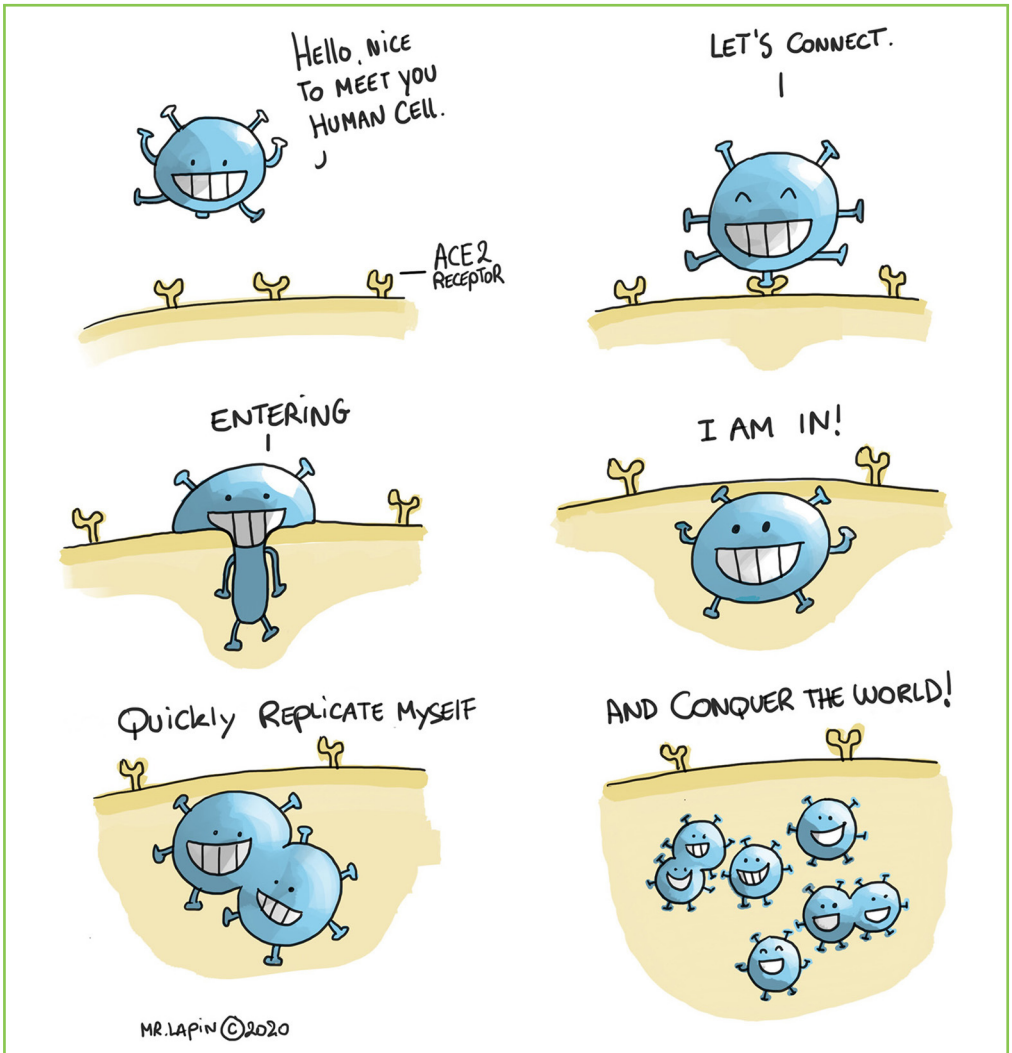

Figure 2

include shortness of breath, sore throat, loss of appetite, loss of sense of smell or taste, and diarrhea [1, 2].

However, it is possible to be infected with SARS-CoV-2 and to spread it without even having symptoms. When this virus first infects a human, it is silent for some time. This is called the **incubation period** and it can last up to 2 weeks. About 3 days before the first symptoms appear, infected people can spread the virus to others. When no measures are taken, they are likely to infect between 1 and 4 other people without knowing it. The newly infected people in turn will be able to infect more people, and so on. That is why the virus is so successful in causing a pandemic. The number of infected people doubles quite rapidly [1, 2].

INCUBATION PERIOD

Time between the encounter with a pathogen (virus or other microorganism causing disease) and appearance of the first symptoms. During that time, the pathogen is multiplying in the body.

AM I AT RISK? AM I A RISK TO OTHERS?

Research is ongoing, but we do know that children are at lower risk of severe infection and they are not the main people spreading the virus.

Only a small portion of confirmed COVID-19 cases are in children. However, since children show no or only mild symptoms, they do not get tested as much as adults [1–3, 5].

The older you get, the more you are at risk of developing serious symptoms from COVID-19, such as severe lung infection. People aged 65 and older, as well as people already suffering from other conditions like lung or heart disease, a weakened immune system, or diabetes, are more at risk. Research shows that men are more likely to get sick with COVID-19 than women are. This could be due to biological differences, or because they tend to smoke more often, or maybe even because they wash their hands less frequently [1–3, 5].

So, if children are less likely to get infected, do not develop severe symptoms as often, and might not spread the disease, then why did almost all schools close? At the start of the pandemic, little was known about SARS-CoV-2. Scientists and governments did not want to take any risks that might help the virus spread further. Schools, shops, and airports closed, non-essential contact between humans was avoided, and most people worked from home. Almost the whole world went in a so-called "lockdown," in which everybody stayed at home as much as possible. Only public services, such as hospitals, public transport, garbage collectors, and food shops continued working. Thanks to these strong governmental measures, the rate of infections slowed down, and hospitals were able to help the people who got really ill. This is what is meant by the term "flattening the curve" (Figure 3) [1–3, 5].

HOW DO WE CONTROL SARS-CoV-2?

Currently, the best measures to prevent infection with SARS-CoV-2 are good hygiene, including washing our hands with soap regularly, sneezing into a paper tissue (and throwing it away afterwards), and sneezing into our elbows. Good ventilation of rooms is also important. Social distancing (also called physical distancing), which means keeping a distance of at least 1.5 m from others, is important because it also prevents the virus from spreading. When we cannot keep that distance, wearing masks over the nose and mouth can help prevent the spreading of SARS-CoV-2 (Figure 3) [1, 2].

Never before have scientists worldwide collaborated so closely—at a safe distance!—to find a way to help people with SARS-CoV-2 and to stop its spread. By means of quick testing with a nose swab, we can detect infected people and quarantine them for 2 weeks, so they stop infecting others. Further, by tracking down other people who were in contact with the SARS-CoV-2-positive patients and quarantining them too, the risk of further spreading is contained. A different lab test can help determine whether people were infected in the past and have already built immunity against the virus [1, 2].

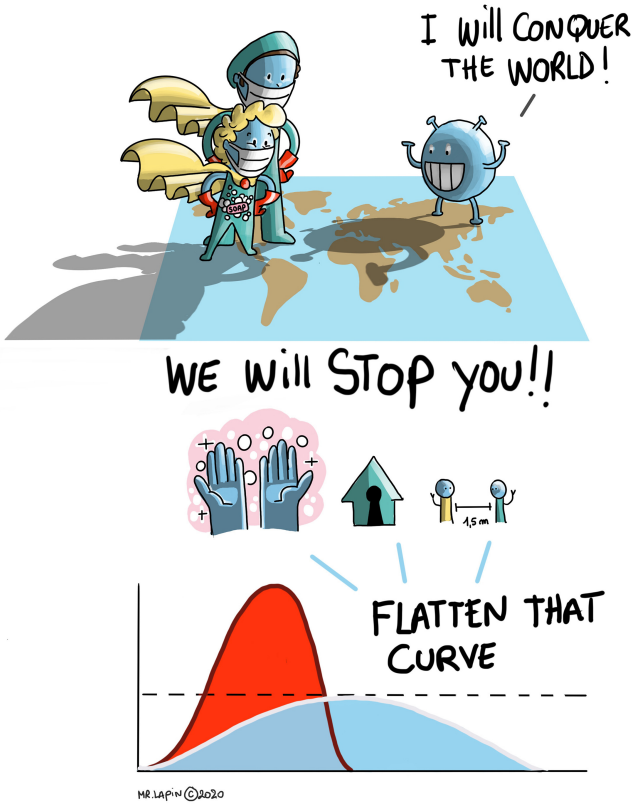

Figure 3

We can help to prevent infection with SARS-CoV-2 and from spreading the virus further by good hygiene: washing our hands with soap regularly, sneezing into a paper tissue (and throwing it away afterwards), sneezing into our elbows, ventilating rooms, social distancing (keeping a distance of at least 1.5 m from others), and wearing masks over the nose and mouth. By doing so, the rate of infections will slow down, and hospitals will be able to help the people who get really ill. This is what is meant by the term "flattening the curve."

Physicians are also currently exploring ways to relieve patients' symptoms. One way might be by testing drugs that are normally given to patients to fight other infections, to see if they are also effective against SARS-CoV-2 [6]. The blood of people who have recovered from COVID-19 is another potential treatment that is being tested. When fighting the virus, people develop antibodies against it, so their bodies can fight the virus quickly if they encounter it again. Those antibodies (called **convalescent serum**) can be isolated from the blood and could be given to others to help them fight COVID-19 [1, 2].

CONVALESCENT SERUM

Blood serum from patients recently recovered from an infectious disease, which is rich in antibodies against the infectious agent and may be used to treat patients with the same infection.

AND WHAT ABOUT THE FUTURE?

A vaccine will be our best chance to protect ourselves against COVID-19. Unfortunately, vaccine development will take at least 1 year. The good news is that there are currently over 165 potential vaccines candidates that are being developed [7].

In the meantime, it is important that each of us continues to fight this virus however we can. SARS-CoV-2 has caused a lot of suffering. Many people got sick, or worse, lost someone they loved. Being quarantined for a long time also caused many people to feel sad and lonely. People could not travel nor go shopping during the lockdown, so the economy also seemed to stop. Consequently, many people lost, or still

might lose, their jobs. Even when the pandemic is over, it will take some time for the world to recover from the damage caused by SARS-CoV-2. For example, people who lost their jobs need to find other ways to support their families. So, the better we follow the hygiene measures (washing our hands regularly and social distancing), the less the virus will spread and the sooner the pandemic will be over.

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YOUNG REVIEWER

CAROLINE, AGE: 15

I am a student and I like the natural sciences. I have two older brothers who are working in science, particularly medicine so I am very interested in knowing more about medical sciences and health related topics. During my free time, I like to read books and eat good food.

AUTHORS

HILDE STEVENS

I am an Associate Professor at the Université Libre de Bruxelles. My research focuses on how people with various cultures and ways of working (e.g., academics or people in the pharmaceutical industry) could optimally collaborate to bring inventions from the lab to the patient much faster, and how patients in low- and middle-income countries also could get access to innovative therapies. I love telling stories to my children about bad bugs and how to fight them, and then we make paintings about it! *hstevens@i3health.eu

MARIE NEUNEZ

I am a part-time research fellow at the I3h Institute and Student in Medicine at the Université Libre de Bruxelles (ULB). I was a Clinical Research Coordinator for 2 years in the Departments of Nuclear Medicine & Radiotherapy at the Institut Jules Bordet (IJB). I also performed a 5-months internship at BASF SE (Mannheim, Germany) in the Human Health & Nutrition department. I hold a M.Sc. degree in Bioengineering with a specialization in Science, Technology and Quality of Food (UCL, Belgium), a Postgraduate degree in Management (ICHEC Business Management School, Belgium), and a certificate in Clinical Studies (Cefochim, Belgium).

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HEALTH
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COVID-19: FIGHTING A VIRUS GONE VIRAL

***Daniel Montelongo-Jauregui*[1*], *Ahmed S. Sultan*[1], *Taissa Vila*[1] *and Mary Ann Jabra-Rizk*[1,2]**

[1]*Department of Oncology and Diagnostic Sciences, School of Dentistry, University of Maryland, Baltimore, Baltimore, MD, United States*

[2]*Department of Microbiology and Immunology, School of Medicine, University of Maryland, Baltimore, Baltimore, MD, United States*

YOUNG REVIEWERS:

NOAH
AGE: 15

SAHASRA
AGE: 14

COVID-19 is the disease caused by the new coronavirus SARS-CoV-2. It has caused a lot of suffering and devastation around the globe. No vaccines or medications are available to treat this disease to date. In this article, we describe the mysterious emergence of this virus and explain how a virus that only infects animals begins to infect humans. Additionally, as this new virus continues to spread around the world, scientists are turning to an old medical remedy to help sick people. This therapy involves harvesting antibodies from the blood of people who have recovered from COVID-19 and passing these antibodies to people to protect them from getting the infection, or to treat them if they are sick. While scientists are earnestly working on developing a vaccine, could this old-fashioned technique buy us the time needed to develop new treatments?

OUTBREAK

Infection caused by a pathogen that spreads in a short period of time.

In 1918, the Spanish Flu, an **outbreak** caused by an influenza virus infected one-third of the world's population. Fortunately, the world has not witnessed a **pandemic** of such proportions since then ... until

now! COVID-19 is a respiratory disease that mysteriously emerged in December 2019 and has been wreaking havoc around the world. This devastating disease is caused by a coronavirus, the same class of virus that causes the common cold. But this new virus, named SARS-CoV-2, is not your typical coronavirus. In fact, at the time of writing this article, more than 11 million people have been infected worldwide, and more than 526,000 people have died. Can you believe that this devastation is caused by life's smallest creature? The world stands helpless, unable to fully control the virus's spread, despite all the scientific and medical advances we have made.

PANDEMIC

An outbreak that affects large populations, such as multiple countries or continents.

VIRUSES CAN MOVE FROM ANIMALS INTO PEOPLE

In December 2019, several patients in Wuhan, China were reported to be suffering from unknown viral pneumonia. Soon after, more patients in that city were diagnosed with the same disease. On January 9, scientists identified a new virus as the cause of the mysterious disease [1]. They found that the new virus belongs to a class of viruses called coronavirus, and so they named it SARS-CoV-2 [1]. The name comes from the disease it causes: **s**evere **a**cute **r**espiratory **s**yndrome; CoV stands for **co**rona**v**irus, and the number **2** was added because it is the second coronavirus that causes a serious respiratory disease [1].

Next, scientists examined the DNA of the virus they recovered from a sick person and the results were surprising. They discovered that the new virus infecting humans is very similar to a coronavirus found in bats (96% similarity) [2]. This outcome led them to think that the virus must have jumped from bats to humans [1]. But did SARS-CoV-2 jump directly from bats to humans? Or did it first infect an intermediate animal before it got to humans? So far, these questions remain unanswered, but scientists seem to agree that SARS-CoV-2 jumped from an animal to humans. The phenomenon in which a **pathogen** jumps between species (like from animals to humans) is known as **zoonotic spillover** [3, 4].

PATHOGEN

An organism that can cause disease in a host.

ZOONOTIC SPILLOVER

Term to describe the phenomenon where a pathogen that only affected a particular species of animals (bats) can infect humans. Mostly as a consequence of close inter-species interactions.

SARS-CoV-2 is not the first example of zoonotic spillover to cause problems for humans. In 2002, a virus called severe acute respiratory syndrome coronavirus (SARS-CoV) emerged as a pathogen. Interestingly,it was also found to have jumped to humans from bats. In just a few months, the virus infected over 8,000 people and killed roughly 10% of those infected [1]. However, by 2003, SARS-CoV suddenly disappeared. By 2012, another coronavirus emerged: Middle East respiratory syndrome coronavirus (MERS-CoV). MERS-CoV was also a result of zoonotic spillover from bats [1]. Fortunately, MERS-CoV did not spread around the world, mostly because the virus was not highly infectious. On the other hand, the MERS-CoV **mortality rate** of around 35% makes it one of the deadliest pathogens to date.

MORTALITY RATE

Represents the number of deaths in a particular location in a given time.

As of now, the mortality rate for COVID-19 is low (~4%). In contrast to the previous epidemics, SARS-CoV-2 is extremely efficient at spreading among people. The virus can survive for hours on surfaces, and this allows for a high level of transmission. Most concerning is the recent realization that most people who are infected do not feel sick for a long time, so they are not aware they are infected. When they are still feeling ok, they could be spreading the virus to others. Since SARS-CoV-2 is essentially new to humans, we do not have baseline defenses in place to rapidly and efficiently combat the virus upon infection. Put together, these factors made a recipe for a world-shattering pandemic of massive proportions.

DO NOT BLAME THE BATS

Scientists agree that although bats are the likely source of coronaviruses, the spillover from bats is the result of human activity. How? Well, when bats are hunted, their **immune system** gets stressed and allows the viruses that live in them to increase in number and spillover into the environment [5]. Another point is that when humans are sick and have fever, most viruses do not survive because they cannot tolerate high temperature. But when bats fly, their body temperature goes up, and so viruses that live in them have to adapt to tolerate higher temperatures. As a result, when these viruses infect humans, they can now survive and cause disease [5].

IMMUNE SYSTEM

A complex group of host cells and cell-forming tissues that orchestrate defense mechanisms against foreign pathogens to prevent and combat disease.

HOW DO WE STOP A PANDEMIC?

Stopping the spread of an efficient virus is close to impossible. The most effective way to protect people against infection is through vaccination. When you are infected with a pathogen, your immune system is alerted to the presence of a foreign invader. In response, your white blood cells produce molecules called antibodies. These antibodies can neutralize the pathogen and help your body to eliminate it. Fortunately, once produced, antibodies usually stay with us for a long time. So, if your antibodies see the same pathogen again, they will quickly neutralize it before it makes you sick.

Learning how the immune system works has led to the development of **vaccines**. How so? Well, a vaccine is basically a formulation made from a pathogen that was rendered harmless. Sometimes vaccines are made with a small piece of the pathogen. Even if the pathogen is harmless, the immune system perceives the pathogen in the vaccine as a threat and makes antibodies against it. Therefore, vaccination is a clever strategy to trick the immune system into producing antibodies that can protect us if we encounter the real pathogen. Researchers all over the world are intensely working on developing vaccines against COVID-19, but this work takes a lot of time. In the meantime, scientists have been trying to find a way to help COVID-19-infected patients.

VACCINE

Substance designed to stimulate the immune system to protect against pathogens. It is generally made with a killed pathogen (or its components) to induce production of antibodies against that specific pathogen.

Luckily for us, they have found an old technique that was used in previous pandemics. Could this old-fashioned therapy buy us time until we develop a vaccine?

FIGHTING COVID-19 WITH THE HELP OF RECOVERED PATIENTS

CONVALESCENT PLASMA THERAPY

Medical treatment against pathogens that consists of the transfer of antibodies from the blood plasma of a convalescent (recovered) individual to an ill individual. It has the purpose of transferring immune protection against pathogens.

Have you ever heard of **convalescent plasma therapy**? It is a kind of treatment that was used during the previously discussed Spanish Flu pandemic. More recently, it was successfully used during the 2009–2010 H1N1 influenza virus pandemic, as well as the in the Ebola epidemic of 2013 [1]. Simply put, it is the transfer of blood plasma from someone with antibodies against a pathogen into other people, in order to protect them from infection with that pathogen [6]. The antibodies our bodies make are present in the plasma component of the blood. So, if you get plasma from a person who was infected with the virus, that plasma is likely to already contain antibodies against that specific virus. This plasma is called "convalescent" because it is taken from recovered (convalescent) patients. Thus, when you give convalescent plasma to a sick person, that person will be getting antibodies that are ready to go fight the virus. Typically, takes weeks for people to produce their own antibodies after they are infected. In the meantime, the virus can replicate, making patients more and more ill. Therefore, giving plasma with antibodies made by another person could save the lives of patients.

A good thing about COVID-19 is that, according to the data, most infected people can recover from it. It is likely that people who recover become immune to the virus, thanks to the antibodies they produced that remain in their blood plasma [6]. Plasma harvested from convalescent COVID-19 patients, containing antibodies against SARS-CoV-2, can be used in two ways, as illustrated in Figure 1. The antibody-containing plasma could be used for prevention, which means giving high-risk people plasma before they get infected, to protect them from getting COVID-19. Moreover, the plasma could be used to treat patients who are *already* infected but are not fighting the virus well.

WHAT HAVE WE LEARNED?

Recently, we have witnessed the emergence of three coronaviruses that have caused significant mortality in humans. Sadly, one thing is for certain: SARS-CoV-2 will not be the last. Therefore, we need to increase surveillance of viruses in animals, which will helpful us understand what causes zoonotic spillovers and how to prevent them. As the COVID-19 pandemic expands, the big question is, can we develop a vaccine soon to stop this pandemic?

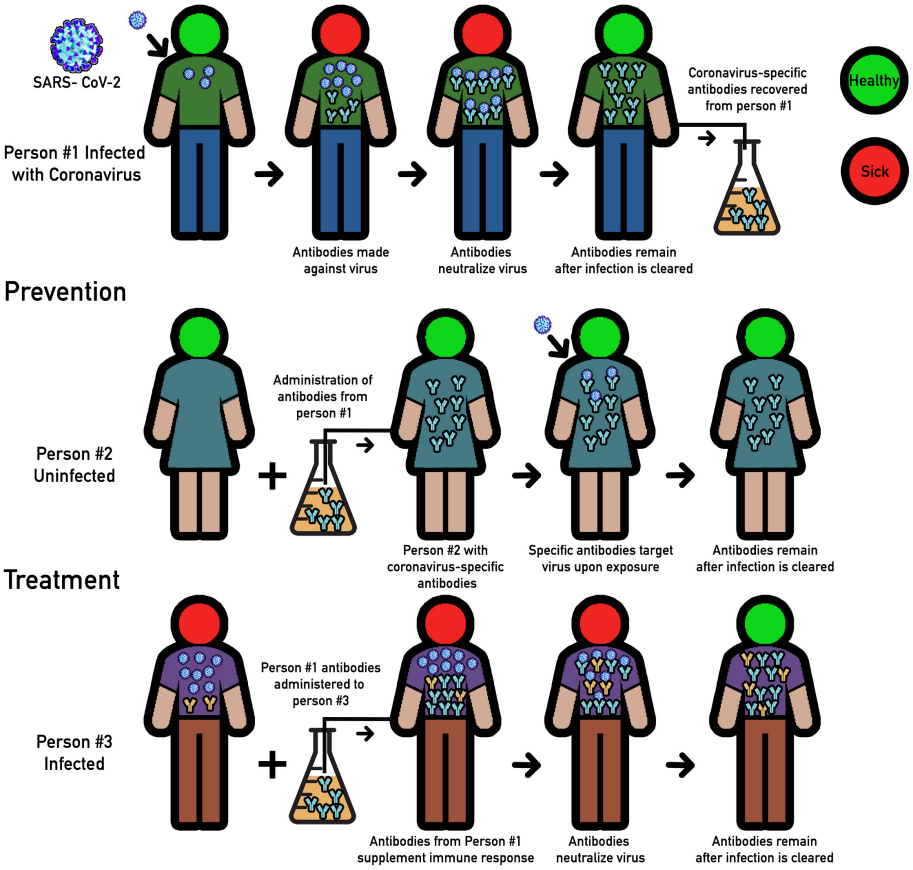

Figure 1

Convalescent plasma therapy. Person #1 represents a patient who gets infected with SARS-CoV-2. Upon infection, Person #1 produces specific antibodies (blue "Y"s) that neutralize the virus. Once recovered, the antibodies remain in the blood plasma. These antibodies can be used for two therapeutic purposes: prevention (see Person #2) and treatment (see Person #3). Person #2 represents someone who is highly susceptible to infection. Using antibodies from Person #1, Person #2 acquires immunity. Person #3 represents a patient who is ill with the virus. Antibodies from Person #1 help Person #3 to clear infection.

