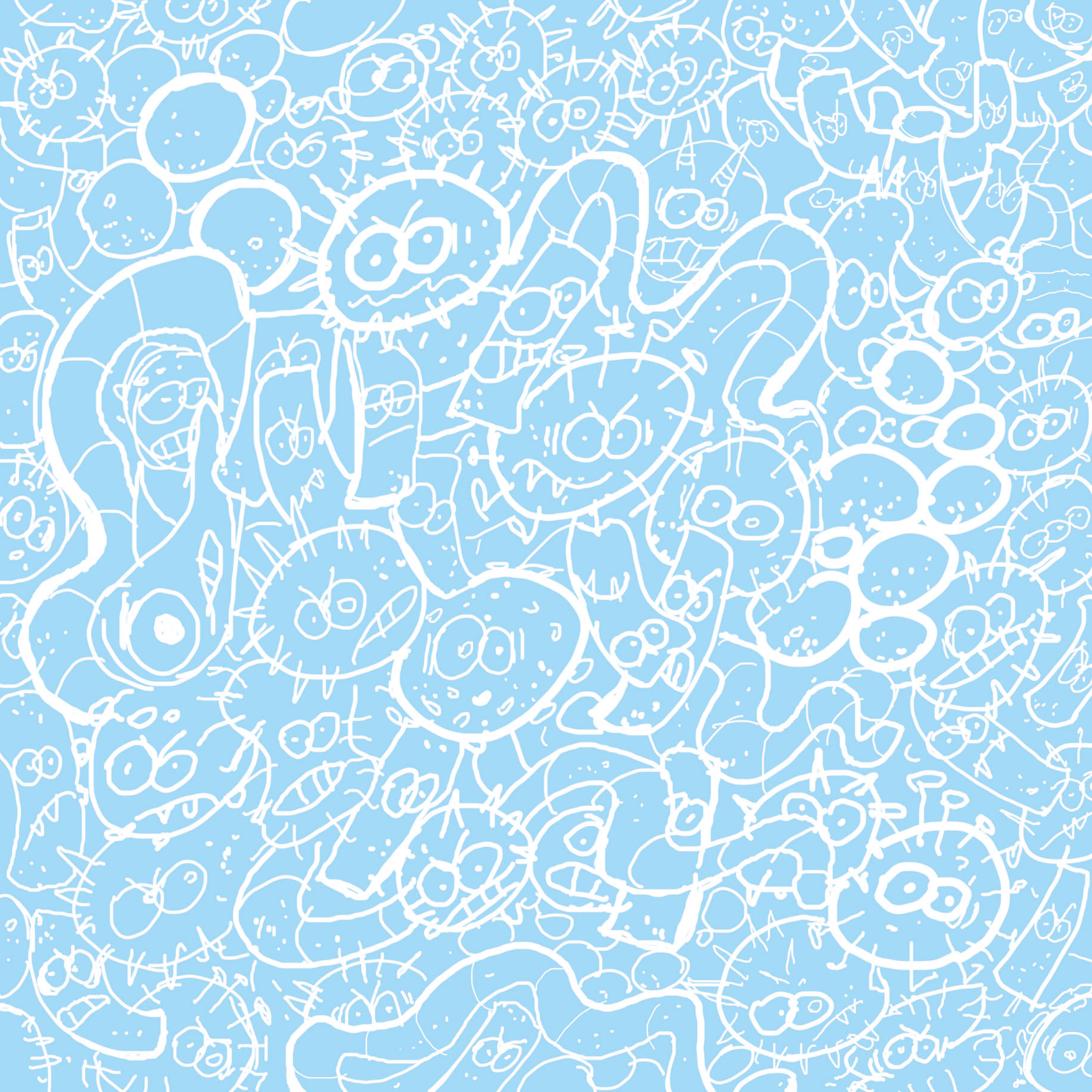
Raquel Carnero Gómez & Luis Marcos Nogales

Vaccinating

Two Centuries and Beyond!

Ediciones Universidad Salamanca



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TWO CENTURIES AND BEYOND!