It is unlikely that a successful vaccine will become available very soon; fortunately however, transferring antibodies from recovered patients to those at risk can save lives. In fact, convalescent plasma therapy against COVID-19 is now being tested as a way to treat very ill patients, with promising results [7, 8]. The other important questions we should be asking are can we learn what caused the pandemic? Could we use this knowledge to prevent future pandemics? And will we be better prepared to deal with the next pandemic? Most importantly, humans should consider this pandemic as a warning that damaging our environment, and destroying natural habitats of animals like bats, can also endanger human life.

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CONFLICT OF INTEREST: 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

NOAH, AGE: 15
My favorite subjects at school are physics—particularly nuclear physics—and drama. Outside of school, I play guitar and have an unhealthy obsession with Green Day. After school, I would love to be an actor or nuclear physicist. I have a weird sense of humor and therefore apologize in advance if you ever meet me.

SAHASRA, AGE: 14

Hello, I am Sahasra, rising tenth 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.

AUTHORS

DANIEL MONTELONGO-JAUREGUI

I am a researcher in the field of Microbiology and Immunology at the University of Maryland, Baltimore. I study how pathogens make us ill with the goal of identifying new therapies. Aside from the lab, I love playing sports, riding my bike and listening to music. *dmontelongo@umaryland.edu; orcid.org/0000-0001-6079-4277

AHMED S. SULTAN

I am a Clinical Assistant Professor at the University of Maryland, Baltimore and I am a specialist in the fields of Oral Medicine and Oral Pathology. I am also a research scientist and my work is focused on understanding infections of the mouth and how to treat them. I enjoy fishing and my friends consider me an up-and-coming food critic! orcid.org/0000-0001-5286-4562

TAISSA VILA

I am a senior research scientist in Microbiology and Immunology at the University of Maryland, Baltimore. My research aims to understand why infections caused by multiple pathogens are more serious and difficult to treat than those caused by only one infectious agent. I am also a coffee lover and in my free time I enjoy reading. orcid.org/0000-0001-5600-4367

MARY ANN JABRA-RIZK

I am a Professor of Microbiology and Immunology at the University of Maryland, Baltimore. My research focuses on understanding the host-pathogen interactions that influence the development of infectious diseases. When not doing science, I enjoy reading, gardening, knitting, and watching movies. orcid.org/0000-0002-4425-3873

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HEALTH
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CLOSTRIDIUM DIFFICILE: BACTERIA THAT CAN INFECT PEOPLE TAKING ANTIBIOTICS

Michel Delmée *

Faculty of Medicine, Université Catholique de Louvain, Brussels, Belgium

YOUNG REVIEWER:

ETHAN

AGE: 15

If I ask you what antibiotics are for, you will probably say that they are used to treat infections, by killing the bacteria responsible for those infections. Well, in this article I will explain to you that there are some circumstances in which antibiotic treatment may instead cause an infection. The microbe responsible for this infection is called *Clostridium difficile*. I will explain which is this curious microbe, how and when it causes an infection, why antibiotics are implicated and how we can treat it ...

CLOSTRIDIUM DIFFICILE AND ITS FAMILY

Clostridium difficile belongs to a family of bacteria that are among the deadliest microbes on earth. Another member of the family, *Clostridium tetani* causes tetanus; *Clostridium botulinum* is responsible for a deadly disease called botulism; and *Clostridium perfringens* is the main cause of gas gangrene. All these bacteria can kill a human within a few hours! Fortunately, *C. difficile* does not kill as easily as its family members but unfortunately it is much

more common and has become one of the most frequent pathogens encountered in hospitals [1, 2].

CLOSTRIDIUM

A bacterial genus including pathogenic species which are anaerobic, produce toxins, and can form spores.

All members of the **Clostridium** family share three properties that explain why they are so dangerous. First, they are anaerobic bacteria. This means that they cannot survive in the presence of oxygen—they can only grow where oxygen is absent. There is one important place in the body where oxygen is absent: our intestines. That is where *C. difficile* can be found.

SPORE

A thick shell made of proteins which allows *Clostridium* to protect themselves against external threats.

Second, members of the *Clostridium* family can form **spores**. A spore is a way for these bacteria to survive every time they are threatened by the environment. Whenever the bacterial cell faces a mortal enemy, like the presence of oxygen, extreme heat, or even an antibiotic, it produces a thick shell and locks itself inside. The bacterium can remain inactive for months or even years! When the environment becomes less hostile, the spore will turn back into an active bacterium and regain the ability to multiply.

TOXINS

Molecules secreted by bacteria that specifically target human or animal cells inducing a toxic effect.

Last, bacteria of the *Clostridium* family produce **toxins**. Toxins are poisons produced by the bacteria, which can recognize and attack specific targets in the human body. In tetanus and botulism, the toxins attack the nerves and cause paralysis, while the toxins of *C. difficile* target the intestinal lining and cause diarrhea.

WHAT DISEASE DOES *CLOSTRIDIUM DIFFICILE* CAUSE?

C. difficile is responsible for severe diarrhea that is associated with damaged tissue in the lining of the colon, which is the final part of the large intestine. Once these bacteria begin to multiply, they secrete toxins that attack the surface of the intestines and destroy the cells [3]. This causes severe inflammation and bleeding. Since the intestinal lining is made to prevent liquids from escaping from the body, its destruction by the toxins creates leaks that spill liquid into the intestines, resulting in diarrhea (Figure 1). However, the most surprising feature of *C. difficile* is that many people contact these bacteria (by eating contaminated meat or vegetables) yet they do *not* suffer from diarrhea. Why?

The intestines are an interesting part of the body. There are billions of bacteria living in the intestines. If you took a gram of fecal matter and counted the number of microorganisms, you would count more than 10,000 billion cells! The number of bacteria in the intestines is higher than the number of human cells that make up the body! These intestinal bacteria belong to hundreds of different species. Most are anaerobic, which is not surprising since there is almost no oxygen in the intestines.

Figure 1

C. difficile secretes toxins that damage the intestinal lining. When cells of the lining die, water, and blood can leak into the intestine (represented by the dotted line), causing diarrhea.

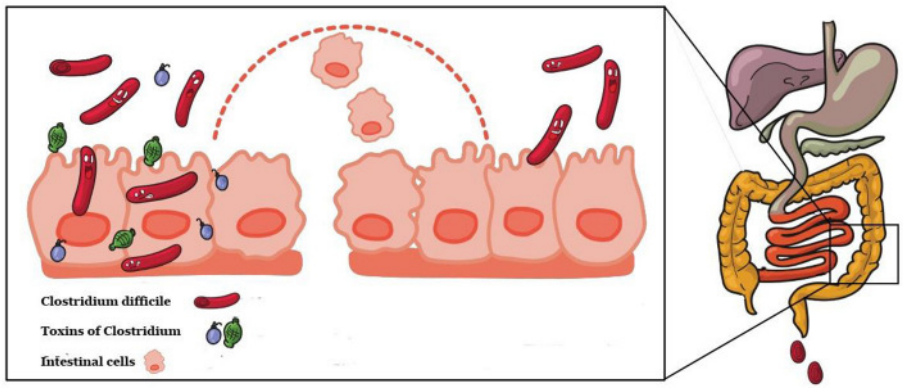

Figure 1

Figure 2

The normal colonic flora is composed of billions of microorganisms (purple). When the colonic flora is healthy, *C. difficile* has nowhere to live and is carried through the intestines and out of the body.

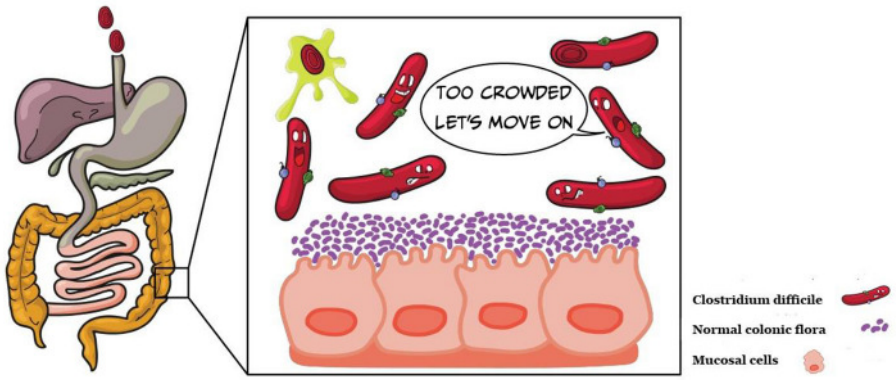

Figure 2

COLONIC FLORA

The collection of billions of bacteria contained in the intestine.

This huge population of microorganisms makes up what is called the **colonic flora**. The colonic flora plays many important roles. In fact, a human being could not survive without this flora. One crucial role of the colonic flora is to prevent invasion by unfriendly bacteria. In other words, when a pathogenic bacterium like *C. difficile* arrives in the intestines, it faces so many bacteria of the colonic flora that there is no place to multiply and produce its toxins, so it passes through the intestines and out of the body (Figure 2). However, there are circumstances in which the colonic flora is disturbed or partially destroyed. This happens most commonly when we take antibiotics to treat an infection.

ANTIBIOTICS: BOTH GOOD AND BAD

In the 1920s, an English microbiologist named Alexander Fleming observed a curious phenomenon: when trying to grow bacteria, he saw that a mold had developed in some of his tubes. Surprisingly, in the tubes with the mold, the bacteria did not grow and were even killed. After a lot of work, he identified a molecule that was produced by the mold, which could kill the bacteria. Since the mold was a fungus called *Penicillium*, he named the molecule penicillin. This was the

Figure 3

When the colonic flora has been damaged by antibiotics, *C. difficile* has room to multiply. The dividing bacteria will produce toxins that damage the intestinal cells and cause diarrhea.

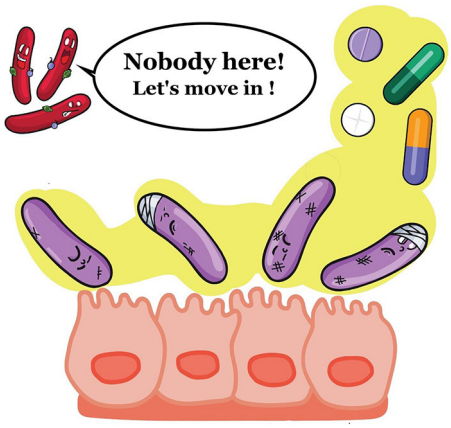

Figure 3

ANTIBIOTICS

A drug that specifically kills bacteria and is used to treat bacterial infections.

first antibiotic. **Antibiotics** are a class of drugs that can specifically kill bacteria. When a human or an animal is suffering from a bacterial infection, the first line of therapy is most often an antibiotic. Antibiotics have been "best sellers" in pharmacies all over the world for the past 80 years. This is the "good side" of antibiotics.

However, antibiotic therapy has some major drawbacks, too. Imagine you wake up tomorrow morning with a sore throat that prevents you from swallowing. You visit your doctor and he diagnoses a bacterial infection and gives you penicillin. Thanks to this wonderful drug, you will be healed 2 days later. But there is a downside! When you take an antibiotic, the drug is absorbed by your intestines into your blood. The blood passes into your throat and the antibiotic carried by the blood kills all the susceptible bacteria that it meets, including those that caused your sore throat. But the antibiotic also kills a lot of other bacteria in your body, including some of those in your intestines. Most antibiotics disturb the colonic flora. This is not usually a reason to panic. The intestinal flora will gradually return to a normal state, but it can take up to a few weeks. However, problems can occur if a person encounters a pathogenic bacteria like *C. difficile* while the intestinal flora is still recovering.

CLOSTRIDIUM DIFFICILE IN HOSPITALS

As mentioned earlier, in most cases if you encounter *C. difficile* in your meal nothing will happen … except if you have recently taken antibiotics. Without your protective colonic flora, *C. difficile* can grow in your intestines, produce a lot of toxins, and cause inflammation and diarrhea (Figure 3). Fortunately, the probability of encountering *C. difficile* in your food is very low, so the chances of developing *C. difficile* diarrhea when you take antibiotics are relatively small.

In hospitals, however, the situation is quite different. Hospitals are places where many patients receive antibiotics. So, outbreaks of diarrhea caused by *C. difficile* occur more frequently in hospitals. When a bedridden patient develops diarrhea, it is easy for the environment (floor, bed, tables, sheets, etc.) to become contaminated with *C. difficile*. Remember how bacteria in the *Clostridium* family can form spores? If *C. difficile* from the feces contaminates patient's room, these bacteria can forms spores that can persist in the hospital environment for a long time, possibly infecting the next patient occupying the room. *C. difficile* outbreaks can be prevented by isolating patients who have diarrhea. If patients are kept alone in their hospital rooms and a thorough daily cleaning of the whole environment is performed with bleach-containing products, spores can be eliminated and spread of *C. difficile* diarrhea can be stopped.

HOW IS *CLOSTRIDIUM DIFFICILE* TREATED?

Fortunately, there are a few antibiotics that act specifically against *C. difficile* and these can be used to treat infected people. In about 20% of the cases however, the infection may relapse, meaning that it returns after treatment. Sometimes multiple relapses may occur [4]. The main way to help people with relapsing *C. difficile* is to restore their normal colonic flora. This can be done with probiotics, for example. Probiotics are pills or capsules containing microorganisms that have been selected and grown in laboratories because they are known to grow well in the intestines and can restore normal colonic flora.

A few years ago, a doctor had a different idea for restoring the colonic flora of a patient suffering relapsing *C. difficile* diarrhea. Why not restore the damaged colonic flora with the help of the flora from a healthy person who has not taken antibiotics? A team of doctors in the Netherlands did this … and it worked! They took 250 g of feces from a healthy person and diluted it in water. Then, they inserted it into the patient's intestines with a tube called a catheter. Most patients were cured! So now we know that fecal transplant is an effective technique for treating patients with relapsing *C. difficile* diarrhea.

CONCLUSION

In this article you have been introduced to a bacteria that can only cause an infection in a human who has taken antibiotics. This is very surprising since antibiotics are meant to treat infections! This bacteria is called *C. difficile* and, in contrast to most other bacteria, can protect itself against antibiotics by forming a spore.

The main lesson to be learned from this article is that antibiotics are valuable medicines that should always be used wisely and only when absolutely necessary.

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YOUNG REVIEWER

ETHAN, AGE: 15
Hi! My name is Ethan. At my regional science fair, I won Best Junior Project, Best Biology Project, Gold Medal, and a qualification to the Canada-Wide Science Fair, where I achieved a bronze medal. I have also been a finalist at the InspoScience Canada IRIC. Besides, I enjoy debating, having won the title of national champion

and second speaker this past year, and public speaking. I am an avid writer, being published for my poems, short stories, and argumentative articles.

AUTHOR

MICHEL DELMÉE

I became a doctor of medicine in 1978 and I was immediately passionate about microbiology which became my specialty. I did a doctoral thesis on this *Clostridium difficile* bacteria (which had just been discovered in 1978) which I presented in 1989. I became professor of microbiology at the university in 1993. I then taught microbiology to medical students while continuing doing research in a laboratory that I actually created in 1990 already. I still work there today as a professor emeritus. *michel.delmee@uclouvain.be

frontiers FOR YOUNG MINDS

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SEPSIS: WHEN A SIMPLE INFECTION BECOMES DEADLY

Andrew G. Farthing[1†], Jessie Howell[1†], J. Kenneth Baillie[2], Taya Forde[3], Alice Garrett[1], Carl S. Goodyear[4], Jennifer Gracie[1,5], Colin Graham[6], Tansy C. Hammarton[4], Michael E. Murphy[7,8], William J. Peveler[5], Simon Pybus[7], Mohammad Saiful Islam Sajib[3], Gill Thomson[6] and Melanie Jimenez[1*]

[1] *James Watt School of Engineering, University of Glasgow, Glasgow, United Kingdom*

[2] *Genetics and Genomics, Roslin Institute, University of Edinburgh, Edinburgh, United Kingdom*

[3] *Institute of Biodiversity, Animal Health & Comparative Medicine, University of Glasgow, Glasgow, United Kingdom*

[4] *Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, United Kingdom*

[5] *School of Chemistry, University of Glasgow, Glasgow, United Kingdom*

[6] *Sepsis Research FEAT, Glasgow, United Kingdom*

[7] *National Health Service Greater Glasgow and Clyde Glasgow Royal Infirmary, Clinical Microbiology, Glasgow, United Kingdom*

[8] *School of Medicine, Dentistry and Nursing, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom*

YOUNG REVIEWERS:

ETHAN
AGE: 15

JADA
AGE: 14

JOSHUA
AGE: 14

The immune system plays a crucial role in maintaining a healthy body by working around the clock to recognize and respond to infection. Inflammation is part of the immune system's protective response to an infection. The inflammatory response is incredibly powerful, so much so that it can damage the body's cells if it is not tightly controlled. Sometimes, inflammation affects the whole body—this is called sepsis. The powerful and complex mechanisms in place to wipe out the infection can cause serious damage to healthy cells and

tissues. Uncontrolled inflammation can cause irreversible damage to the body's organs, such as the kidneys, eventually causing organs to shut down. If sepsis is not treated rapidly, it can lead to death. In this article, we describe the symptoms and diagnosis of sepsis and some of the current research being performed to better understand this dangerous process.

SEPSIS: A DANGEROUS RESPONSE TO AN INFECTION

SEPSIS

An illness where the body's immune system overreacts to a simple infection.

PATHOGEN

An infectious agent that can make us sick and cause disease. Bacteria, fungi, parasites, and viruses are examples of pathogens.

Sepsis is an illness where the body overreacts to a simple infection. Sepsis is responsible for about 11 million deaths per year worldwide. This accounts for roughly 20% of all global deaths, which is even more than from breast and bowel cancers combined [1].

Sepsis is caused by an infection from invading **pathogens**, such as viruses, bacteria, parasites, or fungi, which either come from the environment or even from within our own bodies. Common infections that can lead to sepsis include meningitis (infection of the linings of the brain), pneumonia (infection of the lungs), urinary tract infections (infections of the bladder or kidneys) and cellulitis (infection of the skin, often affecting the foot and leg). However, an infection anywhere in the body has the potential to cause sepsis.

The symptoms of sepsis include[1]

- Fever (high temperature)
- Difficulty breathing
- Rapid heart rate
- Decreased urine production
- Confusion and/or slurred speech
- Cold and/or blotchy hands and feet (mottled skin)

Once sepsis begins, deterioration in physical health can happen incredibly quickly—in just a few hours—so it is crucial to recognize the symptoms of sepsis before it is too late. To understand sepsis and its symptoms, we need to look at the immune system, to see how it works normally and what goes wrong during sepsis.

[1] https://www.sepsisresearch.org.uk/about-us/what-is-sepsis/

THE IMMUNE SYSTEM AND INFLAMMATION

The immune system consists of a very complex network of different chemicals and cells, all working together to recognize dangerous pathogens, kill them, neutralize their toxins, and maintain a healthy body. To do this, the body has two weapons, which scientists call the innate immune system and the adaptive immune system. Think of them like a grenade and a sniper: the innate immune system

damages whatever is in range, while the adaptive immune system homes in with precision, as a sniper would hunt down an enemy. We will focus on the innate immune system. The innate immune system acts immediately and locally; it rapidly employs a cocktail of potent chemicals and mechanisms to contain the infection before it has a chance to do any significant damage. When the innate immune system senses the presence of a pathogen, immune cells send out chemical signals to warn other cells of an invasion and release a host of toxic chemicals to try and kill the invading pathogen. **Inflammation** is one of the mechanisms used by the innate immune system to fight infections.

Think of getting a papercut: microscopic pathogens enter the wound and it becomes swollen and sore; that means there is inflammation. Inflammation is necessary to help the body recover from injury and infection [2]. An inflammatory immune response causes **vasodilation** and increased **vascular permeability** at the wound site, meaning blood vessels dilate (widen) and become leaky, causing blood flow to slow down in that area. At the site of inflammation, special proteins, called **receptors**, are produced on the inside of blood vessels that act like hooks to capture cells of the immune system as they pass by. Slower blood flow makes it easier for more of these cells to get to the site of injury/infection, and the leaky blood vessels help them to pass through blood vessel walls into the site of infection.

INFLAMMATION

A response by the body's immune system to fight an infection. Characterized by heat, pain, redness, and swelling.

VASODILATION

When blood vessels become wider as part of the inflammatory response.

VASCULAR PERMEABILITY

Leaky blood vessels, which allow immune cells to get into the surrounding tissue as part of an inflammatory response.

RECEPTOR

A protein naturally found on the surface of cells and blood vessels which are able to bind and capture cells and pathogens. They can be adapted for research purposes.

SYSTEMIC

Relating to the whole body as opposed to a single location.

SEPSIS: WHEN INFLAMMATION GOES WRONG

The exact cause of sepsis is not known. Most of the time, the immune system can efficiently take care of an infection without a problem. However, during sepsis, the inflammatory response of the innate immune system is not restricted to the location of the infection—it "goes rogue," leading to **systemic** inflammation, which is inflammation all over the body. Instead of being contained at the site of infection, inflammatory chemicals are released into the bloodstream and travel throughout the body, where they cause widespread vasodilation and increased vascular permeability in the blood vessels. This results in a drop in blood pressure, which causes inadequate blood flow to the body's tissues and organs. Blood transports oxygen to the organs, so a lack of blood flow decreases the amount of oxygen organs receive, affecting their functions.

Systemic inflammation and decreased blood flow cause a range of serious symptoms. Each of the organs can be affected in a unique way. To compensate for the inadequate blood flow, the heart and lungs must work much harder to supply the tissues with oxygenated blood, resulting in a faster heart rate and breathing difficulties. Furthermore, the lungs become less efficient at oxygenating the blood, as inflammation causes fluid to collect in the lung cavities and

Figure 1

Normal inflammation compared to sepsis. In a normal inflammatory response, a person with an injured hand would experience symptoms only in the area around the wound. However, in sepsis, the response affects the entire body and can be extremely dangerous, sometimes leading to organ failure and death.

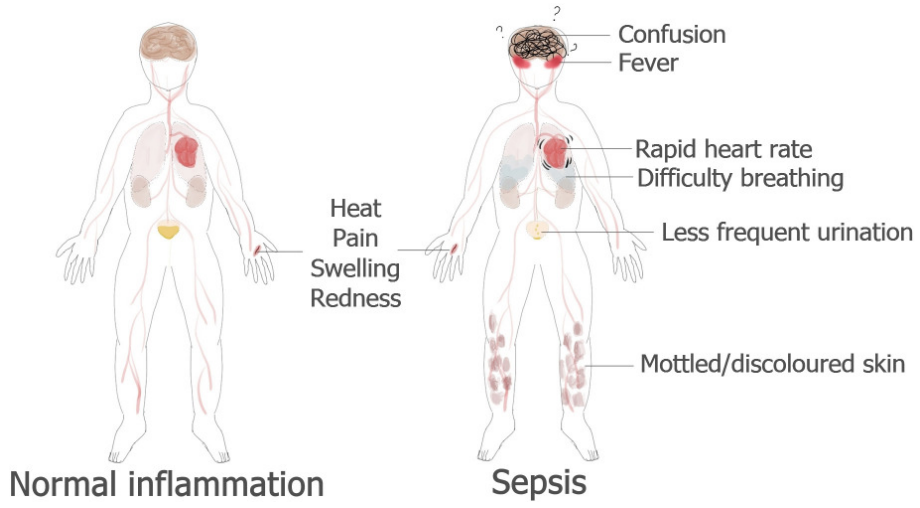

Figure 1

tissues. This means that less oxygen is available in the blood for the body's organs.

The kidneys are responsible for filtering excess water and toxins out of the blood, in the form of urine. Sepsis-associated inflammation and impaired blood flow affect the kidneys' ability to clean the blood and make urine. Pale or mottled skin is a sign that the skin is not getting enough oxygenated blood. Confusion and slurred speech in sepsis patients are caused by changes happening in the brain. Scientists do not know for sure why confusion happens in sepsis, but they think it might have to do with the brain not getting enough oxygen, or it might be caused by chemicals released by cells of the immune system [2]. When inflammatory signals reach the hypothalamus, an area of the brain that regulates body temperature, this causes fever. Fever is a common sign of an inflammatory response to infection; the patient will have an elevated temperature, whilst feeling hot and flushed or cold and shivery [3, 4].

These are all examples of ways sepsis can affect the body (Figure 1), but sepsis is much more dangerous than this. Importantly, during sepsis, normal organ functions can only be sustained for a limited time before the organs become irreversibly damaged and start shutting down, eventually leading to death.

HOW DO WE DIAGNOSE AND TREAT SEPSIS?

Scientists have shown that time is critical in treating patients with sepsis. The earlier the treatment, the better their chances of survival. Figure 2 provides a summary of the tests used to diagnose sepsis.

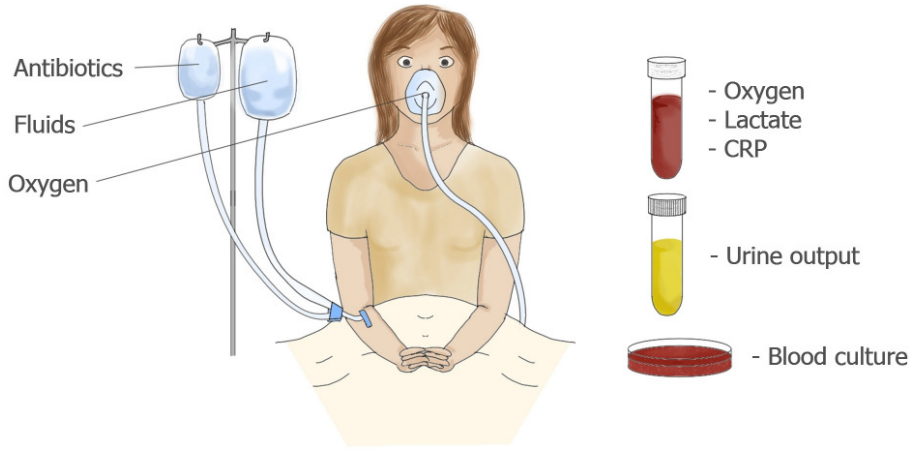

Figure 2

A patient with suspected sepsis may be given intravenous fluids and oxygen. Urine output and the levels of oxygen, lactate, and C-reactive protein (CRP) in the blood are monitored, to assess the severity of infection. Broad-spectrum antibiotics are used as a first line of defense. To identify the pathogen, a blood sample is cultured until the pathogen reaches a concentration that can be detected. Only at this point can the patient be treated with specific antibiotics.

ANTIBIOTIC

A drug that targets bacteria. Some antibiotics are broad spectrum, meaning they work on lots of bacteria, whereas some are more specific.

Patients suspected of having sepsis are kept under close observation. Blood pressure and blood oxygen content are monitored. Urine output is monitored to make sure the kidneys are functioning properly. Patients are immediately treated with broad-spectrum **antibiotics**, to try to kill the pathogens that might be responsible for the infection. They might also receive oxygen or fluids, depending on their condition. Blood will also be taken for laboratory tests to diagnose sepsis. Several molecules in the blood can indicate what is happening in the body. These include C-reactive protein, which is produced by innate inflammatory cells, procalcitonin, which suggests the presence of a bacterial infection (as opposed to viral or fungal infections), and lactate, which is produced in high levels when the body's cells are under stress.

Another test done on patients with suspected sepsis is to try to find pathogens in their blood. Because a blood sample has a really high number of blood cells, finding pathogens can be like finding a needle in a haystack; the blood sample must first be cultured for 1–5 days, until the number of pathogens reaches a concentration high enough that they can be identified. Once the pathogen is identified, the patient can be given antibiotics that can specifically kill the pathogen responsible for the infection. This is a time-consuming process that we, as researchers, aim to improve. Quick identification of the pathogen causing the infection would allow patients to receive the most appropriate treatment more rapidly.

CURRENT SEPSIS RESEARCH

To find pathogens in blood samples, we are engineering microscopic magnetic beads that can recognize various pathogens. When we mix these beads with a blood sample from a patient, the beads will bind to the pathogens and, thanks to the magnetic properties of the beads, we can remove the beads and the pathogens with a magnet (Figure 3A).

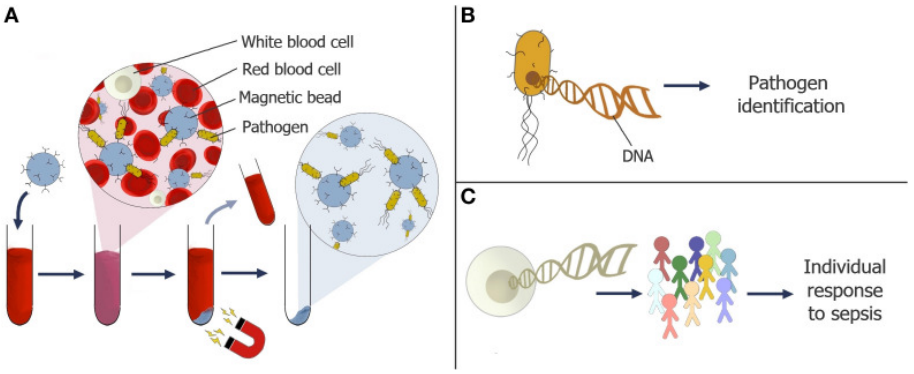

Figure 3

Figure 3

(A) Magnetic particles coated in receptors are being developed to capture pathogens in a blood sample. The pathogens can be separated along with the particles, using a magnet. **(B)** DNA can be removed from the pathogens and "read" to determine the identity of the pathogen and whether it is resistant to any antibiotics [5]. **(C)** Patterns in human DNA can also be studied to better understand why some people develop sepsis while others do not.

Although our beads will bind to the pathogens, we still need to identify the pathogens once they are separated from the blood sample. We do that by extracting and sequencing DNA and then looking for genetic information that is unique to pathogens, kind of like reading a barcode (Figure 3B). With the help of some sophisticated software [5], we can determine not only the identity of the pathogen but also to how it might react to various treatments. This part of our work aims to help doctors know, as quickly as possible, what might have caused sepsis and what the best treatment for a patient is.

Importantly, identifying the pathogen is not the only key to a patient's survival. We are still trying to understand why an infection might turn into sepsis for one person and not for another. In a separate study, we are studying human DNA sequences from blood samples of many sepsis patients, to see if we can recognize specific patterns for people who have had sepsis. Using powerful computers, we are trying to identify what these patients have in common (Figure 3C). The goal of our research is to better understand why some people are more at risk of sepsis than others, and to make sure they can receive the best treatments as quickly as possible if they do have sepsis.

CONCLUSION

The immune response is crucial for maintaining a healthy body. However, systemic inflammation can cause some very serious problems, which are seen in the case of sepsis. Sepsis can eventually cause multiple organ failure and death, but this can be avoided if sepsis is rapidly diagnosed and doctors quickly prescribe the right treatment to target the pathogen. The good news is that, if doctors give the right treatment quickly, most people will get better; therefore it is incredibly important that everyone learns to recognize the signs of sepsis. Hopefully, our research will help doctors to diagnose sepsis more rapidly providing patients with faster and more specific treatment. As time is crucial when treating patients with sepsis, this research may help to save the lives of many people.

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YOUNG REVIEWERS

ETHAN, AGE: 15

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Canada IRIC. Besides, I enjoy debating, having won the title of national champion and second speaker this past year, and public speaking. I am an avid writer, being published for my poems, short stories, and argumentative articles.

JADA, AGE: 14

Hi! My name is Jada from Atlanta, GA. In my free time, I like to draw/sketch, listen to music, write short stories, and watch an array of movies. I play lacrosse, and I swam for about 5 years. When I become older, I want to be a Cosmetic Plastic Surgeon because I want to make all of my patients proud of their bodies and not insecure about themselves. Helping others is one of my motivations in life!!!

JOSHUA, AGE: 14

I am a rising ninth grader and I live in Atlanta, Georgia. During the academic school year I participate in many programs including the Academic team and the Lacrosse team. When I am not studying or at school I love to read books and play lacrosse. I am happy to be a part of this program because I enjoy science, and I am happy that my feedback is so important in helping people publish their articles.

AUTHORS

ANDREW G. FARTHING

Andrew Farthing is a Ph.D. student at the University of Glasgow, UK. His research is focused on developing new methods to rapidly enrich pathogens from blood samples to speed up the process of pathogen identification for people suspected of having sepsis. The faster the identity of the pathogen can be found, the sooner a patient can be treated with antibiotics that specifically target their infection.

JESSIE HOWELL

Jessie Howell is a Ph.D. student at the University of Glasgow, UK. She has a background in immunity and infection and is currently developing methods to separate parasites based on their size and shape. Isolating pure populations of cells makes studying them much easier, aiding further research into their mechanisms of infection and methods of treatment.

J. KENNETH BAILLIE

Dr. Kenneth Baillie is a consultant in the intensive care unit at the Royal Infirmary, Edinburgh, and leads a research programme at the Roslin Institute, University of Edinburgh, to better understand the role of genomics in critical care medicine. He completed basic training in medicine in Glasgow and in anesthesia in Edinburgh. During this time, he led a series of high-altitude research projects in Bolivia and founded a high-altitude research charity, Apex. Currently, Kenny's research group works on topics, such as sepsis, influenza, and COVID-19.

TAYA FORDE

Dr. Taya Forde is a veterinary researcher who uses bacterial sequence data to address questions related to pathogen transmission. Many of her studies are at the interface between humans, animals, and the environment, a concept known as "One Health." She is interested in developing methods to sequence pathogens directly

from patients' blood—be it humans or animals—to rapidly determine the cause of sepsis and identify antimicrobial resistance genes.

ALICE GARRETT

Alice Garrett is a biomedical engineering Ph.D. student at the University of Glasgow, UK, who has worked on new platforms to aid the molecular detection of pathogens. Her work focuses on finding solutions for point-of-care tests that detect pathogen DNA, to diagnose diseases, such as malaria and schistosomiasis in rural areas with limited access to healthcare. Alice is currently working on the frontlines, processing molecular tests in the laboratory to screen for COVID-19.

CARL S. GOODYEAR

Prof. Carl Goodyear's research group at the University of Glasgow is focused on understanding immunopathogenesis of diseases like arthritis, and translating this knowledge into therapeutic agents for patients. In parallel, he also leads a Translational Immunology programme, which provides the critical interface between clinical and basic science.

JENNIFER GRACIE

Dr. Jennifer Gracie is a research associate at the University of Glasgow, where she is developing a test to speed up the diagnosis of sepsis in hospitals. Using her experience in nanotechnology and chemistry, alongside colleagues with expertise in biology and biomedical engineering, she hopes to reduce the time taken to diagnose sepsis in critically ill patients. Jenny's background is in chemistry, and she obtained Ph.D. and master's degrees from the University of Strathclyde.

COLIN GRAHAM

Colin Graham joined Sepsis Research in October 2018, as the charity's first Chief Operating Officer. He is responsible for developing awareness of the charity, overseeing its fundraising and marketing strategy, and developing strategic partnerships. Prior to joining Sepsis Research, Colin worked as the CEO at Cancer Support Scotland, as area fundraising manager for Breast Cancer Care, and as head of fundraising for Erskine Hospital. He started his career as a fundraiser for Macmillan Cancer Care.

TANSY C. HAMMARTON

Dr. Tansy Hammarton is a senior lecturer and parasitologist at the University of Glasgow, Scotland. Her lab studies tiny parasites that cause the nasty and often fatal tropical diseases called sleeping sickness and leishmaniasis, which affect some of the worlds' poorest people. Her group researches how these parasites grow and multiply, and tries to identify essential molecules that could be targeted by novel drugs. Tansy also really enjoys discussing science with members of the public, especially school pupils.

MICHAEL E. MURPHY

Dr. Michael E. Murphy trained as a medical doctor and became interested in infection, undertaking further specialized training in London, Oxford, and Cambridge, as well as periods working in Tanzania, South Africa, and India. He returned to Glasgow, where he works as a consultant microbiologist at the hospital, diagnosing and treating patients with infections. He is also a researcher at the University of Glasgow, with

an interest in using technological advances to speed up the diagnosis of a wide range of infections, as well as evaluating how these tests can be used to improve patient care.

WILLIAM J. PEVELER

Dr. William Peveler is a LKAS Fellow in the School of Chemistry at the University of Glasgow. Will and his team (the Bio Nano Sensing Group) exploit cutting edge molecular- and nano-technologies to build new sensors. Current projects include developing sensors for detecting sepsis and liver disease, as well as a range of other diseases and infections. Their research brings together chemistry, biomedicine, and engineering to solve these sensing challenges. Will studied chemistry at the University of Oxford and was awarded his Ph.D. from University College London.

SIMON PYBUS

Dr. Simon Pybus is undertaking specialized training in medical microbiology and infectious diseases, working in Glasgow, UK. Simon studied medicine and completed his initial clinical training in Liverpool, UK. Early on, he gained a strong interest in infection and antibiotic therapy. Simon treats patients with sepsis on a daily basis. He also provides advice to other doctors on optimal management of a variety of infections, including bloodstream infections, guided by laboratory results. Simon is passionate about improving laboratory techniques to provide high quality patient care.

MOHAMMAD SAIFUL ISLAM SAJIB

Mohammad Saiful Islam Sajib's research focuses primarily on infectious diseases, and he aims to improve public health by generating evidence for future policy decisions. He worked as a microbiologist in the Child Health Research Foundation in Bangladesh for 4 years. Currently, as a Ph.D. student at the University of Glasgow, he is utilizing clinical metagenomics to diagnose sepsis, to improve patient outcomes and reduce antimicrobial resistance.

GILL THOMSON

Gill Thomson is the fundraising, finance, and administration co-ordinator for Sepsis Research. She is the main point of contact for supporters and enquiries. She joined Sepsis Research in June 2019. Gill supports Colin Graham in the delivery of the charity's research and awareness objectives, and she engages with as many supporters as possible to help them with fundraising initiatives.

MELANIE JIMENEZ

Dr. Melanie Jimenez studied engineering in France and is now a researcher in biomedical engineering at the University of Glasgow. Melanie works with clinicians, chemists, biologists, and social scientists to develop new medical diagnostic tools for a healthier nation. More specifically, Melanie and her group are engineering new technologies—at the interface of physics, chemistry, and biology—that can rapidly recognize pathogens in patient samples, to help health professionals treat infected patients faster. *melanie.jimenez@glasgow.ac.uk

†These authors have contributed equally to this work

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HOW DO WE FIND THE SOURCE OF FOODBORNE SUPERBUG OUTBREAKS?

Joy Scaria[1*], *Shruti Menon*[1] *and Maristela Rovai*[2]

[1] *Department of Veterinary and Biomedical Sciences, South Dakota State University, Brookings, SD, United States*

[2] *Department of Dairy and Food Sciences, South Dakota State University, Brookings, SD, United States*

YOUNG REVIEWERS:

JADA
AGE: 14

JOSHUA
AGE: 14

LUANA
AGE: 13

Lately, there have been more foodborne "superbug" outbreaks than ever before, which creates a problem because superbugs are antibiotic-resistant bacteria that are difficult to treat. To reduce such outbreaks, better ways of finding the source of the infection are needed. Superbugs, such as Salmonella are often transmitted through food. The world's food supply system has become so complex that it is often difficult to find the source of an outbreak with older testing methods. A new method called whole genome sequencing (WGS) has now been developed to track superbug infections. Using WGS, it is now possible to identify the source of an outbreak in one country that may be transmitted through food imported from the opposite side of the world. Good outbreak tracing methods help scientists make better predictions about outbreaks. Finding the source of an outbreak early on can lead to better containment and lower costs.

Figure 1

How do people get infected with superbugs? Superbugs, like some types of Salmonella, can live on animals, birds, insects, and vegetables. When people come in direct contact with Salmonella-colonized animals or when they eat contaminated food, they can become infected.

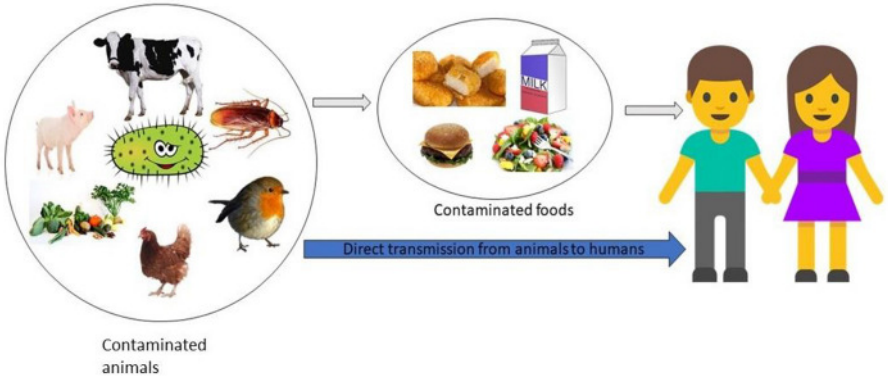

Figure 1

WHAT ARE SUPERBUGS?

SUPERBUG

A bacteria that has devolved resistance to two or more antibiotics.

Have you heard the term "**superbug**" and if so, do you understand what it means? Well, a superbug is simply a bacterium that causes sickness and is not easily treatable using antibiotics. Bacteria become superbugs by gaining genes that make them immune to antibiotics. A bacterium typically obtains superbug status when it is no longer able to be killed by two or more antibiotics. Usually, the development of a superbug is a slow process, but these days, people are using antibiotics when there is not a real need to use them. Excessive or incorrect use of antibiotics speeds up the evolution of superbugs. With no good way to treat superbugs, they have turned into a big problem, infecting thousands of people. If superbugs continue to evolve at the current rate, the world population could be hugely affected: by the year 2050, more than 400 million people could die from superbug infections [1].

HOW DO FOODBORNE OUTBREAKS HAPPEN AND WHAT ARE WE DOING ABOUT IT?

The World Health Organization has identified 12 bacteria that are superbugs. Among these, a bacterium named Salmonella is particularly problematic because it can not only infect animals but can survive in soil, water, and food. There are more than 2,000 different kinds of Salmonella [2]. Among these, only about 50 types cause human disease and have superbug status. The types of Salmonella that cause human infections are passed on to people through direct contact with Salmonella-colonized animals or when people eat contaminated food (Figure 1).

Contaminated food is a common source of Salmonella outbreaks. Food can be contaminated at multiple different stages in the supply chain. For example a chicken could catch Salmonella at the farm or its meat me be exposed to Salmonella at the meat packaging facility. In a foodborne Salmonella outbreak, a large number of people are

Figure 2

Figure 2

The food supply system in America is complex. As an example, meat could be supplied from multiple sources, some close, such as within the same city or town, and some far away, even in other countries. The meat first goes to processing and packaging centers and from there is distributed to grocery stores, schools, restaurants, and hospitals. If bacterial contamination occurs at the source or in packaging centers, this could expose large numbers of people to infection.

often infected in a short time. This happens because the world's food supply system is very complex. For example, in the United States, food comes from many national or international suppliers who then package and distribute food through a complicated supply system (Figure 2). Contamination anywhere in the supply system could expose millions of people to infection, which triggers an outbreak. Every year, more than $700 million is spent dealing with Salmonella outbreaks alone. Now that you know how an outbreak begins, you may be wondering how scientists stop them.

Since many antibiotics are not effective at treating superbugs, such as Salmonella, one strategy to limit infections is to find the source of contamination and remove the contaminated food from the supply system. This is called **outbreak tracing**. Outbreak tracing is very important because after finding the source, it becomes easier to contain the outbreak and stop it from spreading. A common method of outbreak tracing is taking a sample of the bacteria from an infected patient and then growing it in the lab. After this, the scientists take samples from all suspected sources, grow them also, and then compare their chemical properties to those of the patient sample. This method of outbreak tracing is both expensive and time consuming. Another problem with this method is that it is not specific enough to differentiate the type of Salmonella that caused the outbreak from other types that may simply be present in the environment.

OUTBREAK TRACING

The process of tracing an outbreak to its source to stop more people from being infected.

This older method of outbreak tracing is also not as useful if the source of the outbreak is very far away. For example, this method would probably be unable to find the source of a multi-state Salmonella outbreak in the USA caused by fish from India, because it is hard to get a fish sample from India in the USA. Thanks to advances in technology, a new method called whole genome sequencing (WGS) has been

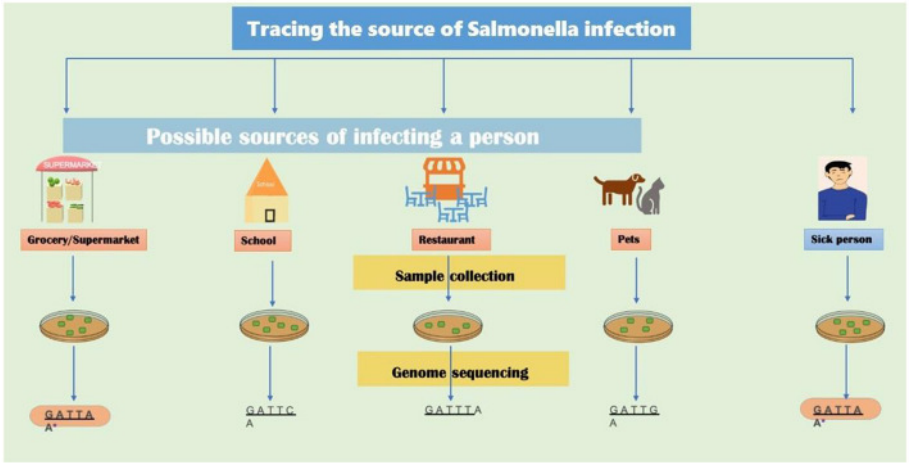

Figure 3

Figure 3

WGS-based outbreak tracing. To identify the source of a foodborne outbreak, samples are taken from the sick person and all suspected sources of infection. In this case, the sick person went to the grocery store, to school, and to a restaurant, and also had a pet. Salmonella is isolated from samples taken from each of these possible sources and the DNA sequences of all samples are determined using WGS. A computer program is used compare the DNA sequences. In this example, the DNA sequence from the grocery store sample and the sick person are identical, showing that the grocery store is the most likely source of infection.

developed, which can identify the sources of outbreaks even when they originate in far-away places [3].