Raquel Carnero Gómez

& Luis Marcos Nogales

Artwork: Ansola

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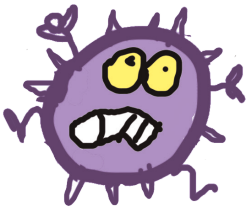
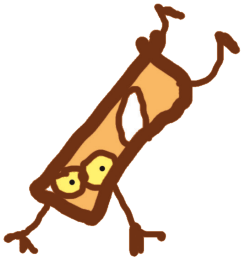
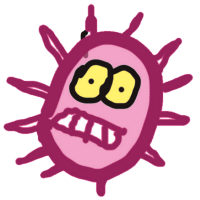
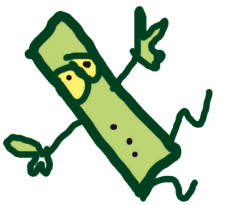
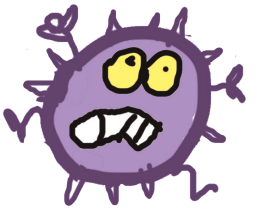
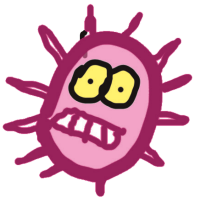








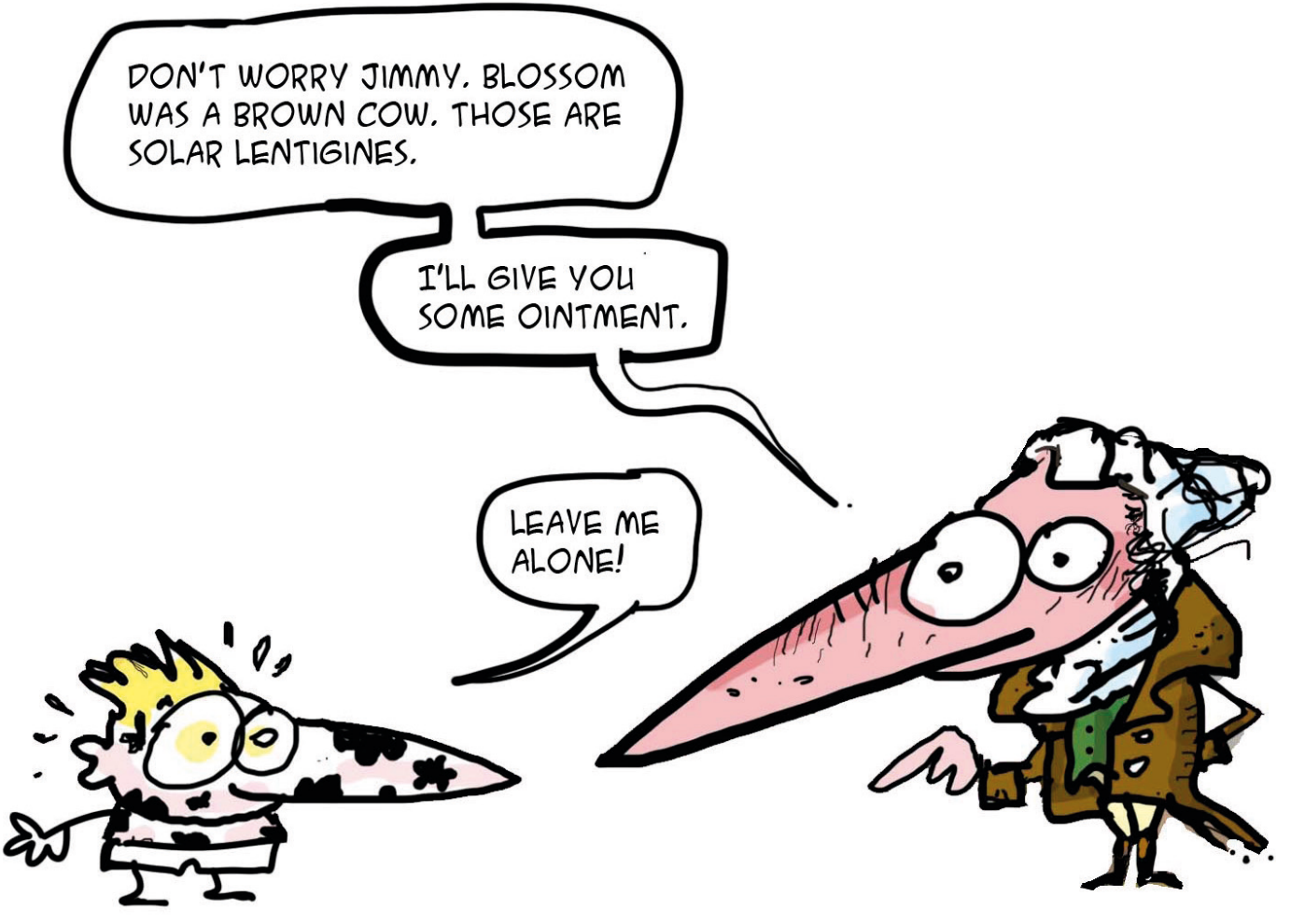

Presentation

You do not need to go back on time a lot of years to realize that in the past, families had many kids being born, but only some of them became adults. Parents often experienced the death of one or more sons or daughters due to infectious diseases caused by microscopic organisms named microbes. There is a great variety of microbes. The majority don't cause any harm. Some are even beneficial and we use them to make bread and cheese, for example. But a few make us very sick specially the first time we encounter them, usually during our childhood. And in some cases they kill us. And so, the child mortality in the past was very high.

But thanks to the scientists of the last century, this is not the case today, and this was due to two major scientific discoveries, the antibiotics that are used to treat most of bacterial infections, and the vaccines that protect us from being infected by bacteria and viruses. This book documents the fascinating story of the discovery of vaccines, explains why vaccines are specific for each microbe, and the impact that vaccination has in reducing disease and mortality.

Today is difficult to imagine a world where death during childhood due to infection was common. We owe this to the discovery and use of vaccines. Vaccines can also prevent severe disease due to microbes that cause infections in adults, and some of the newest vaccines have been developed for the prevention of adulthood diseases. One of the most recent developed vaccines even prevents some type of cancers. But, we also need more research to develop vaccines for some diseases that have been difficult to prevent by traditional vaccination strategies, such as most of the chronic diseases, and for the improvement of some of our existing vaccines. Maybe you could be one of the future scientists that develops some of the still needed vaccines. In any case, we hope you enjoy this book while learning the role that vaccines have in making as safe from nasty microbes and healthy.