WHAT IS WGS, AND HOW IS IT USED FOR OUTBREAK TRACING?

Whole genome sequencing was first developed in the mid-1990s [4]. The basic discoveries that led to the development of WGS are credited to a team of scientists from the University of Cambridge. WGS does not directly find the source of the outbreak or the bacteria causing the outbreak. Instead, WGS provides data that can be used to find all this information and more. WGS works by reading the entire **DNA sequence** of a bacteria, which is made up of four smaller pieces called **bases**, represented by the letters A, T, G, and C. The entire DNA sequence of an organism is called its **genome**, and every type of organism has a unique genome. While the older outbreak tracing method provides a maximum of 1,000 data points to compare two bacteria, WGS offers more than 300,000 data points for comparison.

The data generated by WGS is used compare sequence differences between bacterial samples, using computer programs. To make these comparisons, scientists compare the DNA sequence of the bacteria causing the outbreak to the DNA sequences of bacteria that are possible suspects. For Salmonella, scientists would extract the Salmonella from the contaminated food that was causing the outbreak, then select the sequences, stored in the computer, of the different types of Salmonella that they think might be causing the outbreak. The computer program checks how similar each "suspect" DNA sequence is to the sample from the contaminated food source, and then generates an output that that shows how closely related the actual bacteria is to the possible suspects. The more closely the

DNA SEQUENCE

The genetic instructions that are encoded in bacteria and other living organisms.

BASES

The four building blocks of DNA, represented by the letters A, T, G, and C.

GENOME

Is the entire DNA sequence of an organism.

DNA sequences match, the more likely the suspect is the cause of the outbreak (Figure 3). You may find it interesting that WGS is not only used to trace bacterial outbreaks, but this method has also been used to trace people's ancestry through their DNA.

CONCLUSION

Normally, when people get infected by a bacterium, they are treated with antibiotics. With superbugs however, antibiotics are ineffective, so these infections are extremely difficult to treat. Worse yet, if a bacterium is not treated quickly, there is a better chance for it to spread to other people. Foodborne infections with superbugs sicken 47 million and kill thousands of people annually.

Whole genome sequencing is extremely important because it can track superbugs accurately. Due to the complexity of the world's food supply system, it has become difficult to find the source of outbreaks of superbugs, such as Salmonella. Better tracking methods, such as WGS are necessary to help scientists contain outbreaks. Better tracking can also lower the cost of tracking outbreaks and the amounts of supplies used. Good tracking also helps scientists to make better predictions about where and when an outbreak could happen, which will ultimately help us to reduce the number of superbug outbreaks that occur and save thousands of lives.

ACKNOWLEDGMENTS

The authors thank Alex Kidangathazhe for helping with the preparation of the figures, writing the manuscript, and the revisions. He is a seventh-grade student at the Mickelson Middle School, Brookings, SD. His hobbies include playing the piano, cooking, baking, and reading! He hopes to be a doctor 1 day and research new cures and vaccines. Writing is another one of his passions. He feels that writing gives him a better understating of the topic and helps someone else as well. He also loves traveling and getting to know new people.

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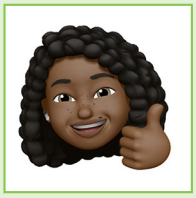
YOUNG REVIEWERS



JADA, AGE: 14
I am a 14-year old who currently lives in Atlanta, Georgia, and I am a rising Freshman. I enjoy watching documentaries and shows about medicine. I have always been fascinated with medicine since I was a toddler. From trying on my father's lab coat when I was little to shadowing a Doctor's office, I have always known I wanted to become a doctor in the future. Problem solving and challenges motivate me to think outside of the box. Since I love science, I enjoy reading articles about science and giving important feedback to improve the article.

JOSHUA, AGE: 14
I am a rising ninth grader and I live in Atlanta, Georgia. During the academic school year I participate in many programs including the Academic team and the Lacrosse team. When I am not studying or at school I love to read books and play lacrosse. I am happy to be a part of this program because I enjoy science, and I am happy that my feedback is so important in helping people publish their articles.

LUANA, AGE: 13
I was born in the USA, and have lived in Canada for 5 years. That is why I can speak

English so well. Both my parents are scientists (microbiologists), so I think that is why I always have loved science.

AUTHORS

JOY SCARIA
Joy Scaria is an Associate Professor at the Department of Veterinary and Biomedical Science, South Dakota State University, Brookings, SD. His research interest is to understand how antibiotic resistant bacteria, such as Salmonella spread between animals and people. His research group is also developing non-antibiotic alternatives to treat antibiotic resistant bacterial infection. *joy.scaria@sdstate.edu

SHRUTI MENON
Shruti Menon is a graduate student at South Dakota State University pursuing an M.S. degree in Veterinary Microbiology. She is passionate about Biology since high school. She had been introduced to the microbiome world in my undergraduate years. Since then, she has always been curious to understand how gut bacteria play a role in health and disease.

MARISTELA ROVAI
Maristela Rovai is an Assistant Professor at the Department of Dairy and Food Science, South Dakota State University, Brookings, SD. She is passionate about the research on how to control all the "bugs" that negatively affect milk quality and dairy products. She enjoys cooking, hiking, photography, and traveling. She speaks more than three different languages, which helps her connect with many other people and cultures.

frontiers FOR YOUNG MINDS

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THE INTESTINAL UNIVERSE—FULL OF GUT HEROES WHO NEED SIDEKICKS

Bahtiyar Yilmaz [1*], ***Joana C. Carvalho*** [2] ***and Marta Marialva*** [3]

[1] *Maurice Müller Laboratories, Department for Biomedical Research, University Clinic of Visceral Surgery and Medicine, Inselspital, University of Bern, Bern, Switzerland*

[2] *Evolution and Development Laboratory, Instituto Gulbenkian de Ciência, Oeiras, Portugal*

[3] *Ginkgo Educa, Bern, Switzerland*

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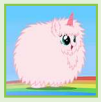
SAHASRA
AGE: 13


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.

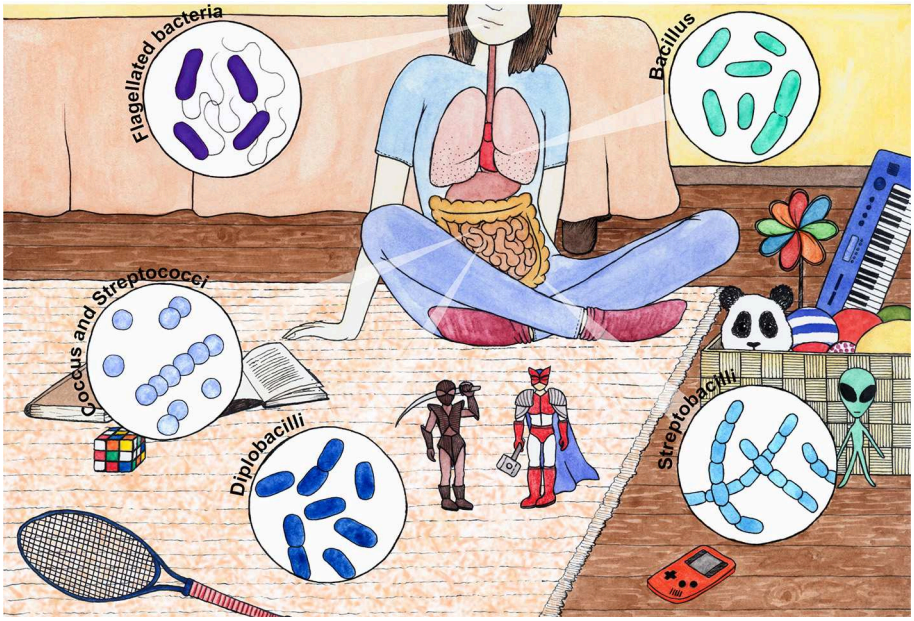


Figure 1

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

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.

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.

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.

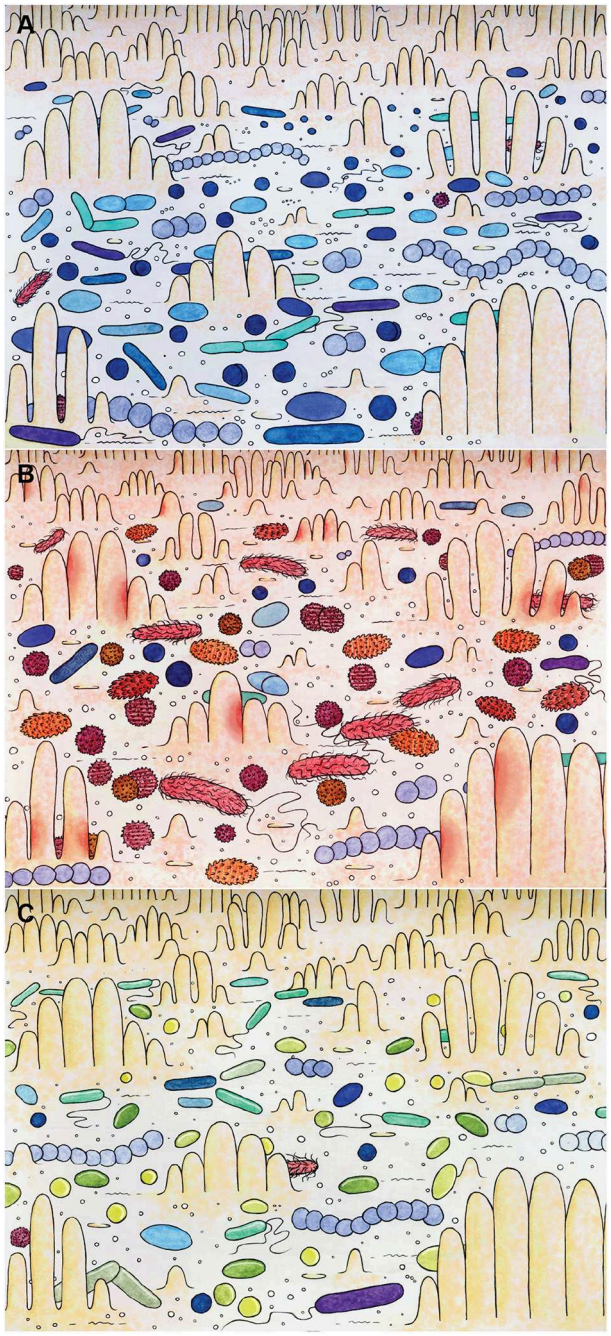


Figure 2

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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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.

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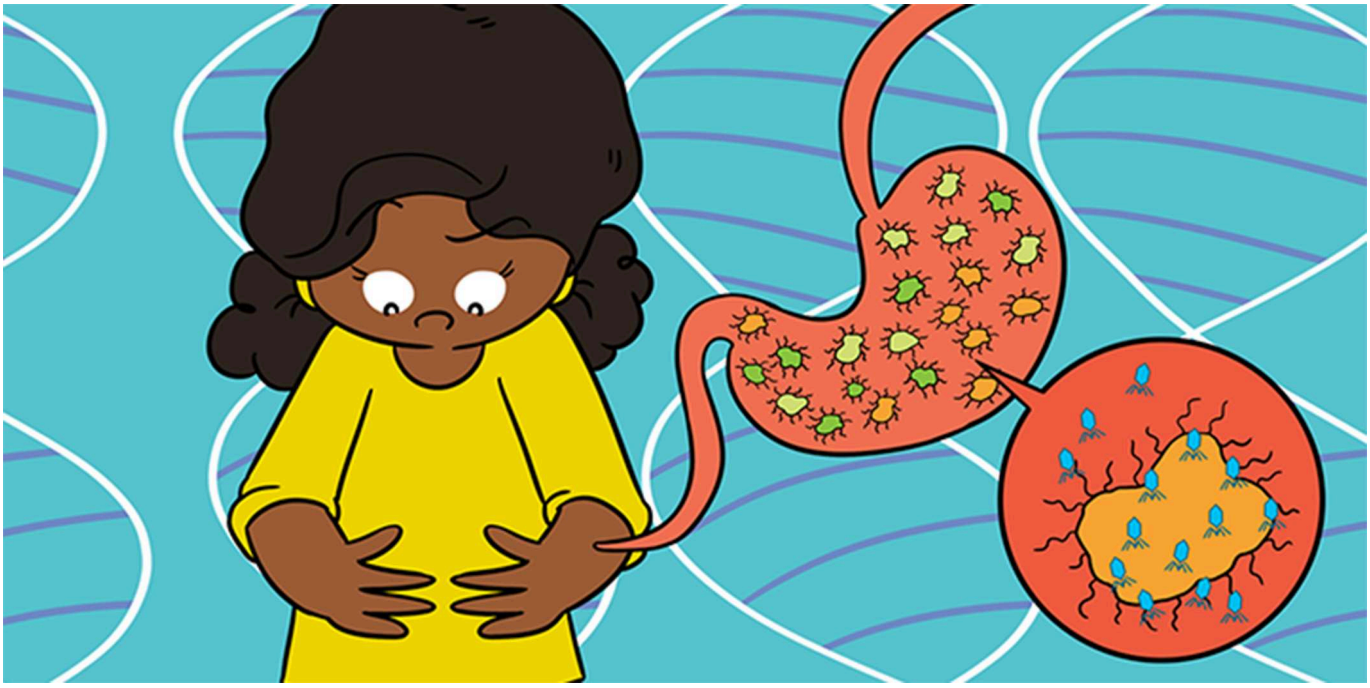

BACTERIOPHAGES: VIRUSES THAT INFECT BACTERIA

Colin Hill *

School of Microbiology and APC Microbiome Ireland, University College Cork, Cork, Ireland

YOUNG REVIEWERS:

JUNALUSKA ELEMENTARY SCHOOL

AGE: 15

Bacteria can be infected by tiny viruses called bacteriophages (phages). Bacteriophages are so small they do not even have a single cell, but are instead just a piece of DNA surrounded by a protein coat. When they attack a bacterium, bacteriophages can multiply very quickly until the bacterium bursts and releases lots of new phages. Trillions of bacteria and bacteriophages live in and on the human body and they are vital for a normal, healthy life. We are interested in seeing if we can use phages to help doctors to treat diseases and to help people live healthy lives.

MICROBIOME

The collection of all the microbes in a particular environment, like in the human body.

MICROBE

Microscopic organisms, such as bacteria, fungi, and bacteriophages.

THE MICROBIOME—A NEW HUMAN ORGAN?

Imagine the excitement if doctors suddenly discovered a new organ in the human body! This is exactly what has happened in the last few years. We now know that, in addition to the lungs, kidneys, brain, liver and heart, we have another organ to consider—the **microbiome**. This new organ is completely different, because it is made of **microbes** rather than human cells. Microbes are tiny organisms that include

BACTERIA

A type of microbe. A bacterium is a single cell that can divide to form two cells.

bacteria. One amazing thing about this new organ is that we are born without it. As we are being born, we get bacteria from our mothers and then we continue to add more and more bacteria from the environment, until we have about 1,000 different types of bacteria on and inside our bodies. Bacteria are tiny, but they can multiply very quickly, and within only a few hours, one bacterium can become thousands or even millions of new bacteria. Everyone has a unique microbiome, different from everyone else. We have our microbiomes for our entire lives. The microbiome is mostly located in the gut, but there is also a skin microbiome and a lung microbiome.

But wait—bacteria live with us our whole lives? Most of us think of bacteria as being present only on dirty things, but they are everywhere, including inside of us. Bacteria do not just make us sick—they can do lots of useful jobs, like converting milk into yogurt and cheese, or helping plants to grow. We need the bacteria in our microbiomes to help us to digest our food and to "train" our immune systems, amongst other important roles. Hundreds of laboratories around the world are working to understand the other roles that the microbiome plays in human health. Research has found that people with certain diseases and conditions like Inflammatory Bowel Disease or certain cancers have different microbiomes than healthy people, but it has been difficult to show whether changes in the microbiome are responsible for these diseases. In addition to linking the microbiome to gut and skin problems, recent work has even provided convincing evidence that bacteria in the gut can influence our brains! For example, when researchers transferred the gut microbiome from humans suffering from depression into rats, the animals started to demonstrate behaviors which are also characteristic of depression. The microbiomes from non-depressed humans did not have this effect.

VIRUS

A type of microbe that can infects cells. Human viruses infect human cells, plant viruses infect plant cells, etc.

BACTERIOPHAGE

A virus that infects bacteria, also called a phage.

DNA

The molecule that carries all the information in the form of genes needed to produce proteins. All organisms get their DNA from their parents.

BACTERIOPHAGES—VIRUSES THAT INFECT BACTERIA

Our microbiomes contain trillions of bacteria living in and on our bodies, but the diversity of life living within us does not stop there. Jonathan Swift was an Irish poet who wrote the lines:

> *So, naturalists observe, a flea*
> *Has smaller fleas that on him prey;*
> *And these have smaller still to bite 'em,*
> *And so proceed ad infinitum*.

Swift had never heard of the microbiome, but he described it perfectly. We have bacteria that live on us, and bacteria have bacterial **viruses** that live on them (Figure 1). These viruses are called **bacteriophages** (or phages). Viruses differ from bacteria in that they are not made of cells, but instead consist of a piece of **DNA** (or RNA) packed within a protein coat. Viruses are so small that we cannot see them with

Figure 1

Humans contain lots of bacteria in our microbiomes, mostly in the gut. These bacteria can be attacked by bacterial viruses called bacteriophages.

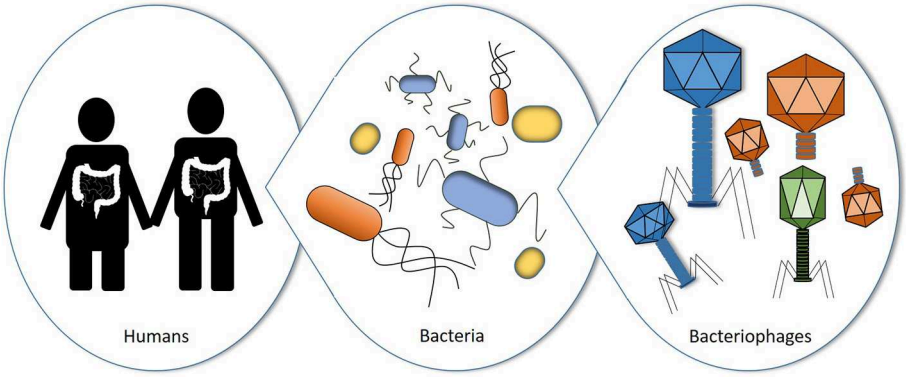

Figure 1

normal microscopes. To give you a sense of their size, if a phage were the size of the period at end of this sentence, then humans would be almost 4 miles (6 km) tall! Phages are the simplest and most abundant organisms on earth.

Phages are really very beautiful (Figure 2) and the way they reproduce is quite interesting. A phage attaches to a bacterium and injects its DNA into the bacterial cell. The bacterium then turns into a phage factory, producing as many as 100 new phages before it bursts, releasing the phages to attack more bacteria. This means that phages can grow much more quickly than bacteria. In some countries, particularly in Eastern Europe, phages are actually used to treat bacterial infections. Each phage can only kill one type of bacteria, so if a doctor knows what kind of bacteria is infecting a patient, it might be possible to give the patient a phage that can infect and kill that type of bacteria. Phages cannot infect human cells, and so they pose no threat to us.

PHAGES WITHIN US

We have known for years that lots of phages are present in the gut, but we really did not know very much about them. So, we started to study them. First, we separated the phages away from everything else in the gut, and then we sequenced them. Sequencing allowed us to "read" the phage DNA and predict how many and what types of phages are present. We were amazed to learn that there are tens of thousands of different phages in the human gut. Most of them were completely unknown. Some of the gut phages are very simple and only have three genes, while others are huge and have more than 500 genes.

If there are lots of phages present in the gut and they replicate very quickly, why do they not just wipe out all of the gut bacteria? Well, as is often the case in science, the answer is quite complicated. Sometimes the phage just cannot find its correct bacterial target in the very crowded environment of the gut. Also, bacteria can defend themselves

Figure 2

Bacteriophages have protein heads and tails, which are packed with DNA. When a phage attacks a bacterium, it injects its DNA. The bacterium them makes more phages that are released when the bacterium bursts.

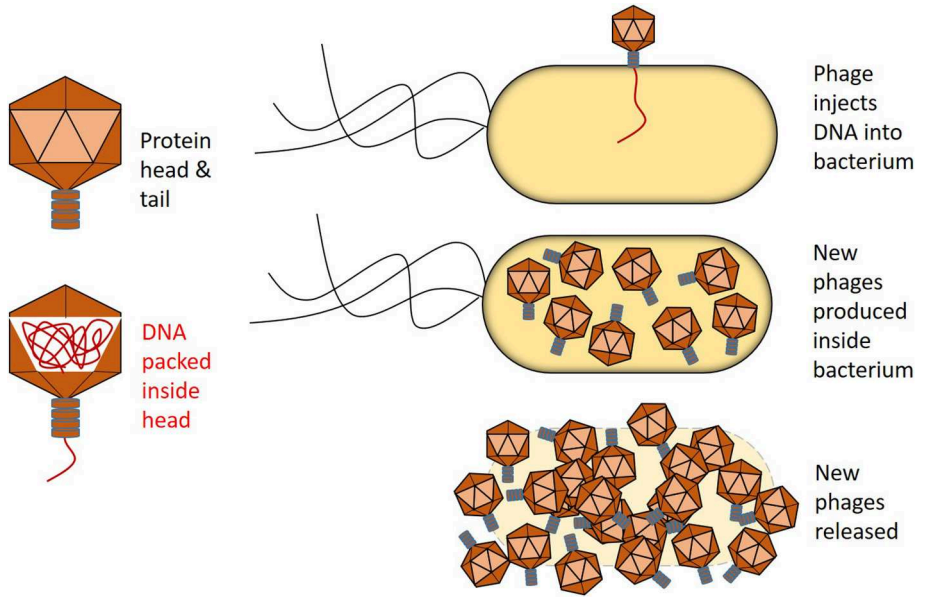

Figure 2

against phages in various ways, including preventing the phage from attaching, chopping up the phage's DNA as it enters the cell, and even taking the drastic step of committing "suicide" to prevent the phage from multiplying and attacking the bacteria's close relatives. As a result, there is a complex balance between phages and bacteria in the gut, and a stable relationship is formed. Bacteria are constantly evolving to combat phages and the phages are also rapidly evolving to overcome bacterial defenses.

WHY IS IT IMPORTANT TO STUDY BACTERIOPHAGES?

Why are we interested in studying phages in the gut? Why is anyone funding labs like ours and others that are trying to understand these simple yet complex creatures? One excellent reason is that we can learn a lot of fundamental biological principles by studying phages. Quite a few Nobel prizes have been awarded to phage researchers for that very reason. As recently as 2018 the Nobel Prize in Chemistry was awarded to George Smith and Gregory Winter who used the fact that phage grow and mutate quickly to develop new antibodies that have been used to cure many diseases, including some forms of cancer.