Adolfo García-Sastre
Professor of Microbiology at the Icahn School of Medicine at Mount Sinai, New York


DON'T WORRY JIMMY. BLOSSOM WAS A BROWN COW. THOSE ARE SOLAR LENTIGINES.
I'LL GIVE YOU SOME OINTMENT.
LEAVE ME ALONE!

Introduction

If Edward Jenner, who did not invent variolization process, but coined the term "vaccine" over 200 years ago after observing that people who milked cows were immune to the smallpox virus, were to see the current anti-vaccine movement, he would probably recall the challenges he faced with this new preventive method in his time. Grotesque representations or caricatures depicting people with cow faces were forms of protest against this new methodology. However, years later, after the success achieved both in the United Kingdom and through the philanthropic expedition led by the Spanish doctor Javier Balmis in America and other parts of the world, the British Parliament honored Jenner and awarded him a lifetime pension of 10,000 pounds sterling.

In the summer of 1881, Louis Pasteur forgot a culture of Pasteurella multocida in his laboratory. Upon returning in the autumn, he inoculated this culture into chickens and observed that it did not cause disease. From this experiment, the hypothesis of attenuation as a strategy for making vaccines was developed. Years later, scientists such as the Spaniard Jaime Ferrán, the Ukrainian Waldemar Haffkine, the Dane Thorvald Madsen, and the Frenchman Gaston Ramon applied similar methods to create vaccines against cholera, plague, whooping cough, and tetanus.

Alfred Bernhard Nobel, a chemist who died on December 10, 1896, stated in his will that all his assets should be used to award annual prizes to those who had conferred the greatest benefit to humanity. This led to the creation of the Nobel Prizes, which are awarded every year on the anniversary of his death. The first prize was awarded in 1901, and the winner, Emil Adolf von Behring, received the Nobel Prize in Medicine and Physiology for his work on using serum as a vaccine to cure diphtheria. It took fifty years for the South African Max Theiler to win the Nobel Prize for developing the first vaccine against yellow fever, and three years later, the Americans John F. Enders, Thomas H. Weller, and Frederick C. Robbins received the Nobel Prize for their discoveries about the polio virus.