Another reason we study phages in the gut is that we hope they might provide us with a very precise way to manipulate or engineer the microbiome. Our hypothesis is that phages are one of the most important parts of the microbiome, and we are designing and performing experiments to test that idea. One thing we are doing is transferring the phage from a healthy microbiome into a microbiome

that has been damaged by antibiotics, to see if we can restore a healthy microbiome.

Even if our hypothesis turns out to be wrong, we will almost certainly still learn lots of things along the way. But if we are right, then someday doctors might be able to use phages to re-shape the microbiome from an unhealthy to a healthy state, which could possibly help to cure several diseases or disorders. Perhaps by adding very high numbers of phages against a few specific target bacteria, we could change the microbiome in a positive manner. Maybe there will be a time in the future when we can "fix" a damaged microbiome using phages, similar to the way surgeons can currently operate precisely on a damaged heart or liver. But this will only be possible once we have a much better understanding of the numbers and nature of our phages, and so many experiments need to be done in order to get to that point.

A famous scientist named Sir Peter Medawar once described viruses as "a piece of bad news wrapped up in a protein," but, in the future, we hope to show that phages are "an opportunity wrapped up in a protein."

ORIGINAL SOURCE ARTICLE

Shkoporov, A. N., and Hill, C. 2019. Bacteriophages of the human gut: the "known unknown" of the microbiome. *Cell Host Microbe* 25:195–209. doi: 10.1016/j.chom.2019.01.017

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YOUNG REVIEWERS

JUNALUSKA ELEMENTARY SCHOOL, AGE: 15

Ms. Fox's third grade class is located in the beautiful mountains of North Carolina!

AUTHOR

COLIN HILL

Colin Hill is a Professor of Microbiology at APC Microbiome Ireland who is interested in how our microbiomes may influence our health. He works with lots of talented researchers in his laboratory to study the viruses within the gut, especially the viruses that attack bacteria—bacteriophages. He hopes that in the future we will be able to use bacteriophages to deliberately change the microbiome and improve health of patients with various diseases. *c.hill@ucc.ie

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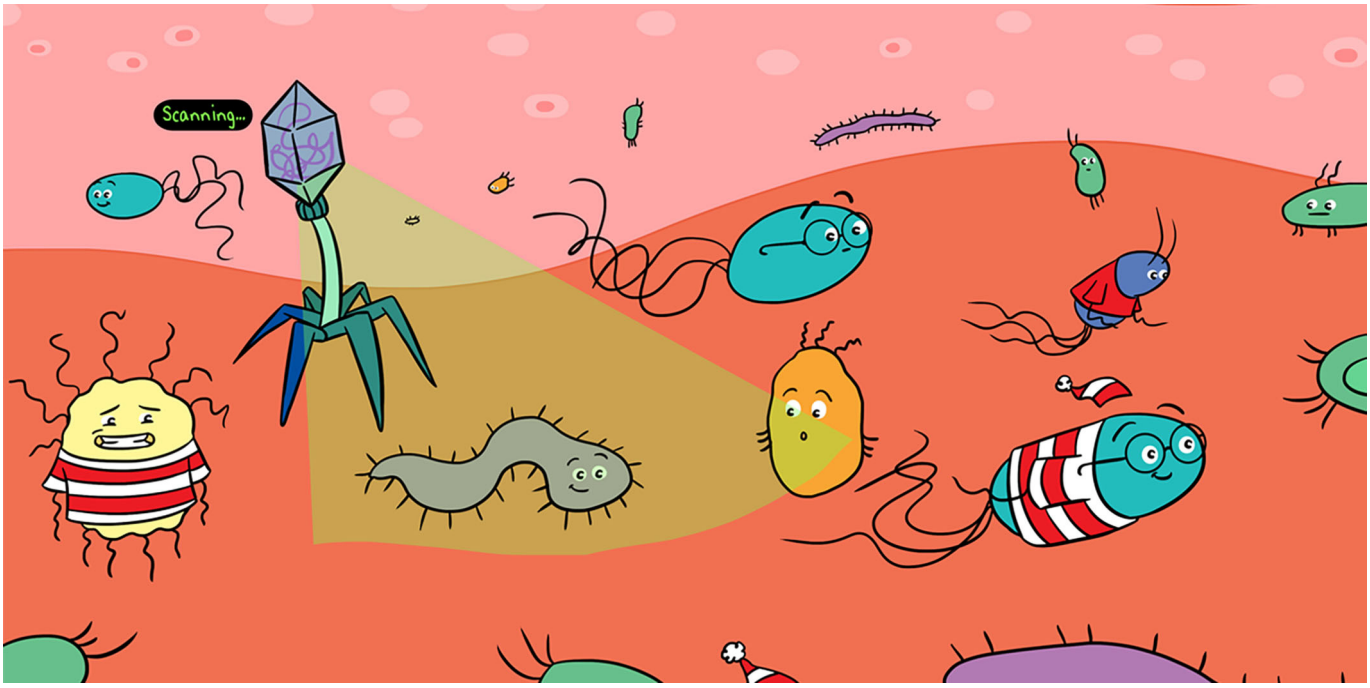

NATURAL BACTERIA KILLERS: HOW BACTERIOPHAGES FIND AND ELIMINATE THEIR HOSTS

Floricel Gonzalez * ***and Birgit E. Scharf***

Scharf Laboratory, Department of Biological Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA, United States

Bacteriophages, also called phages, are viruses that kill bacteria. They do not kill humans, animals, or plants. Phages only kill one or a few types of bacteria. Therefore, we can use phages that only kill disease-causing bacteria as medicines. Using phages ensures that the helpful bacteria stay alive. How do phages kill some bacteria and not others? They recognize specific parts of a bacterial cell. In this article, we describe how phages find their target bacteria even when other microbes are around.

YOUNG REVIEWERS:


ARIA
AGE: 8


RUH-FAIDA
AGE: 12


SAMIHA
AGE: 12

BACTERIA

A one-celled microbe that can be found everywhere in nature and can either cause disease or be beneficial.

PHAGES ARE ALL AROUND US

Earth is jam-packed with **bacteria**—and the **viruses** that infect them! These viruses are called **bacteriophages**, or just phages (pronounced feyj-es) for short. There are 10 times more phages than bacteria on earth [1]. Bacteriophages are fun to look at because they come in different shapes (Figure 1A). Some have tails that are flexible, rigid, or

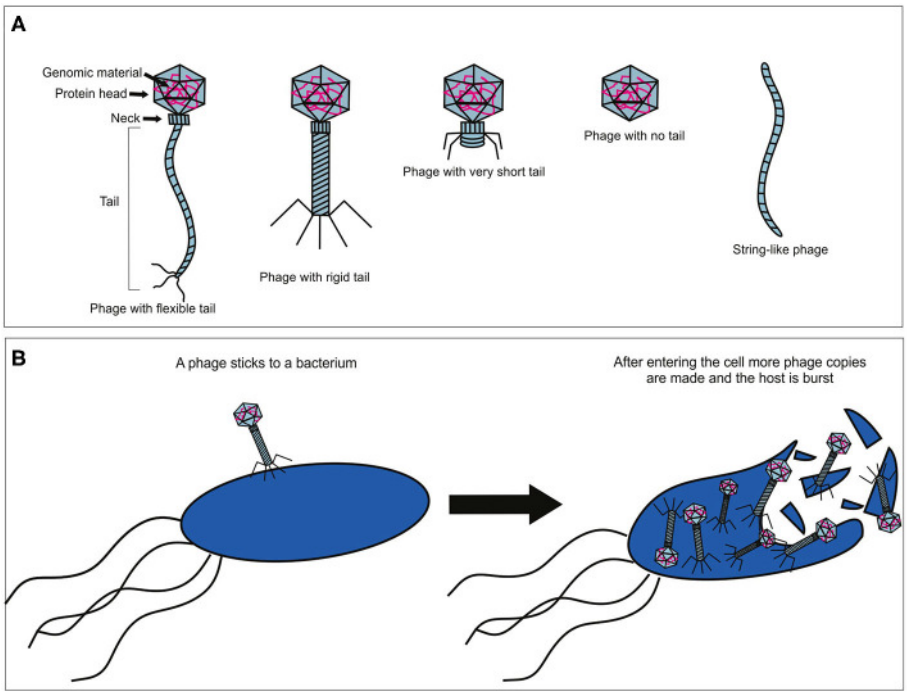

Figure 1

Diversity of phages and how they attack bacteria. **(A)** Phages have many shapes. They can have different types of tails or no tail, or simply look like a string. **(B)** Phages attack bacteria by recognizing and sticking to the bacterial cell. Then, the phage enters the cell, makes many phage copies, and the cell bursts open, which releases hundreds of new phages.

VIRUS

A microbe that must infect a cell to reproduce.

BACTERIOPHAGE

A virus that infects bacteria.

MICROBE

A small organism that is typically not visible with the naked eye. Microbes include bacteria and viruses.

HOST

A cell used by a virus to reproduce.

ANTIBIOTIC-RESISTANT

A term used to describe bacteria that are no longer sensitive to the medicines normally used to kill them or stop their growth.

very short. Others look like floating heads or even like long strings. Just like other **microbes**, phages are made from a set of genetic instructions known as DNA or RNA. These instructions are safely housed in the phage head, which is made of protein (Figure 1A).

Phages (like all viruses) cannot reproduce by themselves nor make new phage copies. Viruses always need a cell to infect, called a **host** cell, to reproduce themselves. Bacteriophages take advantage of bacteria for this purpose. These microscopic pirates begin their attack by sticking to a bacterial cell. Then, the phage enters the cell and makes more copies of itself. How many copies are made? Hundreds! For every bacterial cell that is attacked, hundreds of new phages are created. These copies are freed as the bacterial cell explodes (Figure 1B) [1, 3, 4]. All of this begins with one phage. This process is happening in the soil, oceans, and even in your own body!

Humans are using these natural enemies of bacteria for the greater good. For example, phages can be used as medicines to kill disease-causing bacteria that are **antibiotic-resistant**, meaning that normal drug treatments used to kill them are no longer effective. In other cases, phages are applied to cooking surfaces, meat, or produce. This prevents bad bacteria that can cause fever and diarrhea, like *Salmonella* and *Listeria monocytogenes*, from getting on our food [2, 3]. As you can see, phages are the good viruses. They help us stay healthy and protected from disease-causing bacteria.

Figure 2

Phages find their specific hosts with a microbial version of Where is Waldo®? Phages use receptors on the surface of bacterial cells to recognize their hosts, just like players of Where is Waldo® recognize Waldo by looking for his outfit. Can you find the Waldo bacteria?

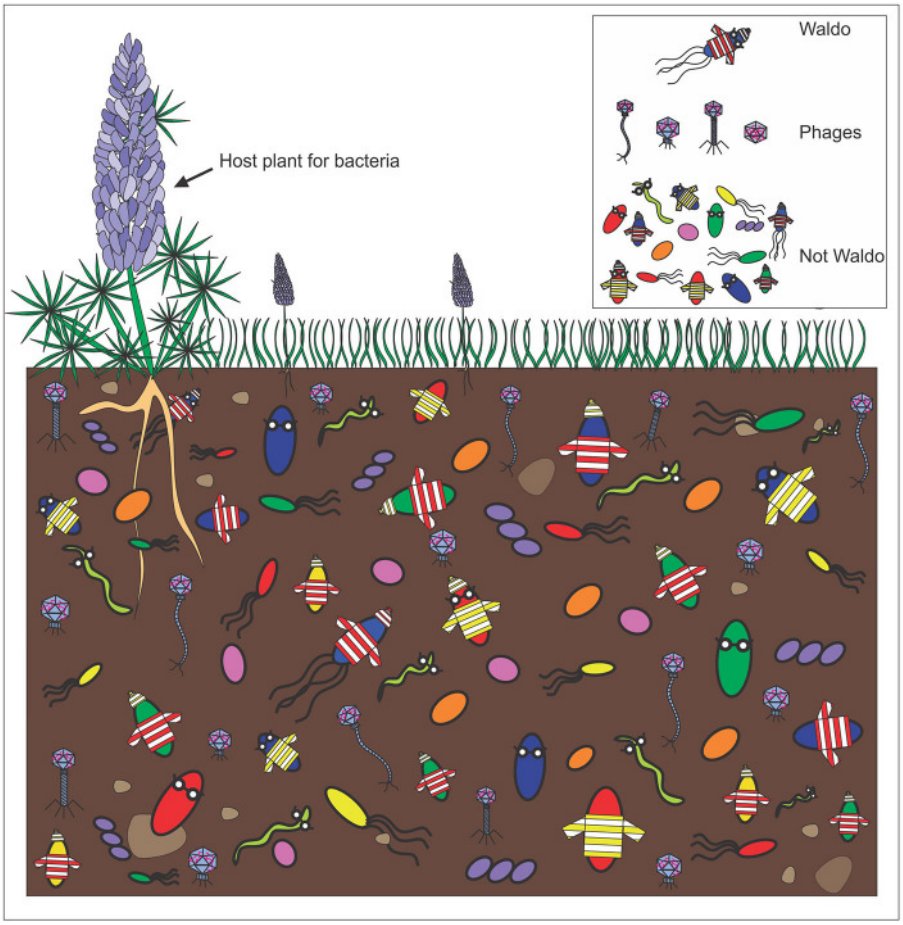

Figure 2

PHAGES RECOGNIZE SOME BACTERIA AND LEAVE THE REST ALONE

Even though there are many types of bacteria everywhere, phages only attack some of them. How do phages know which bacteria to kill? It turns out that phages are picky! Each phage is only able to use certain types of bacteria as hosts. Phages search for their hosts by sifting through all the microbes around them. This is like playing the Where is Waldo® puzzle game. To find Waldo, you search for a character with glasses, brown hair, a red-and-white striped beanie with a matching shirt, and blue jeans. There may be others in the picture who are wearing similar outfits or parts of Waldo's outfit, but only Waldo is wearing the complete, correctly colored outfit. Phages play a microbe version of this game with bacteria (Figure 2).

To find their hosts, phages look for special parts of the bacterial cell. These parts recognized by the phage are called **receptors** [3]. The receptors serve the same purpose that Waldo's outfit does in Where is Waldo®. They make the hosts stand out from other microbes around them. Therefore, bacteria without the right receptors are safe from phage attack. The receptors are also the areas where the

RECEPTOR

A unique feature of the host cell that is recognized by a virus.

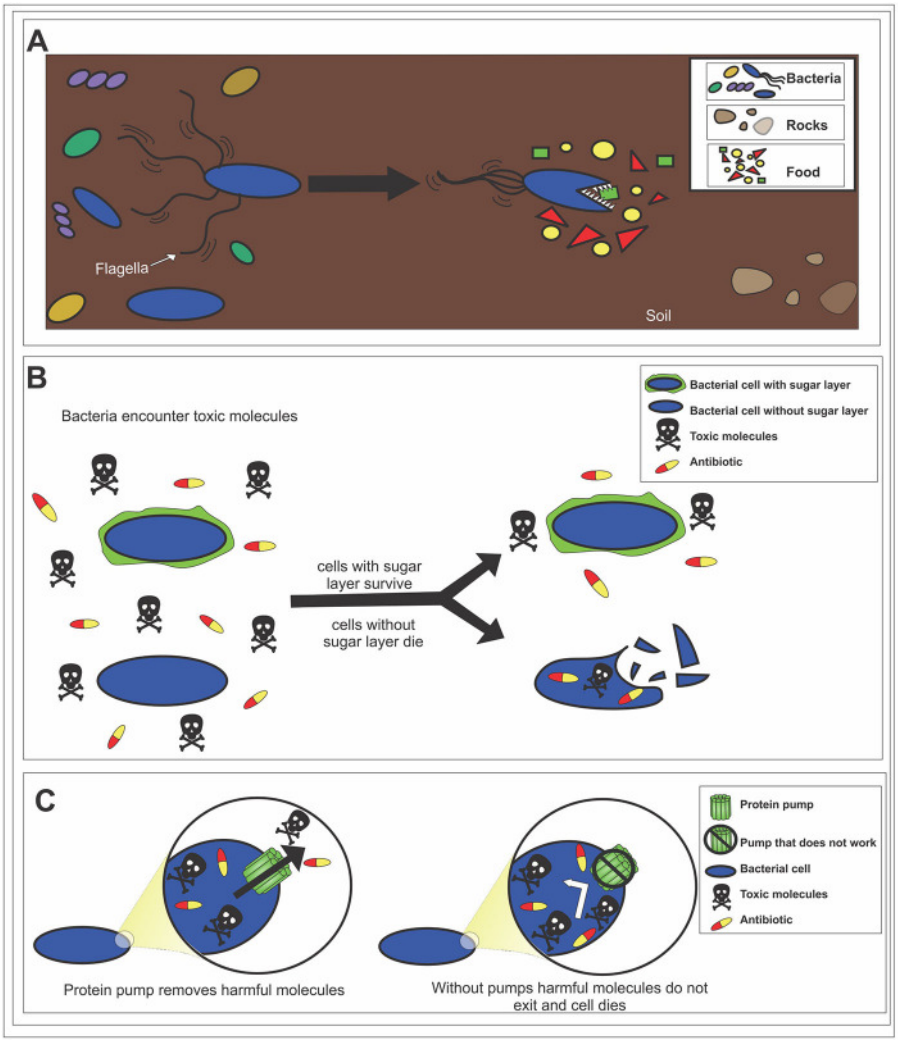

Figure 3

Functions of some bacterial structures that bacteriophages use as receptors to attach to bacterial cells. **(A)** Flagella are used for movement. Bacteria that move are better at reaching food than bacteria that do not move. **(B)** Sugar molecules on the surface of bacteria can be used as receptors. These sugar layers protect bacteria from toxic molecules in the environment. **(C)** Protein pumps in the cell membrane of a bacterial cell can also be used as receptors. These pumps remove toxic molecules from inside the bacterial cell.

phage attaches, or sticks, to the bacterial cell at the beginning of the attack.

RECEPTORS USED BY PHAGES ARE IMPORTANT FOR BACTERIA

What kind of bacterial cell parts are used by phages as receptors? It depends on the phage! Some phages stick to **flagella** (pronounced fluh-jeh-lah), which are long, wavy threads used by bacteria to move in a swimming motion (Figure 3A). Other phages stick to sugars found on the surface of the bacterial cell that normally protects bacteria from toxic substances (Figure 3B). Protein pumps found in the bacteria's cell membrane are also used as receptors. The cell membrane is the barrier around the cell that helps it keep its shape, and the protein pumps normally get rid of things that can harm or kill the cell (Figure 3C).

FLAGELLA

Long threads that are part of a bacterial cell. Flagella are used to move around in a swimming motion.

Although we will only mention these three receptors, keep in mind that there are more [3, 5]. Not all bacteria have sugars, flagella, or protein pumps. Depending on where they live, bacteria may need other specialized parts that allow them to survive. Interestingly, the parts that make each type of bacteria unique are what phages recognize. The receptors used by phages determine which bacteria are their hosts. Phages can have either a broad or narrow host range. Phages with a broad host range can attack many different types of bacteria. Phages with a narrow host range attack only one or two types of bacteria.

Bacteria can protect themselves from phages by removing or changing the receptors on their surfaces. However, this comes at a cost to the bacterial cells. Receptors play important roles in the life functions of bacteria. The primary job of receptors is to help bacteria perform those functions, not to make phage attack possible. Removing or changing the receptors can leave the cell unable to perform certain critical functions. For example, bacteria that can move can travel to new areas where more food is present, which means they can out-compete bacteria that cannot move (Figure 3A). If bacteria change to get rid of their flagella, they would be resistant to the phage, but no longer able to move and look for food. Similarly, if the protein pumps or sugar layers are gone, then the bacterial cell is more likely to die in harsh environments (Figures 3B,C). Despite these downsides, some bacteria still change or remove receptors to avoid phage attack.

Surprisingly, phages can overcome the defenses of bacteria. Phages can learn to recognize a different cell part or the altered receptor. How does this happen? Mostly by chance. When new phages are made, some are different from the original phage that first infected the bacterial cell. This is caused by mutations, small changes that naturally occur in DNA or RNA. Mutations happen in bacterial, animal, and human cells. Mutations sometimes give cells advantages over other cells. In fact, humans can walk on two legs thanks to mutations. In phages, these mutations can result in the ability to infect bacteria that would otherwise be phage resistant. This cycle of bacteria becoming phage resistant and phages overcoming that resistance repeats itself over and over. In this way, bacteria and phages are constantly in competition with each other [4, 5].

WHY SHOULD YOU CARE ABOUT PHAGES?

Even though viruses are often thought of as bad, phages are helpful viruses that we want to have around. These natural killers of bacteria are extremely good at what they do! So, we can use them to kill the bad bacteria that cause diseases and hard-to-treat infections. In fact, phages have already made news headlines for saving lives. Bacteriophages have cured humans from bacterial infections of the heart, brain, and urinary tract. These infections are caused by problematic bacteria, such as *Pseudomonas aeruginosa* or

Acetinobacter baumannii [5], which quickly become resistant to many antibiotics. Some problematic bacteria also form sticky layers called biofilms that are hard to break apart. For these reasons, antibiotics are not always an effective option for treatment. Therefore, phages may be the only way to get rid of these dangerous infections.

By using phages that only kill these troublemakers, we can make sure that the good bacteria in our bodies survive. We need to study phages in more detail, just like we study other medicines we use. These studies will help us choose the best phages to use in treatments. In the meantime, you can help spread the word about these incredible viruses. Next time you hear someone talk about viruses, be sure to tell them what you know about phages—the good viruses that can help treat infections!

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YOUNG REVIEWERS

ARIA, AGE: 8

Aria loves playing with her two guinea pigs and feeding the birds and squirrels in her backyard. She gave each squirrel a unique name and lots of peanuts. Aria is always curious about science and she has a lot of questions about nature, animals, and the universe. She also likes singing and drawing in her spare time.

RUH-FAIDA, AGE: 12

My name is Ruh-Faida and I am 12 years old. At school, I am in year 7. I was born in Bangladesh, but my family and I moved to Australia when I just 3 months of age. I have a younger sister who was born here, and she is 8 years old. We have lived in four different cities after coming to Australia, but we occasionally do go back to Bangladesh to visit the rest of our family. I love nature and animals.

SAMIHA, AGE: 12

My name is Samiha and I am 12 years old. I am grade-7 student. I have many hobbies and passions. First of all, my favorite subject is definitely math. I specifically love geometry and anything to do with angles. I like to read, but, only books that I find interesting (books about mysteries, horror, and secret organizations). I have always wanted to visit France and I really like to cook and bake, mostly because they both involve food which I love!

AUTHORS

FLORICEL GONZALEZ

Floricel is a microbiologist at Virginia Tech. Her love for viruses began in college where she learned about the crafty ways viruses infect their hosts. When she was taught about bacteriophages, the viruses of bacteria, she knew she had to work on them. Now, she is a Ph.D. candidate studying how phages recognize and attack bacteria that move. She is also interested in the discovery of phage proteins that can kill bacteria. The goal of her work is to use phages, or parts of phages, to get rid of disease-causing bacteria in agriculture. *floric1@vt.edu

BIRGIT E. SCHARF

Dr. Birgit Scharf is a molecular microbiologist at Virginia Tech. She is interested in flagellar-driven bacterial movement and how bacteriophages use this trait for

infection. Dr. Scharf has studied disease-causing and beneficial microbes at several research institutions in Germany and the U.S.A. Her current research group primarily investigates both how plant-growth-promoting bacteria find host plants, and how phages that use flagella as receptors infect various bacterial species. This research may eventually help us to increase crop yields and establish alternative methods to treat and eliminate pathogenic bacteria from plants and meat products.

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HEALTH
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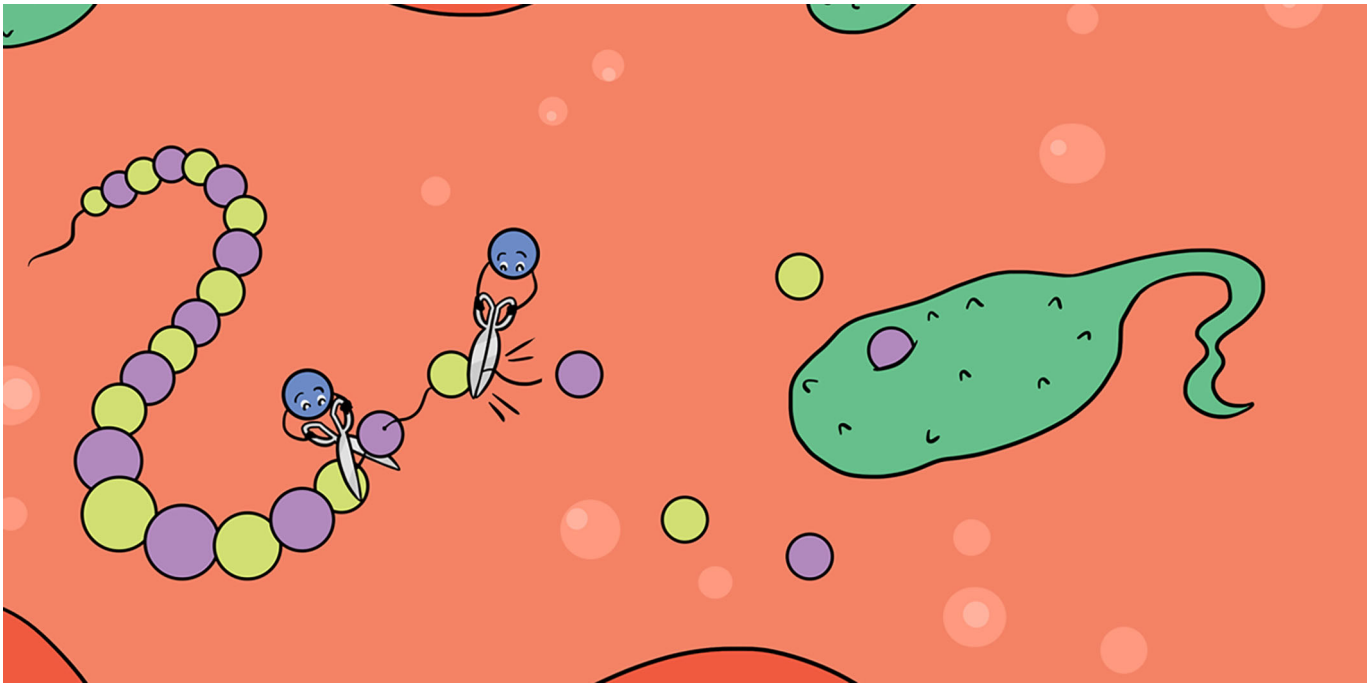

ANTIMICROBIAL PEPTIDES AND HOW TO FIND THEM

Barbara Spellerberg [1*], ***Ludger Ständker*** [2], ***Rüdiger Groß*** [3] ***and Jan Münch*** [3]

[1] *Institute of Medical Microbiology and Hygiene, University Hospital, Ulm, Germany*
[2] *Core Facility Functional Peptidomics, Ulm University Medical Center, Ulm, Germany*
[3] *Institute of Molecular Virology, Ulm University Medical Center, Ulm, Germany*

YOUNG REVIEWER:

ANISHA
AGE: 14

Bacteria and viruses may enter our bodies through mucous membranes of the airways or the gut. To prevent infections, one defense mechanism of our immune system is antimicrobial peptides (AMPs). Most AMPs are composed of 10–50 amino acids and insert into bacterial cell membranes to destroy the cell. Some AMPs are also active against viruses and fungi. AMPs can be generated by chopping up bigger proteins like hemoglobin. The hemoglobin fragments can inactivate bacteria and viruses, while the whole hemoglobin protein cannot. To identify new AMPs, peptide libraries consisting of thousands of different peptides can be generated from human body fluids and organs. These libraries are tested for antibacterial or antiviral activity and can be further purified to identify the responsible peptide. This method may lead to the development of new antimicrobial substances with a potential for treating infections.

HOW DO BACTERIA AND VIRUSES GET INTO OUR BODIES?

We are constantly in contact with bacteria and viruses that are present in the surrounding environment or other people. Some of these bacteria and viruses may cause human infections and are called **microbial pathogens**. Two important ways for microbial pathogens to get into our bodies are through the respiratory and gastrointestinal tracts. The oral cavity, the nose, and the throat belong to the upper respiratory tract, while the bronchi and the lungs are part of the lower respiratory tract. Through the constant exposure of the respiratory tract to the air that we breathe, which may contain little droplets of fluid harboring bacteria or viruses, microbial pathogens can get into the lungs and cause a severe infection called pneumonia. The mouth, esophagus, stomach, and intestines are part of the gastrointestinal tract. Food and fluids continuously transport microorganisms into the gastrointestinal tract. Most bacteria and viruses that we take up through food are killed or inactivated in the very acidic gastric fluid of the stomach. However, some may reach the gut and can cause gastrointestinal infections and diarrhea. While the respiratory and gastrointestinal tracts are the most common entry sites for microbial pathogens, there are also other ways to infect humans, including transmission through blood, open wounds, sexual contact, and insect bites, to name just some.

MICROBIAL PATHOGENS

Germs, infectious microorganisms, or agents, such as viruses, bacteria, parasites, and fungi that can cause infections.

HOW DOES THE BODY DEFEND ITSELF?

To successfully fight off bacteria and viruses, the human body has developed multiple ways to prevent infections. These include physical barriers like the skin, which limits access of microorganisms to deeper tissues, as well as the mucus and fluids on our mucous membranes, which wash away bacteria and viruses and also contain molecules that kill and inactivate them. A more specific defense against unwanted microbial pathogens is called the immune system, which consists of two branches. The **innate immune system** is ready to attack microbial pathogens the very first time we see them, by recognizing specific microbial patterns. To be better prepared for a second attack, the **adaptive immune system** learns from the first contact with a microbial pathogen and can remember microbes it has seen before, responding more quickly and powerfully if the pathogen returns.

INNATE IMMUNE SYSTEM

Part of the immune system that attacks microbial pathogens upon first contact.

ADAPTIVE IMMUNE SYSTEM

Part of the immune system that has been acquired through first contact with microbial pathogens, mounting a specific and efficient response to eliminate microbial pathogens.

ANTIMICROBIAL PEPTIDES

Small peptides that can destroy bacteria and viruses.

In this article, we will concentrate on one important part of the innate immune system, called **antimicrobial peptides** (AMPs), which can be found in many different organs and tissues or on the surfaces of mucous membranes or the skin. On human skin alone, more than 20 different AMPs have been found.

WHAT ARE ANTIMICROBIAL PEPTIDES?

AMPs are an ancient defense mechanism that can be found in almost all living organisms [1]. Most AMPs are rather small, consisting of about 20–50 amino acids, which are the building blocks of peptides and proteins, which are larger than peptides. AMPs can be generated by skin cells and cells of the immune system that are present on our mucous membranes or skin. Some cells of the innate immune system make their own AMPs, but AMPs can also be generated by chopping up other large proteins that normally perform entirely different functions in the body. The small fragments of larger proteins gain the ability to attack microbial pathogens, so these larger proteins, called **AMP precursors**, serve two functions.

AMP PRECURSORS

Larger protein that is cut down to a fragment with antimicrobial activity.

EXAMPLES OF HUMAN AMP PRECURSORS

To ensure that enough AMPs are generated when the precursor is chopped up, the precursor protein itself should be present at high concentrations. Indeed, all proteins known to release AMPs are highly abundant and can be found almost everywhere in the human body. One example is hemoglobin, the iron-containing red pigment in red blood cells, which gives rise to many AMPs with antibacterial and antiviral activity [2]. Another important example is fibrinogen. Fibrinogen is involved in blood clotting and wound healing, which means that fibrinogen might speed up the wound-healing process by both helping with clotting and producing AMPs to help keep the wound uninfected. Thrombin is another important source of AMPs. Thrombin plays an important role in the blood coagulation pathway. Other examples of AMP precursors include prostatic acid phosphatase and semenogelins, which are highly abundant in human semen. When these semen proteins are cut up into AMPs, they form fibers that can capture bacteria in the female reproductive tract, helping the cells of the immune system to more effectively destroy bacteria [3].

HOW ARE THE PROTEIN FRAGMENTS GENERATED?

PROTEASE

Enzyme that cuts proteins.

The large AMP precursors are chopped up into AMPs by special cutting proteins called **proteases**. Proteases are enzymes that cut proteins into smaller fragments. Protein fragments are called peptides if they are less than ~100 amino acids long. Proteases are mainly found in the gut, for the digestion of proteins in food. Proteases cannot distinguish between the proteins of the human body and food proteins that need to be chopped up. Therefore, protease activity is tightly regulated to prevent uncontrolled digestion of our own proteins. However, several proteases also cleave the hemoglobin that gets into our tissues when injury or bleeding occur. The AMPs produced from chopped-up hemoglobin have antibacterial and antiviral activity, which the complete hemoglobin protein does not have.

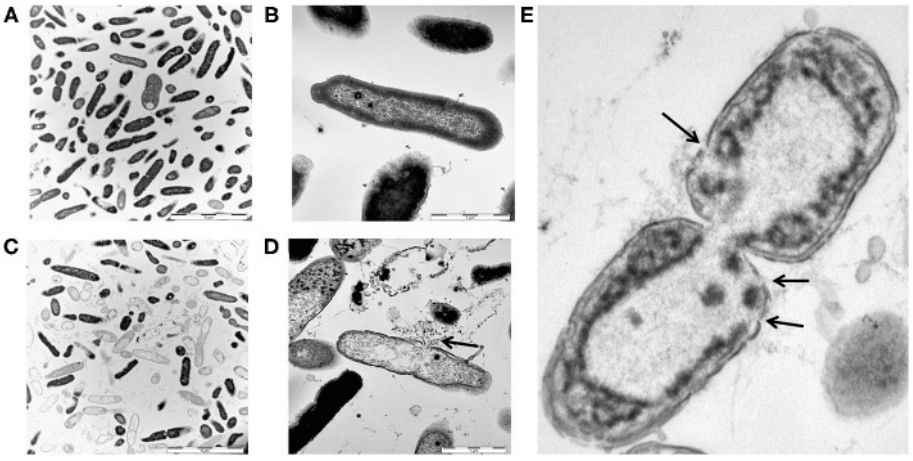

Figure 1

Electron microscopy pictures of bacteria (*Pseudomonas aeruginosa*) with and without treatment with an AMP originating from hemoglobin [2]. **(A,B)** Bacterial cells that were not treated with the AMP are healthy and whole. **(C–E)** Bacteria that were treated with the AMP from hemoglobin for 1 h. Black arrows indicate destroyed bacterial cell membranes and the spilling of the content from inside the bacterial cells.

Figure 1

HOW DO AMPs STOP BACTERIA?

AMPs often have a positive charge, and bacterial membranes often have a negative charge. Positive and negative charges attract each other, making it easy for AMPs to bind to the bacterial surface. Furthermore, AMPs are often **amphipathic**, meaning part of the peptide molecule is attracted to water, while another part is more attracted to lipids (fats). The amphipathic nature of AMPs helps them to bind to the bacterial membrane, because the membrane consists of both lipids and some water-like parts.

AMPHIPATHIC

Characteristic of a molecule that has a part being attracted to water and a part being repulsed by water and attracted to lipids (fats).

After attaching, the AMPs insert into the bacterial membrane and may form a small tunnel, called a pore. This process resembles punching a hole into the bacterial cell, which leads to leakage of the cell's contents and death of the bacterium. The whole process can be seen using an electron microscope (Figure 1). There are also AMPs that do not attack the bacterial cell membrane directly, but instead disturb the function of important molecules inside the bacterial cell, such as the molecules that help build the bacterial cell wall. Some AMPs can bind directly to bacterial DNA, destroying the DNA's ability to pass on genetic information for the building of new proteins or bacterial cells.

HOW DO AMPs INHIBIT VIRUSES?

Viruses are different from bacteria in that they can only multiply within cells—so viruses must get into human cells before they can replicate and make us sick. Some AMPs can interfere with the various steps of virus multiplication. AMPs called magainins, from frog skin, interact with the outer surface of the virus and disrupt the virus's structure. A human peptide called VIRIP, isolated from blood, is an AMP that can inhibit the entry of human immunodeficiency virus into human cells. Some AMPs can block the attachment of viruses to cells. One example

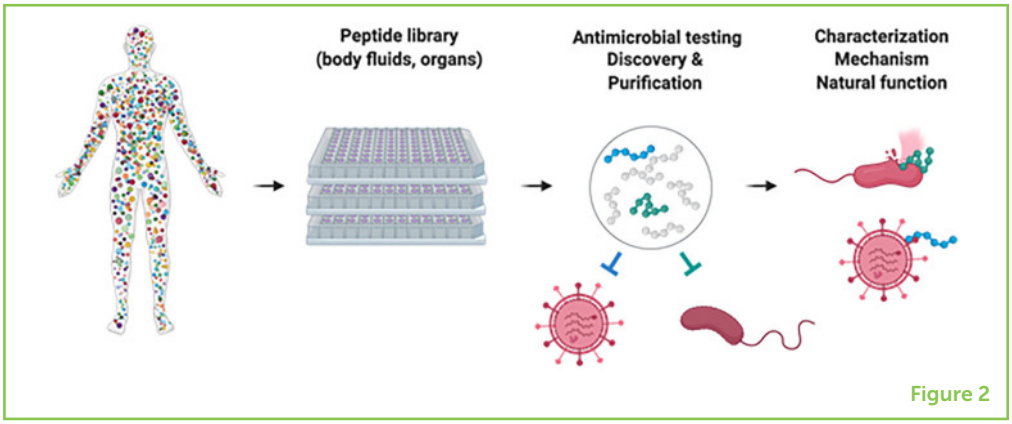

Figure 2

How to find new antimicrobial peptides: human organs or body fluids are homogenized and small molecules extracted. Peptides are separated by chromatography, yielding hundreds of fractions. Antiviral and antibacterial activity of these fractions is evaluated and those with antimicrobial activity are further separated. Eventually, the antimicrobial peptide is discovered and its mechanism of action can be determined. Figure created with biorender.com.

is a blood-derived peptide that inhibits the initial binding of a virus called cytomegalovirus to human cells. Human AMPs called defensins and cathelicidins are also known to help prevent viral entry into cells, but they also interfere with later steps of virus multiplication.

FINDING NEW AMPs

While many different human AMPs have been identified in recent years, there are certainly many that we have not yet found. Microbial pathogens are becoming more and more resistant to common antibiotics and antiviral drugs, making these drugs useless to fight infections. It is therefore important to find additional AMPs with antibacterial or antiviral activity, so that these may eventually be developed into new drugs. To detect new human AMPs, it is possible to generate large peptide libraries from various organs and body fluids, containing hundreds of thousands of different peptides. With the consent of the donor, tissues removed during surgeries and body fluids collected during medical procedures are used to generate peptide libraries for research purposes.

To make a library from tissues, the tissues must first be liquified to make an extract. Body fluids or tissue extracts are immediately cooled, acidified, and then frozen to prevent the peptides within them from breaking down. A special filter is used to concentrate the peptides, and larger proteins are removed. The peptides are then separated using a method called **chromatography**. Following chromatography, many thousands of different peptides are available as a peptide library, which can then be tested for peptides that inhibit bacterial growth or virus infection [4, 5] (Figure 2). A fraction of the peptide library that shows antibacterial or antiviral activity can be further purified, retested, and eventually the identity of the AMP can be determined. Finally, the AMP can be recreated in the lab and analyzed for its level of activity, its role in preventing infections, and its ability to be used as a medical treatment.

CHROMATOGRAPHY

Method to separate a mixture of different substances.

CONCLUSION

Multiple antimicrobial peptides are present in our bodies that help prevent infections. They are part of our innate immunity and can be generated from larger human proteins that have other purposes. To find new AMPs large peptide libraries can be searched and AMPs may eventually be developed into antibacterial or antiviral treatments.

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YOUNG REVIEWER

ANISHA, AGE: 14

I have always been interested in the fields of science and math and so when I grow up I wish to be a biomedical engineer. In school, my favorite subjects are math and all the sciences. In my freetime, I enjoy playing the piano as well as reading. Some of my favorite books include The Wonderful Wizard of Oz and the Harry Potter series. I also enjoy trying new experiences and foods.

AUTHORS

BARBARA SPELLERBERG

Barbara Spellerberg studied medicine in Aachen and started her medical career in the department of pediatrics at the University Hospital of the RWTH Aachen. During a post-doc at Rockefeller University in New York in the laboratory of Molecular Infectious Diseases, she began to work on the molecular biology of Streptococci. She subsequently returned to Aachen to the National Reference Center for Streptococci and did a residency in medical microbiology. In 2002, she became an Associate Professor for Medical Microbiology and Hygiene at the University of Ulm. She has more than 80 publications in peer-reviewed journals. *barbara.spellerberg@uniklinik-ulm.de

LUDGER STÄNDKER

Ludger Ständker obtained a degree in biochemistry from the University of Hannover (Germany) in 1994. In 1996, he received his Ph.D. in peptide chemistry in the lab of Prof. W.G. Forssmann, Hannover Medical School, Germany. After positions as post-doc and laboratory head at Pharis Biotec company, habilitation in biochemistry in 2001, from 2005 to 2006 Dr. Ständker was Marie-Curie fellow at the at the Center for Biological Investigation (CIB, CSIC), Madrid, Spain. Since 2012, he has headed the Core Facility of Functional Peptidomics at Ulm University. Dr. Ständker has published more than 60 scientific articles and several patent applications.

RÜDIGER GROß

Rüdiger Groß studied biochemistry at Ulm University, graduating with a master's degree in 2017. He joined the lab of Jan Münch for his master thesis work and subsequently started his Ph.D. studies in 2018, which are funded by a scholarship awarded by the International Graduate School in Molecular Medicine, Ulm. He has published more than 15 articles in peer-reviewed journals.

JAN MÜNCH

Jan Münch studied biology at the Friedrich-Alexander-University Erlangen-Nuremberg and graduated in 1998. He then joined the lab of Frank Kirchhoff at the Institute of Virology and received his Ph.D. in 2002. Thereafter, he was a post-doctoral at the Institute of Virology at Ulm University, where he was appointed as W1 professor 2 years later. In 2010, he was appointed full professor at the Institute of Molecular Virology at Ulm University and in 2017 was appointed Director. He has published more than 130 articles in peer-reviewed journals and received many prestigious awards from academia and industry.

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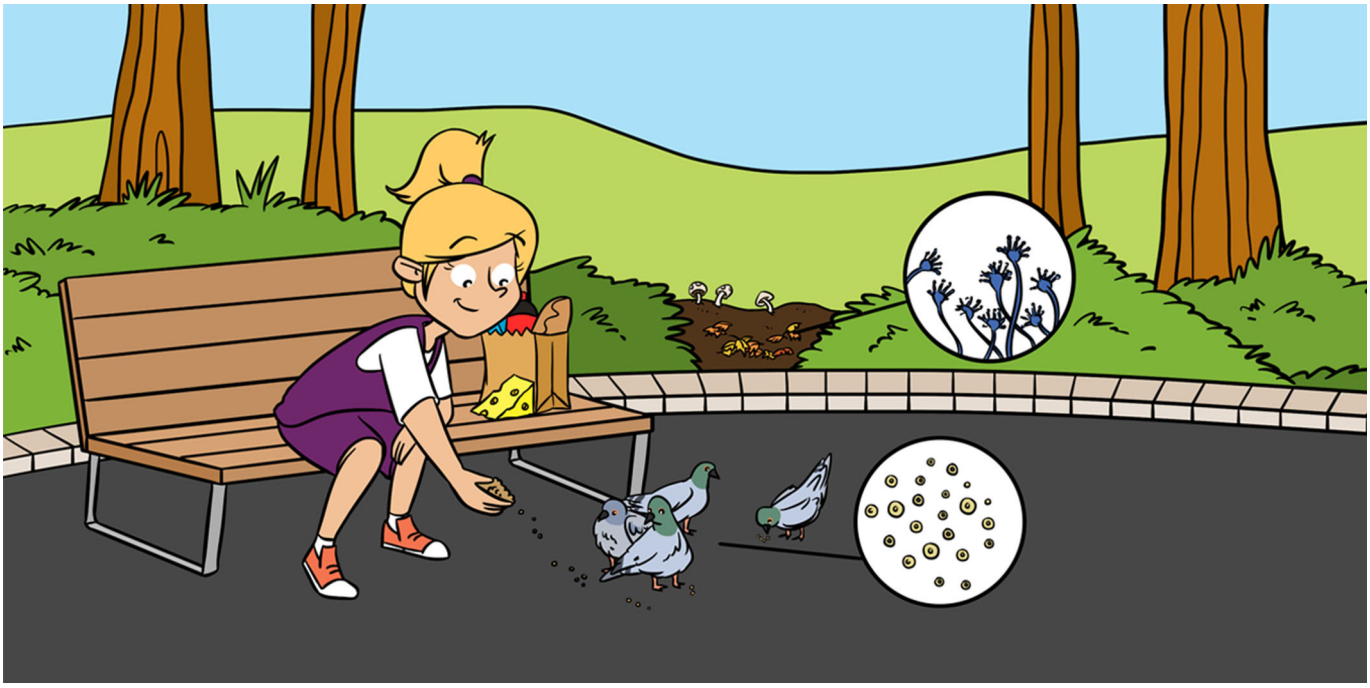

THE FUNGUS AMONG US: WHY THE TREATMENT OF FUNGAL INFECTIONS IS SO PROBLEMATIC

***Katrin Haupt*[1], *Lysett Wagner*[1,2], *Antje Häder*[3] *and Slavena Vylkova*[1*]**

[1] *Septomics Research Center, Leibniz Institute for Natural Product Research and Infection Biology–Hans Knöll Institute, Friedrich Schiller University, Jena, Germany*

[2] *Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany*

[3] *Fungal Septomics, Leibniz Institute for Natural Product Research and Infection Biology–Hans Knöll Institute, Jena, Germany*

YOUNG REVIEWERS:

CHINMAYA
AGE: 14

SHARVARI
AGE: 15

SOPHIA
AGE: 11

When we think of microbes that can make us sick, it is usually bacteria that cross our minds first. We tend to forget about another major microbial type that can also cause severe diseases: the fungi. Yeasts and molds make up the majority of microscopic fungi and both types can cause various infections in humans, from mild skin rashes to deadly blood infections. These fungi have found several ways to cause us harm, such as using the body's nutrients, escaping the surveillance of the immune system, or hijacking and destroying our cells. On cellular level, we have a lot in common with fungi. These common features between human cells and fungal cells makes the development of antibiotics and vaccines to treat fungal infections very difficult. In this article, we will describe some fungal infections and explain current options for their treatment.