And more than a century later, now in the 21st century, Katalin Karikó was awarded the Nobel Prize in Physiology or Medicine in 2023. She received this honor along with Drew Weissman for their groundbreaking work on nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19.

Finally, I would like to conclude this brief introduction with three reflections:

Currently, there are more than 30 vaccines available. These vaccines save approximately 11 million lives each year, which translates to about 30,000 lives saved every day.

The generation and interpretation of genomes discovered in numerous microorganisms are key to developing new vaccines. Clinical trials are underway with mRNA vaccines, DNA vaccines and synthetic peptide vaccines that aim to protect against devastating diseases such as HIV, tuberculosis, and malaria. Recent advancements have shown promising results, with several candidates in various stages of clinical trials.

I consider the anti-vaccine movements to be extremely irresponsible, as they risk public health by spreading misinformation and populist lies without any scientific basis.

Antonio Muro Álvarez
Professor at the University of Salamanca
Coordinator of the Infectious and Tropical Diseases Group

Acknowledgments

Neither this translation of "Vacunando" nor the project itself would exist without the collaboration and commitment of people and institutions who believed in what we do. It's been a few years since @vacunando started. Back then, it was just a square, blue book. Today, it's a national project with aspirations to become international, educating about health worldwide. It sounds ambitious, but it's necessary.

We want to thank you all for your support, especially those who first supported the 2019 book: the University of Salamanca, through its publishing house and its (our) Faculty of Pharmacy, as well as the College of Pharmacists of Salamanca. The Spanish edition was reviewed by Víctor Jiménez, Professor of Microbiology and Parasitology at the Faculty of Pharmacy of the Complutense University of Madrid, and Luis Félix Valero, Associate Professor of Preventive Medicine and Public Health at the Faculty of Medicine of the University of Salamanca. The work is dedicated to our friend and pediatrician Ángel Luis Sesma.

Over the years, we've made new friends, and today, we can say that this next step has been made possible thanks to the NGO Farmamundi and the "La Caixa" Foundation. A special mention goes to Natalia Díez from this foundation, who has always supported us.

The introduction to the Spanish version was written by Antonio Muro, who was then the dean of the Faculty of Pharmacy. He is a Professor of Parasitology at the Faculty of Pharmacy of the University of Salamanca and the Rector's Delegate for the USAL30 Strategy. He is doing it again for a very simple reason: to make our dreams possible.

Adolfo García-Sastre is an incredibly unique and special person. He is one of the finest from Burgos and the University of Salamanca. From his role as a professor and researcher in the Department of Microbiology at the Icahn School of Medicine at Mount Sinai in New York, he has revolutionized our understanding of viruses. Moreover, he has nurtured a new generation of researchers of unparalleled caliber.

One of them is Michael A. Schotsaert, a vaccine expert and Adolfo García Sastre's colleague at the same institution. This Belgian scientist, with his calm and charming demeanor, excels both in his laboratory and at the Strand Book Store. We share a love for the latter... well, and our passion for vaccines. A heartfelt thanks to our friend Sara Cuadrado for introducing us and supporting this project.

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We are deeply honored to have them sign the foreword and epilogue of this book. It means the world to us, and we are profoundly grateful.

Our gratitude also extends to Susana González Knowles, the translator of this text, with whom we previously collaborated on "An Epic History of Pharmacy". It is always a pleasure working with you. Lastly, a warm hug to César Cobo and Fernando Lanza from Visible Estudio Creativo.

The Characters

Consejo Interterritorial del Sistema Nacional de Salud -CISNS-

The CISNS is the body that adopts agreements to harmonize important aspects of health programs across autonomous communities, such as the common vaccination schedule throughout life. This schedule was approved by the CISNS on 8 May 2019, and is reviewed annually. All autonomous communities and the Ministry of Health are represented in the CISNS, and decisions are made based on scientific and technical evaluations and always by consensus. To decide on the inclusion of a new vaccine in vaccination programs or to make modifications (such as introducing or eliminating a vaccine dose or changing the administration schedule), an evaluation of scientific evidence and the epidemiology of the disease in Spain is conducted.