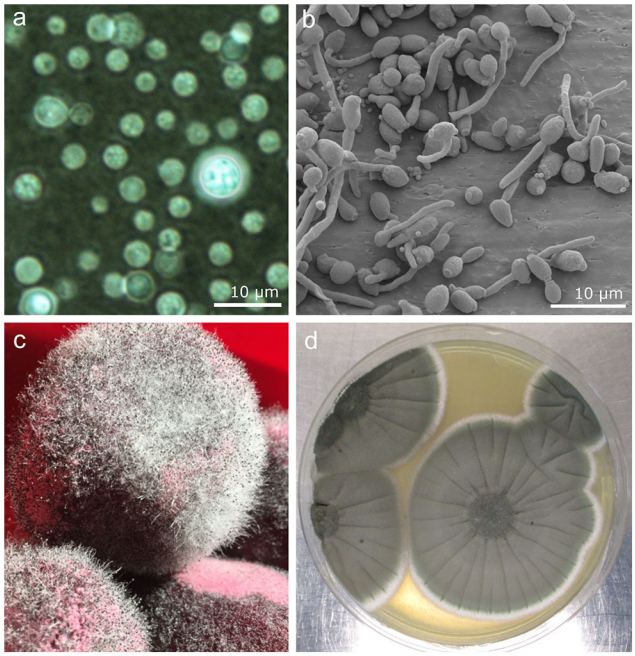

Figure 1

Images of fungi that infect humans. **(a)** Microscopic image of *Cryptococcus neoformans* stained with ink. **(b)** Seen through a scanning electron microscope, *Candida albicans* starts to form mycelium. **(c)** *Rhizopus* species growing on cooked beetroot. The fur-like substance is the mycelium and the tiny black dots on top contain the spores. **(d)** *Aspergillus fumigatus*, isolated from soil, as seen with the naked eye as it grows in the lab.

FUNGI AMONG US: FRIENDS AND FOES

In the tree of life, fungi are classified in their own kingdom. They are different from bacteria, plants, or animals. "Fungus" in Latin means mushroom. That is why we tend to think only about mushrooms as the fungi among us. However, the fungal kingdom is very diverse and there are thousands of fungi that we find only when we dive into the microbial world, where organisms are so tiny that they can only be seen under a microscope. The microscopic fungi come in many different shapes and forms (Figure 1), and can be found everywhere in nature, like in the soil or attached to living creatures. They play many important roles in our lives, such as decomposing organic matter in the compost pile or bringing nutrients to plants. For thousands of years, we have been using fungi to produce foods and beverages like bread, cheese, soy sauce, and beer. Fungi are also used to make the antibiotic penicillin, which kills bacteria, and to produce citric acid, which is what gives juices and sodas a sour note.

Some fungi even live in our bodies. Together with more than 10,000 other microbial species found in our guts and on our skin, fungi make up our **microbiota**. The microbiota is composed of millions of harmless microorganisms that inhabit the human body. Usually we live happily together. We can come into contact with other fungi from the environment by breathing them in, for example. But we almost never notice them, as the mucus that covers our airways usually clears them out. However, sometimes this is not the case: both types of fungi—the ones living in harmony inside us and the kinds in the environment—can cause infections.

MICROBIOTA

All the millions of harmless microorganisms that inhabit the human body.

Interestingly, only a few hundred fungal species of the almost 5 million that inhabit the Earth can cause infections in humans [1]. In contrast, about 50,000 species of fungi infect insects. Why is the number for humans so low? First, the relatively high and always stable body temperature of ~37°C keeps them away. Most of the fungi favor much lower temperatures [2]. Next, most fungi are successfully fought off by the human immune system, which does a very good job of eliminating fungi when they infect healthy people.

Fungi can cause a range of infections in humans, from unnoticeable to deadly. We barely notice the fungus that can cause dandruff, for example. This condition is annoying and embarrassing, but rarely causes us harm. Other fungi can cause life-threatening infections that shut down the entire body. Typically, people with disturbed or defective immune systems, such as patients being treated for cancer, organ transplant recipients, or the elderly, suffer the most. Such infections are very difficult to treat.

WHICH FUNGI ARE THE MOST DANGEROUS AND HOW DO THEY MAKE US SICK?

Cryptococcus

Cryptococcus species, and particularly *Cryptococcus neoformans,* are like kryptonite for humans. Normally, this fungus lives on plants or in animals worldwide. Pigeons, for example, have a lot of *Cryptococcus neoformans* in their droppings, and although this does not bother them, it can bother us. The dust from pigeon droppings is spread in the air that we breathe. In healthy people, if *Cryptococcus* enters the lungs it is defeated by the immune system, but in people with immune defects it can survive, grow, and reach other parts of the body, such as the brain. If left untreated, it can cause death [3].

Candida

Candida species, particularly one called *Candida albicans*, are the most common fungi that cause diseases in humans. *Candida albicans* is normally part of our microbiota, but can, if given the chance, turn against us. *C. albicans* can cause infections of the skin or the mouth and can even enter the bloodstream and cause a life-threatening blood infection called **sepsis**. *Candida* cells can transform from a rounded shape into a long filament called a **mycelium**. The mycelium can easily grow deep into the tissue or form complex structures that can resist the immune system's attack or drug treatment. Scientists do a lot of research to figure out what allows *Candida* to switch from one form to the other, because the switch could be a potential target for new drugs [3].

SEPSIS

The most severe form of an infection, which can lead to organ failure and often death.

MYCELIUM

Thread-shaped cells of a fungus.

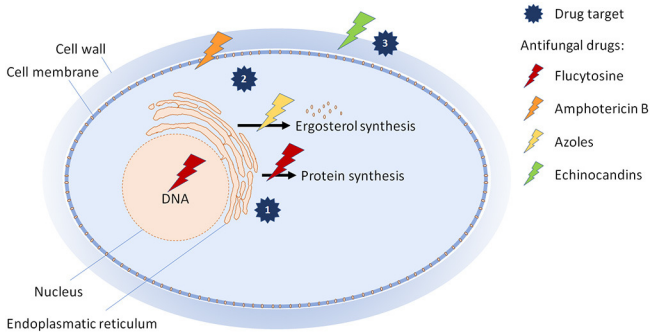

Figure 2

Figure 2

How common antifungal drugs work. Currently, antifungal drugs are directed against three different targets in the fungal cell: **(1)** The drug flucytosine disturbs the production of DNA and proteins in the fungal cell; **(2)** amphotericin B and azoles target the cell membrane by interfering with a fat called ergosterol; and **(3)** echinocandins block the building of the sugar molecule glucan, which is an essential brick of the fungal cell wall.

SPORES

Round-shaped reproduction units of a fungus, similar to seeds, which can grow into a mature mycelium.

Molds

Molds usually live in soil and on dead, decaying matter. They produce mycelium with thousands of tiny **spores** on top. These spores function as seeds as they can be used for reproduction or to withstand harsh conditions. The spores are easily spread by air and enter our lung when we breathe. As mentioned above, this is typically problematic only for people with weak immune systems. The most important molds that cause disease are *Aspergillus* species, mostly *Aspergillus fumigatus*, and the Mucorales species *Rhizopus*, *Lichtheimia*, and *Mucor*. In the lungs of vulnerable individuals, *Aspergillus fumigatus* spores can grow into a mature fungus, enter the bloodstream, and spread around the body to cause a severe, and often fatal, infection called invasive aspergillosis. Mucorales species cause a similar course of infection: once in the body they can breach the immune barriers, spread, and become potentially deadly. Mucorales are fast-growing fungi that resist many drugs, so immediate diagnosis and treatment are necessary [3, 4].

HOW DO ANTIFUNGAL DRUGS FIGHT THE FUNGI?

On the cellular level, we have much in common with fungi. So, it is likely that a substance directed against fungi could also harm us. Therefore, it is quite difficult to design drugs that kill only the fungi. Any potential antifungal drugs have to pass toxicity tests on human cells and other rigorous tests to make sure they are safe for human use.

So far, only three fungus-specific vulnerable spots are targeted by drugs (Figure 2). First is the cell membrane. The cell membrane of fungal cells has a certain type fat called **ergosterol**, which is only produced by fungal cells. Without ergosterol the fungus cannot survive. Two antifungal drugs successfully target this molecule: Amphotericin B targets ergosterol itself, while drugs called azoles disturb its production. Amphotericin B is used only as a last-resort drug, because it is somewhat toxic to human cells.

ERGOSTEROL

A type of fat found in cell membranes of fungi. Ergosterol serves similar functions as cholesterol serves in human cells.

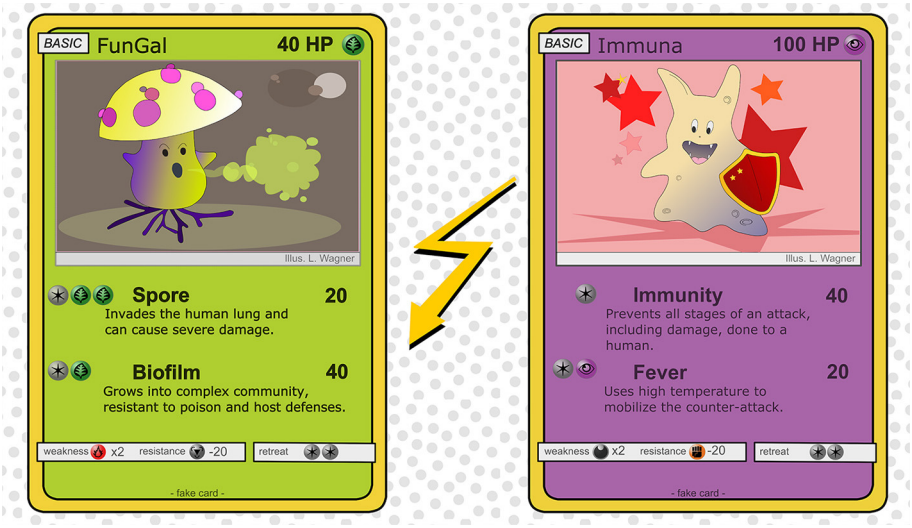

Figure 3

The immune system fights fungal invaders. FunGal (a.k.a. fungus) lives in the environment or associated with the human body, but sometimes can invade the human to cause infection. The powerful Immuna (a.k.a. human immune system) attacks and defeats FunGal. However, in some people, Immuna is weakened, so FunGal can cause infection and antifungal drugs are urgently needed to stop FunGal's attack.

Another way to eradicate fungi is with a substance called flucytosine, which targets essential for fungal survival processes, such as production of DNA and building of proteins. But this medicine also leaks into human cells and has many severe side effects. So, this drug is used mainly in combination with Amphotericin B and only for very serious cases.

The third drug target is the fungal cell wall. In contrast to human cells, fungal cells are surrounded by a thick wall made from a substance called **chitin**, as well as sugars and proteins. A class of drugs called echinocandins interferes with the building of a sugar molecule called **glucan**, an essential brick of the cell wall. Echinocandins are very safe for humans, but they work only when injected into the bloodstream, which is not very practical.

So, with only three types of drugs, each with some disadvantages, doctors are facing a problem choosing the most effective and safe treatment for fungal infections. Therefore, there is an urgent need to find new targets and treatment strategies for these infections [5].

CHITIN

A sugar that is the major part of the fungal cell wall. Chitin also forms the exoskeleton of insects and other arthropods.

GLUCAN

A complex sugar molecule that composes the fungal cell wall, a structural layer that surrounds the cell and provides support and protection.

NEW ANTIFUNGAL THERAPIES ON THE HORIZON

One way to fight drug-resistant fungi is to combine several medicines. In this way therapy could be much more powerful. This has already worked to fight other deadly diseases. Combining two antifungal drugs has also proven successful for *Cryptococcus* infections [5]. Other attempts aim at inhibiting the infectious properties of these fungi. But what if we could prevent humans from getting fungal infections in the first place? We could protect ourselves by keeping our immune systems healthy, or by vaccination. While there are numerous vaccines against viruses and bacteria, no vaccine can protect us from fungal

diseases. Fortunately, many attempts to design vaccines against fungal infections are in progress.

CONCLUSION

Even though our body temperature and powerful immune system keep infections away, fungi can still cause us harm (Figure 3). Patients with weak immune systems are particularly prone to invasive fungal infections. The number of patients at risk is continuously increasing. At the same time, treatment of these infections is complicated because of the limited number of drugs and the increase in drug-resistant fungal species. Doctors urgently need more safe and effective medicines against fungal infections. Fungi are not only dangerous for humans: plants, insects, and cold-blooded animals like fish and amphibians get infected too. For example, the fungus *Batrachochytrium dendrobatidis* has already caused the extinction of over 100 frog species worldwide [1]. Therefore, researchers must keep working to find out more about how fungi cause infections and how to fight these potentially dangerous organisms.

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CONFLICT OF INTEREST: 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

CHINMAYA, AGE: 14
My name is Chinmaya. I am in ninth grade. I love Mathematics. I am extremely interested in Science and Sanskrit language as well. I am a voracious reader. My hobbies are playing flute and writing poems.

SHARVARI, AGE: 15
My name is Sharvari. I am very interested in theater and I have acted in a few plays, but I also find science as interesting and fascinating. In my free time, I like to read and paint. I love being with nature, and that is why I like science. When there is free time I like to hike, trek, etc.

SOPHIA, AGE: 11
My name is Sophia, I am 11 years old. I am Brazilian and love to play with my friends and watch videos on the internet.

AUTHORS

KATRIN HAUPT
Katrin holds a Ph.D. degree in Biology. She is a scientific coordinator at ZIK Septomics—a research institute of the Friedrich Schiller University in Jena, Germany. Her task is to support scientists in administrative matters of their research projects. She is fascinated by infection biology and the interaction between pathogens and

humans. In her spare time, she likes watching movies, riding her bike, and being outdoors in nature.

LYSETT WAGNER

Lysett is a microbiologist who loves fungi and likes to put things in the right order. That is why she classifies microorganisms in a scientific way. In addition, she is very curious about microbes that cause infections. Currently, she studies biofilms built by fungi and bacteria that can cause sepsis in patients. Even in her spare time, while cooking or gardening, she thinks a lot about microorganisms and how they are doing, for example the yeast in dough or the organisms growing on the roots of her pampered tomato plants.

ANTJE HÄDER

Antje is a Ph.D. student in the Leibniz Institute for Natural Product Research and Infection Biology–Hans Knöll Institute in Jena, Germany. She investigates how small differences in the DNA sequences between individuals influence the immune response toward fungal and bacterial infections. The analysis of variability in human DNA is an interesting topic, because it helps scientists to understand why the susceptibility to certain diseases differs between individuals.

SLAVENA VYLKOVA

Slavena is a leader of a young team of microbiologist at ZIK Septomics. She and her group study the interactions between infectious fungi and humans, with respect to factors that allow fungi to survive in the body and cause harm. Slavena's favorite subject at school was biology, an interest that turned into her hobby and career. She is an energetic and creative person who likes to "infect" young minds with her science enthusiasm. *slavena.vylkova@leibniz-hki.de

frontiers FOR YOUNG MINDS

HEALTH
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A MOLDY WAY TO FIGHT INFECTIONS—THROUGH METAL NANOPARTICLES

Jessica Berry [1]***, Cristiane A. Ottoni*** [2] ***and Marta Filipa Simões*** [3,4*]

[1] *Royal Hallamshire Hospital, Sheffield Teaching Hospitals National Health Service (NHS) Foundation Trust, Sheffield, United Kingdom*

[2] *Bioscience Institute, Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), São Vicente, Brazil*

[3] *State Key Laboratory of Lunar and Planetary Sciences, Macau University of Science and Technology, Macau, China*

[4] *China National Space Administration (CNSA), Macau Center for Space Exploration and Science, Macau, China*

YOUNG REVIEWER:

MRITTIKA

AGE: 13

Many microbes, which are tiny organisms capable of causing disease, have developed resistance to the common drugs used against them. Alternative drugs are being developed to fight these resistant microbes. One of these alternatives is the use of metal nanoparticles, which are extremely tiny particles of metals like silver, gold, or copper. Metal nanoparticles can be used directly against microbes or as complements to traditional therapies. They can also be used for many other applications in various industries. Filamentous fungi, commonly called molds, can be used to produce alternative ways to fight microbial infections. Here, as an example, we explain the production of silver nanoparticles by filamentous fungi, and how these nanoparticles could be used.

INTRODUCTION

Fungi are a diverse group of organisms and they are everywhere. There are many known species, but we have not discovered them all yet. In fact, we have only managed to describe 8–10% of all fungal species. This leaves much to be explored, studied, and understood [1]. Fungi can have different appearances, sizes, and colors, depending on where they grow. When observed under a microscope, we can see their structures in detail like in Figure 1. The amount of detail depends on the type of microscopy that we use (see Box 1).

You can see an increase in detail from stereomicroscopy (Figure 1C), to optical microscopy (Figure 1D), and then to scanning electron microscopy (SEM) (Figure 1E).

Fungi have adapted to each place they inhabit. One adaptation is their ability to create several chemical substances, called **metabolites**. Fungi use their metabolites as weapons against bacteria or even other fungi. Humans can also make use of some of the metabolites as **antibiotics** to fight infections caused by bacteria, or even use them to fight cancer [1].

METABOLITES

Chemical substances released during the active metabolism of a microbe, in our case fungi. Some types of metabolites are drugs, like antibiotics, as well as pigments used for food coloring.

ANTIBIOTIC

Substance used to treat or prevent infections caused by bacteria.

WHY DO WE NEED FUNGI TO HELP US FIGHT INFECTIONS?

Drugs are becoming less and less effective against pathogenic microbes. This is a worrying worldwide problem, leading to diseases that are not easy to treat and microbes that are not easy to kill. When exposed to medicines, microbes can adapt. Then, if they develop the capacity to survive, they turn into superbugs, with the capacity of **antimicrobial resistance**. We need urgent alternatives to our current drugs. **Metal nanoparticles** (MNPs) are part of the ongoing wave of exploration of such alternatives. These are extremely tiny particles of metals that can be made of silver, gold, or copper.

Scientists have discovered that fungi can be used to produce MNPs. Production of MNPs by fungi is sustainable, meaning that large amounts can be produced faster and cheaper than other production methods, and it does not produce chemical hazardous waste. The most useful types of fungi for production of MNPs are molds. Molds, also known as **filamentous fungi**, are different from mushrooms. They form filaments or mycelia (Figure 1C). Molds are very sturdy organisms and can accumulate metals from the surrounding environment. This makes them ideal producers of MNPs.

ANTIMICROBIAL RESISTANCE

Capacity of some microbes to resist to the exposure of drugs intended to kill them, and to continue to grow.

METAL NANOPARTICLES

Very small particles, with sizes ranging from 1 to 100 nm, of metal. Much smaller than most microbes.

FILAMENTOUS FUNGI

Fungi that form filaments called mycelia.

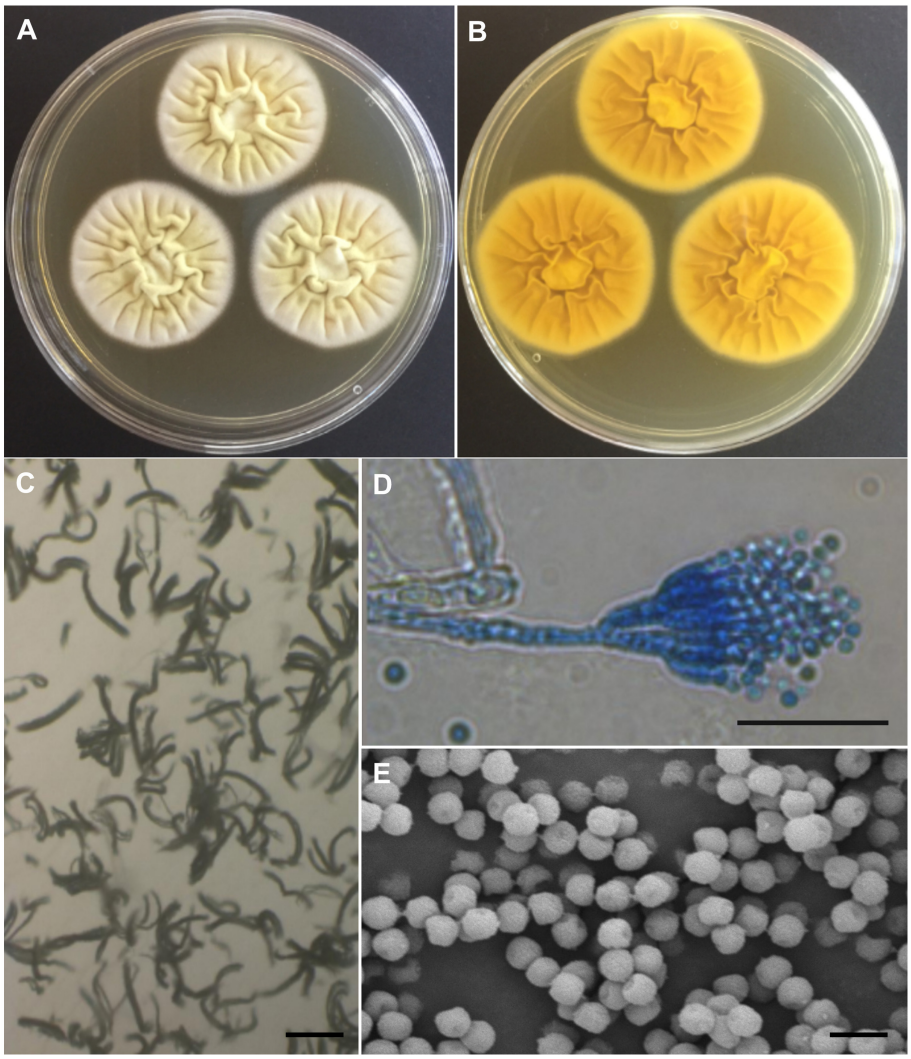

Figure 1

Different views of one strain of *Penicillium* sp., with increasing detail. **(A,B)** Petri dishes (diameter = 90 mm) with colonies as seen with the naked eye, from the front **(A)** and the back **(B)**. **(C)** Stereomicroscopy analysis of fungal mycelia or filaments (×10 magnification, scale bar: 75 μm). **(D)** Optical microscopy (400× magnification, scale bar: 20 μm). **(E)** Scanning electron microscopy image of fungal spores (8,000× magnification, scale bar: 5 μm).

HOW ARE METAL NANOPARTICLES PRODUCED?

MNPs can be made of different metals, including copper, cobalt, palladium, selenium, platinum, and lead. But, the most researched and used MNPs are silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs). AgNPs and AuNPs have been shown to have antimicrobial activity, which means they can kill or prevent the growth of many microbes. This activity is not completely understood. However, we know that some metal ions released from the MNPs (AgNP, Figure 2E) can inhibit bacterial and fungal growth [2]. We also know that both AgNP and AuNP work by damaging the cell membranes of microbes. The antimicrobial activity of the nanoparticles can be affected by their surface, composition, and amount. MNPs also have different effects depending on the type of microbes they are used against [3].