PEDIATRICIAN

Parents' best ally when it comes to providing information and answers to their questions and concerns about their **children's health**. She has a consulting room where they go for checkups on their baby's health and often when the child is sick.

Those routine checks are when vaccination is suggested, provided that the baby's health allows it.

NURSE

He always works closely with the pediatrician and is well-acquainted with vaccines. He's the best at delivering the shot so that you don't feel the sting. After giving it, he stamps and enters the required information on the **immunization record:** brand name, manufacturer, and lot number of the vaccine. All this is very important and must be recorded in the **patient's medical history.**

PRIMARY CARE PHYSICIAN

A key player in any country's health system. **Primary Care Centers** are where the vaccinations that are required throughout adulthood are advised and prescribed.

She's the patient's first point of contact with the healthcare system. She takes every opportunity to check whether her patients' **vaccines are up-to-date** and also answers their questions

COMMUNITY PHARMACIST

Community pharmacy is part of healthcare and offers professional pharmaceutical services. Community pharmacists are involved in the promotion of health and disease prevention, as well as providing pharmaceutical care.

The **pharmacy** is an **accessible healthcare center** where you can obtain information about vaccines and also get those that are not included on the immunization schedule but have been prescribed by a physician.

INDUSTRIAL PHARMACIST

Working in **pharmaceutical laboratories' production, quality control, and quality assurance departments**, they are in charge, alongside other professionals, of ensuring compliance with good manufacturing practices. The Department of **Registration and Pharmacovigilance** works for the approval and marketing of the vaccine in accordance with current regulatory requirements and for any potential side effects to be notified to the competent authorities

TRAVELER

Now more than ever, traveling around the world to exotic places makes any citizen a target for diseases that are not present in their environment and which they are not vaccinated against. They must go to the nearest **International Vaccination Center (IVC)**, where they will be given personalized advice depending on where they are traveling to and their health condition.

Certain vaccines are subject to international regulations, and an **International Certificate of Vaccination** may be required by the local authorities of the country that is being visited.

BABY

It usually cries when it is given the shot, but, deep inside, its pain is much worse when hit by a swing in the park. Vaccination is a child's **right**. Diseases that can be prevented through vaccination could have a considerable impact on its health.

Since it's not mandatory, vaccination in our country remains a **voluntary decision.**

PREGNANT WOMAN

She's a mother-to-be and wants to **protect her child** against potential diseases. Therefore, she pays close attention to her gynecologist and midwife's advice, which includes some recommendations on vaccination

SENIOR CITIZEN AGED OVER 65

He's convinced that he catches his diseases from his grandchildren, but there are many illnesses for which he is actually the main carrier. He'd never want to spread the flu or pneumonia among children or immunocompromised people around him, so he's always mindful of **healthcare appointments** to get vaccinated.

Some history of microbiology

Let's not be deluded. Microorganisms have always been and will always be around as faithful companions on our evolutionary journey. The human body hosts a large amount of bacteria living on our skin, in our mouth... but especially in our colon.

The nowadays so commonly referred to bacterial flora has only recently started to be given its due value –which is a lot. We know how important its balance is for our health; indeed, health is, as the physician Alcmaeon of Croton said back in the sixth century, the balance of its properties. Well, our microbiota is one such property.

Of course, this was not known in the past. That microbes (or rather microorganisms) live inside our body and work for its benefit was unthinkable. As was that other not-so-good ones were trying to inhabit us, causing infections and, frequently, death.