MNPs can be made by several different processes. These processes can be physical, chemical, or biological [4]. Chemical synthesis uses potentially hazardous chemicals and generates toxic waste products.

Box 1 | Microscopy types

There are several different microscopes that vary in the type of images obtained, size, price, and complexity. More complex microscopes will show higher amounts of detail, but will be bigger, more complex to use, and more expensive. You can see an increase in detail from stereomicroscopy, to optical microscopy, and then to electron microscopy. Electron microscopy can be scanning electron microscopy (SEM) or transmission electron microscopy (TEM). See Figure 1 for an example of the levels of detail that can be seen with different kinds of microscopes.

Microscope	Description
Stereomicroscope	Also called dissecting microscope, uses regular light to form images, provides a low magnification of up to 300 times.
Optical microscope	Also uses regular light to form images but can provide a magnification of up to 1,000 times. It is the most common type of microscope used.
Scanning electron microscope (SEM)	Uses electrons instead of light to form images from samples analyzed in vacuum. Can produce a magnification of 1–3 million times.
Transmission electron microscope (TEM)	Also uses electrons instead of light, but forms images from samples prepared in slides or grids (like slices of bacteria) and with some degree of transparency, presenting increased details. Offers much higher magnifications up to 50 million times.

These waste products, if released into the environment, will affect the ecosystem. Physical synthesis uses mechanical methods (like crushing) to change large-sized pieces of metal into nano-scale sized particles [4]. **Biological synthesis** of MNPs, which means their formation using living organisms (in this case fungi), is often the preferred method. It is considered an eco-friendlier technique when compared to others. Its resulting MNPs are more compatible with living tissues and less toxic for medical analyses; and, many microbes, including fungi, can serve as eco-friendly nanofactories of MNPs [3].

BIOLOGICAL SYNTHESIS

Production or formation of compounds from simpler elements, mediated by living beings or organic substances from organisms. In our case the biological synthesis of MNPs is promoted by fungi.

Biological synthesis of MNPs using fungi is a relatively simple process. This is because fungi secrete large amounts of metabolites that can be used to produce MNPs. For example, to produce AgNPs from filamentous fungi (Figure 2), the fungi must first be grown in an appropriate growth medium (one where the fungus grows better and which might be different for each fungal species), which is like a broth. After they have grown for a while, the fungal cells are removed from the broth and put in water, where the cells release metabolites. The fungal cells are then removed and the water containing the metabolites is kept. This solution, free from fungi, is called the **supernatant**. The supernatant is used to form MNPs through a biological process that happens when certain chemicals are added to the supernatant. Formation of MNPs is noticeable by the change of color from yellow to brown, but it can then be further analyzed by

SUPERNATANT

Remaining liquid solution, after removal of all solid substances.

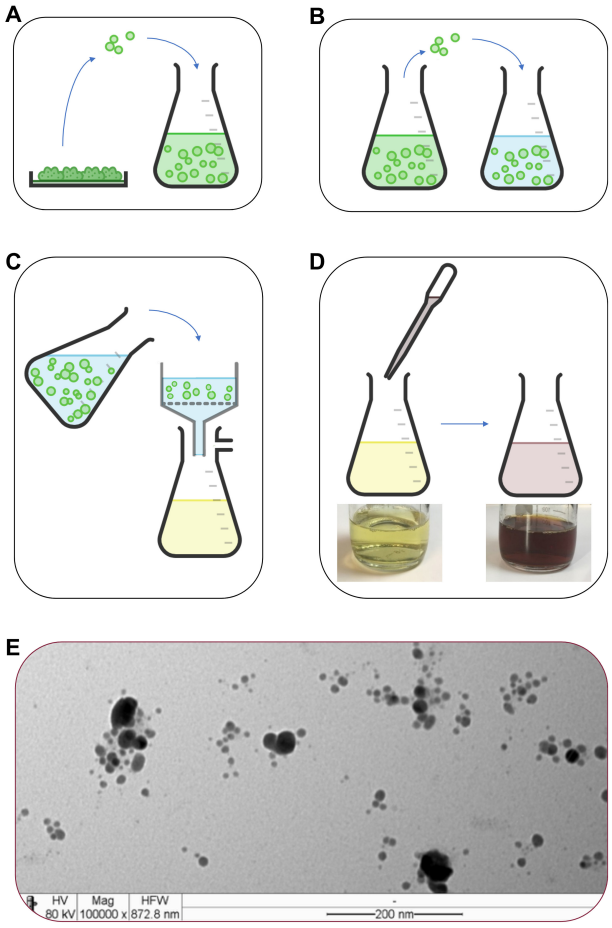

Figure 2

(A) Small pieces are cut from fully grown fungal colonies (in Petri dishes) and transferred into liquid broth where further growth will occur (4–5 days). **(B)** The fungal cells are removed from the broth and placed in sterile water, where they release metabolites. **(C)** After 1 day, the fungal cells are removed by filtration and the supernatant is kept. **(D)** A chemical is then added to the supernatant and left for some time (varies from hours to days) until MNPs are produced. Their production is detected by color change or microscopy. **(E)** Here you see a TEM image of AgNPs synthesized by a strain of *Penicillium citrinum*.

Figure 2

several complex techniques, like electron microscopy, to make sure MNPs have been produced (Figure 2E) [3]. For the formation of AgNPs, the chemical added to the supernatant is silver nitrate. The yellow supernatant obtained from the fungus *Penicillium* sp. will turn brown after 4 days of incubation with silver nitrate, resulting in AgNPs.

OTHER USES OF MNPs

As mentioned, MNPs can be used to fight infections caused by bacteria, fungi, or viruses. But they can also be used to detect infections as part of medical tests, or in food packaging, to help prevent microbes from contaminating the food. They can be added to the materials used to make medical equipment, preventing microbes from attaching to this equipment. This could help in preventing infections, for example during surgeries. MNPs in the form of ointments, topical creams, or solutions can be applied directly to wounds. MNPs can be mixed with other materials or chemicals, as a part of other antimicrobial drugs, or can even be used as a vehicle to deliver other compounds, by carrying them to specific target cells. MNPs can also have anti-cancer activity, they can be used as an ingredient in cosmetics, or used in batteries and textiles. They have applications

in industries very different from the medical and pharmaceutical sectors, including agriculture, food industry, in energy and automobile industries, and in many biotechnology fields [2, 4].

CONCLUSION

Filamentous fungi (or mold) are easy to manipulated in the laboratory, simple to grow, able to form large amounts of cells, at relatively low costs. This makes them ideal organisms for biological processes, such as the production of MNPs.

As you have learned, there are many uses of MNPs in the fight against a wide range of infections. But there is much yet to explore. With the discovery of new filamentous fungal species, we might be able to develop better and more efficient biological processes to produce MNPs with higher antimicrobial activity against infectious microbes. Such MNPs might help in the fight against superbugs.

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YOUNG REVIEWER

MRITTIKA, AGE: 13

Mrittika loves hanging out with her friends and family. Her interests include: playing the viola and ukulele, dancing, poetry, singing, reading, and calligraphy. Math, Social Studies, and Music are among her favorite subjects. Her favorite sports are volleyball, karate, and running. Mrittika's favorite accomplishments are becoming a senior editor on her yearbook editing team, and getting onto her school's show choir. She is also her school's geography bee champion and aspires to be a more open-minded and knowledgeable person.

AUTHORS

JESSICA BERRY

I am a Biology graduate from Edge Hill University (EHU), England, where I took a particular interest in both microbiology and laboratory research. I carried out a summer research internship on fetal growth restriction in mice, in which I gained histological and laboratory skills. My research for my final year project focused on the antimicrobial potential of metallic nanoparticles, specifically those synthesized by fungi, to combat harmful microbial diseases, such as tuberculosis. I currently work within the National Health Service (NHS), as part of the Histopathology team, where I process and prepare diseased tissue for diagnosis by trained pathologists.

CRISTIANE A. OTTONI

I am currently a lecturer at the Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), São Paulo, Brazil. Most of my work combines chemistry, biotechnology and microbiology. I have been developing my research in applied nanotechnology, where I focus on studying nanoparticle synthesis and characteristics, as well as their application in several diverse industries and their environmental impact. I also study several other biotechnological processes and different designs and applications of microbial fuel cells.

MARTA FILIPA SIMÕES

I work in astrobiology at the State Key Laboratory of Lunar and Planetary Science (SKLPlanets), at Macau University of Science and Technology (MUST), China. I am a microbiologist who has worked with a myriad of microorganisms (mycobacteria, environmental and clinical bacteria, mycobacteriophages, and filamentous fungi) in several different countries (UK, Saudi Arabia, and Portugal). I study mostly fungal ecology and diversity in environments that are similar to outer-space conditions, I search for new filamentous fungal species or species with new and useful capabilities, and I look into fungal growth to control and stop potential contaminations. *msimoes@must.edu.mo

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DRUG REPURPOSING: A QUICK AND EASY WAY OF FINDING NEW MEDICINES

Álvaro Mourenza[1†], *Natalia Bravo-Santano*[2†], *José A. Gil*[1], *Luís M. Mateos*[1] *and Michal Letek*[1*]

[1]*Área de Microbiología, Departmento de Biología Molecular, Universidad de León, León, Spain*

[2]*ANGLE PLC, Guildford, United Kingdom*

YOUNG REVIEWER:

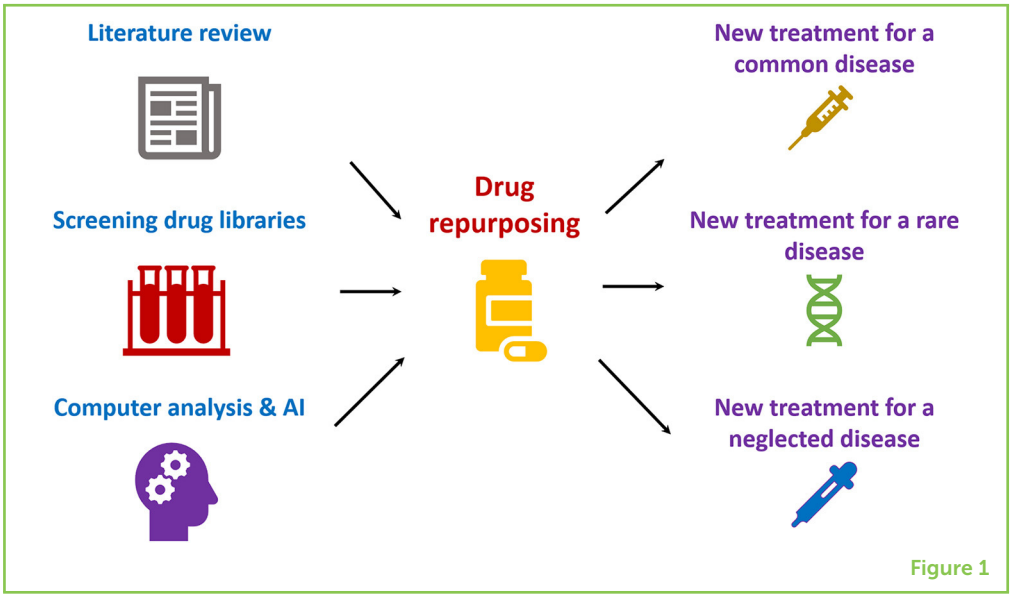
KIERAN

AGE: 13

Every year, we face infectious outbreaks produced by harmful microorganisms commonly called superbugs. Often, there is not enough time to find new treatments to cure infected patients. On average, it takes a decade to develop a promising new drug to the point where it can be used on patients! Also, many of the compounds that we identify in the laboratory as promising anti-infectives are not useful for treating patients, mainly because they have unexpected, unsafe side effects. However, researchers have already found thousands of drugs that can safely be used to treat specific diseases. These compounds are approved to be used on patients for particular illnesses, but many of them have not been tested to treat any other diseases. Some of these drugs could be repurposed to treat infections caused by new superbugs. In this article, we summarize some exciting strategies used to find new anti-infectives by drug repurposing.

Figure 1

Drug repurposing can be achieved by literature search, screening collections of drugs in the laboratory, or by using computers and artificial intelligence (AI). Drug repurposing can identify new treatments for diseases that are very common, as well as rare or neglected diseases for which there is not enough funding to develop new drugs.



INTRODUCTION

Antibiotics were discovered in 1928 by Alexander Fleming [1]. Before antibiotics, bacterial infections were one of the leading causes of death worldwide and human life expectancy was only about 47 years. Since then, we have almost doubled that age in many countries. However, bacteria become resistant to antibiotics very quickly. New, harmful bacteria are still causing many deaths, because it takes time to find an effective cure or a new vaccine. These bacteria, as well as other dangerous microorganisms like viruses that appear rather suddenly and are difficult to treat, are often called **superbugs**.

The drug-development process is very costly and time consuming. The discovery of a new drug usually happens in the laboratory, and it may take years. New drugs are tested on animals to determine their safety, which is called preclinical research. This usually takes several months. If everything goes well in the preclinical phase, the drug is then tested on a small group of people to make sure that it is safe in humans, and then on larger groups of people until its safety and effectiveness are verified. Human testing might take several years [2].

However, instead of starting from scratch to develop a new drug each time a new superbug comes along, we could look at the thousands of safe drugs that have already been developed to treat other diseases, to see if they are effective against the new superbug. This is called **drug repurposing** (Figure 1), and it can allow us to uncover hidden talents of existing drugs. In this article, we will look at different examples of drug repurposing, a quick and easy way of finding new **anti-infectives**.

ANTIBIOTIC

A chemical produced by a microorganism that may kill bacteria or slow down their growth.

SUPERBUG

A microorganism that is difficult to treat or has become resistant to the drugs that are used to treat the infections it causes.

DRUG REPURPOSING

Is the use of known drugs for new medical applications, which shortens the time and costs required to test their safety.

ANTI-INFECTIVE

A drug that could be used to cure people infected with a microorganism.

AN INVISIBLE ENEMY ON OUR DOORSTEPS...

PANDEMIC

A global disease outbreak.

We have all suddenly realized how damaging and disruptive a **pandemic** can be. The new virus that we are all fighting by staying at home with our families is making us very aware of how exposed we are to infections. Scientists and medical doctors all around the world have started a race against the clock to find new ways of protecting and treating people who are at high risk of developing a dangerous disease caused by the virus called SARS-CoV-2. This is a new strain of coronavirus that apparently jumped from animals to humans in late November 2019, in China. Since then, the whole world has stopped in its tracks to make sure that our hospitals do not become overwhelmed with people infected by the virus. If hospitals are overwhelmed, patients with severe complications of COVID-19 may not receive the proper treatment.

So far, there is no vaccine or known medication that can cure people with severe COVID-19. In many countries people is being vaccinated against SARS-CoV-2 but it will take quite a lot of time to produce it in sufficient amounts to protect everyone. As we mentioned earlier, it takes a long time—an average of 10 years—to develop a new drug that could be used in the clinic to treat people who are already sick with COVID-19. Many compounds that are identified in the laboratory as promising drug candidates do not pass all the trials, because they are not safe enough. We clearly need a Plan B to save infected people who are at risk of having a severe form of COVID-19. This group includes the elderly, people with liver or kidney disease, or people who have poor immunity, diabetes, obesity, chronic respiratory diseases, such as asthma, or serious heart conditions.

DRUG REPURPOSING TO THE RESCUE!

Luckily, over the years, researchers have already developed hundreds of new drugs against many different diseases. Many of these drugs have passed all testing and are now being used in the clinic to treat infections, strokes, or cancer. We know almost everything about those drugs, including the way they should be administered to patients, their maximum doses, and their side effects. Could we repurpose these well-known drugs to treat other diseases? The answer is yes! Often, drugs are developed for a specific purpose, such as treating one particular disease or condition. Scientists do not have time to check whether the drugs they are developing may be useful for treating other conditions as well. Fortunately, the many safe drugs that have already been developed are classified and distributed by the Broad Institute (Cambridge, Massachusetts) through an initiative called the Drug Repurposing Hub[1]. The collection currently includes over 6,500 compounds and it is growing every day. Anyone anywhere in the world can buy "libraries" of these drugs, consisting of small samples of each compound in laboratory tubes.

[1] https://clue.io/repurposing#conduct-screen

The Drug Repurposing Hub is only one of many similar initiatives! All of this is making the work of finding a compound that could be repurposed to treat a new superbug much easier. We can do now massive screenings thanks to these collections of drugs, and we have already found several compounds that could be repurposed to treat COVID-19 [3]. We may be able to repurpose drugs that were used to treat malaria or infections caused by other viruses, such as HIV or Ebola. These drugs are being tested in extremely ill COVID-19 patients and we will know soon if they are truly effective.

Drug repurposing is not a new strategy—we have already repurposed drugs to fight against other superbugs. For instance, the bacteria causing the disease called **tuberculosis** are becoming resistant to most antibiotics. We urgently need treatments against this superbug, which is causing hundreds of thousands of deaths worldwide every year. Many drugs that were not originally developed as anti-infectives may be effective against tuberculosis, including drugs used to lower cholesterol levels or to treat diabetes [4].

TUBERCULOSIS

A respiratory disease caused by a bacterium called *Mycobacterium tuberculosis*.

Computers can help us with drug repurposing. A group of scientists from the Massachusetts Institute of Technology have recently used artificial intelligence to find new antibiotics from the Drug Repurposing Hub. They found a new drug that could be repurposed as an antibiotic to kill many different superbugs that are becoming resistant to antimicrobials [5]. A computer can process a lot of data without any of the scientists' preconceptions that may limit their search. Instead, the computer teaches itself how to find new drugs. This is speeding up the discovery of new anti-infectives. Most of the drugs have never been tested against infections because scientists did not think they could be useful as antimicrobials. In addition, the software used in this research work has been made freely available!

OUR GROUP'S RESEARCH ON DRUG REPURPOSING

Our research group also looked at repurposing drugs to treat infections caused by an extremely dangerous superbug, ***Staphylococcus aureus*** [4]. These bacteria are quickly becoming resistant to all available antibiotics. Antibiotic-resistant strains are being isolated from patients even when a new antibiotic has only been used in the clinic for 1 year. The rate at which we are discovering new antibiotics is not fast enough to deal with this crisis. Moreover, many big pharmaceutical companies have lost interest in working to find new antibiotics. After all, they may lose all the money and time invested as soon as a superbug becomes resistant to a newly discovered drug. In the case of *S. aureus*, the situation is even more complicated, as this bacterium can hide and replicate inside of human cells. Unfortunately, many antibiotics do not get into infected human cells because they cannot get through the cell membrane. So, *S. aureus* bacteria may survive inside the cells of infected people, even if the bacteria are susceptible to the antibiotics used to treat the patients.

STAPHYLOCOCCUS AUREUS

An important human pathogen that may cause skin, lung or blood infections, and it is becoming resistant to antibiotics.

In our laboratory, we searched for drugs that could be repurposed to fight *S. aureus*. We found hundreds of very promising drugs that could be combined with traditional antibiotics to treat human cells infected by *S. aureus* [4]. Many of these drugs have been identified to treat other diseases, but they have never been used to cure infected people.

OXIDATIVE STRESS

A process that can use oxygen to damage proteins, DNA, or lipids in bacteria. This process can kill bacteria.

In addition, we recently found that some antibiotics have a hidden superpower—they may produce a condition called **oxidative stress**, which may kill bacteria [6]. Oxidative stress is a process that can use oxygen to damage proteins, DNA, or lipids in bacteria. Most of the antibiotics that induce oxidative stress are not very effective against superbugs if they are used individually, but they are very effective when we combine them. In the lab, we produced mutant superbugs that were extremely susceptible to oxidative stress. We used these mutants to look for antibiotics that have this new powerful effect on bacteria. By doing so, we found some antibiotics that are normally used to treat urinary tract infections, which could be repurposed to treat respiratory infections [6].

CONCLUSION

We are living in a world that is changing very quickly. Old and new superbugs can completely stop our lives in a matter of days. We need new strategies to combat the viruses and bacteria that are causing infections for which we do not yet have a treatment. Vaccines are often extremely difficult to develop because many pathogens are very good at hiding from the immune system, which is why many vaccines fail. In addition, many bacteria are becoming resistant to antibiotics. This is threatening one of the pillars of modern medicine [1]. Without antibiotics, all progress made on organ transplants or cancer treatment is in danger. Even a small wound could suddenly become dangerous if antibiotics are not effective. Wounded people could develop bacterial infections that could make their lives much shorter. Without antibiotics, we could be back at the beginning of the last century and live a maximum of 47 years in many countries. Today, that short life expectancy is doubled, due in great part to the drugs available to treat infections. We need to increase the list of drugs that could be used as anti-infectives, and drug repurposing can be a cheap and easy way to recycle many of the thousands of medications that have already been discovered and safety tested!

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CONFLICT OF INTEREST: 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 REVIEWER

KIERAN, AGE: 13

My name is Kieran, I am 13 years old and I am in third grade of secondary school. I love playing basketball and eating pizza. My parents are doctors, so they talk a lot about science to me and my older brother—an important thing I have learned is to always check what the source is for any piece of information I come across.

AUTHORS

ÁLVARO MOURENZA
I have focused on the molecular biology of microorganisms. I studied biofuels' production by microorganisms, and now I am focused on the mechanisms used by pathogens to overcome the defenses of their hosts, which allows their survival and growth during infection. I am also interested in antibiotic resistance and how science can fight against antimicrobial-resistant bacteria.

NATALIA BRAVO-SANTANO
I am interested in finding cures for human diseases. Working at the university, I studied how bacteria survive inside host cells, and I tried to identify new treatments against these bacterial infections. Now, working in a biopharmaceutical company, I develop tools to detect cancer cells in our bodies and improve cancer diagnosis.

JOSÉ A. GIL
Once upon a time (during the last century), I worked with *Streptomyces*, a type of bacteria that produces a vast amount of different antibiotics, and we developed genetic engineering strategies to clone genes involved in antibiotic production. During the last 20 years, we have studied how industrially-important bacteria, such as *Corynebacterium*, grow and divide and how they cope with toxic compounds, such as arsenic.

LUÍS M. MATEOS
My research interests have always been focused on studying a broad group of bacteria belonging to the corynebacteria cluster: mostly *Corynebacterium, Rhodococcus*, and *Mycobacterium*. My initial research was focused on bacterial primary metabolite production, including amino acids and nucleotides. However, more recently, we looked at bioremediation opportunities by using bacteria as containers for heavy metals accumulation, and we also studied the oxidative stress generated when toxics agents are inside the bacterial cells.

MICHAL LETEK
My research work has always been focused on identifying new ways to control bacterial pathogens. Over the last few years, I have studied how bacteria grow and divide, how they interact with their host during infection, and the host response to bacterial infection. I aim to find novel therapies to control bacterial pathogens and to understand what makes us susceptible to infections caused by microorganisms, such as *Staphylococcus aureus* or *Mycobacterium tuberculosis*. *michal.letek@unileon.es

†These authors have contributed equally to this work

Our Mission

To foster a love for science from a young age by involving young people in the peer-review process in the latest, cutting-edge research.

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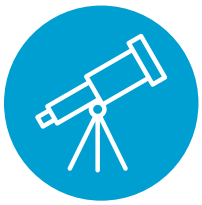

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1

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