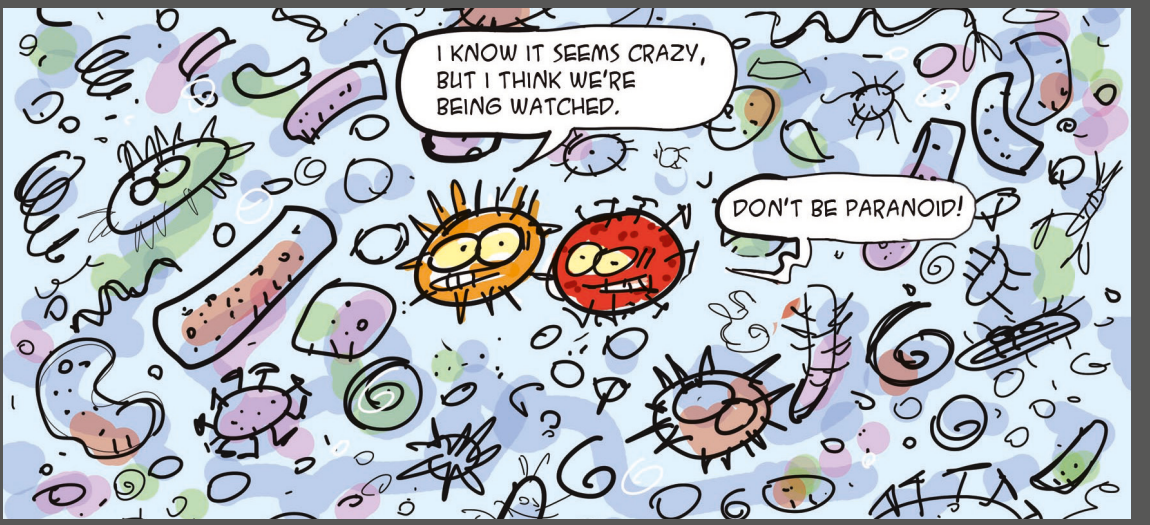
Infectious diseases were baffling, and it was common practice to attribute them to supernatural causes. This was only logical in times so imbued with all kinds of mythological creatures and whimsical deities. Anything that could not be explained was supernatural. Diseases were caused by the gods. Plagues were a form of divine punishment.

But this began to change when a Dutch man, from Delft to be more specific, called Anton van Leeuwenhoek, a successful and inquisitive merchant, started to poke about with a magnifying glass. First using low magnification lenses, then, higher, and when his thirst was no longer quenched by the performance of those available, he simply started to make them himself. Indeed, he made hundreds using a polishing method that he never revealed and remains a mystery.

Microscopes were already known, but he managed to create some simple and efficient ones that could yield over 200 times magnification, thus exploring the microscopic world as no one had before. He observed microorganisms for the first time in 1674, peering into a water sample from a nearby pond. He became so fascinated by the discovery that he started to study and draw everything that could be placed under his lenses: blood cells, sperm, bacteria, plants, etc.

The evolution of microscopes began tentatively until, in the nineteenth century, the German Ernst Abbe, together with Carl Zeiss, improved their performance and laid the foundations for their optical works. Little more could be done, and the number of magnifications was limited. This changed in the 1930s with the creation of the electron microscope.

After Leeuwenhoek, microbiology sailed slowly until, in the late nineteenth century, the Polish Cohn stepped in, investigating microorganisms and classifying them for the first time. In his research, he collaborated with two great names in the history of science: the very famous Louis Pasteur and Robert Koch.



Pasteur is renowned for developing the rabies vaccine –we'll eventually get there- but we can't forget to mention his research in microbiology and chemistry, his first great passion. In fact, he solved the famous mystery of tartaric acid: how could it exist in two forms, also with different properties but with the same chemical formula ($C_4H_6O_6$)?

Pasteur racked his brains in an attempt to understand why tartaric acid had different behaviors. It was a very well-known acid and had been isolated in 1769 by the Swedish pharmacist Carl Wilhelm Scheele, but why its crystals sometimes polarized light to the right and others to the left remained a mystery.

Well, Pasteur solved it at the age of 26 with the help of a microscope, revealing tartaric acid's merit as the molecule that helped to decipher what is currently known as optical isomerism. Tartaric acid is a chiral molecule with two enantiomers or mirror images, like our hands. They are the same, but the fingers on each of them are arranged differently. To understand this, you only have to place your left hand in front of a mirror: its reflection looks like your right hand. Both hands have five fingers, but they are not identical.

Once again, armed with his microscope, he provided the winemaking industry with proof that microorganisms are involved in fermentation –the belief was that it was just a chemical reaction- and he came up with a system to eliminate them: pasteurization, which, by controlled heating and cooling managed to eliminate many pathogens. This is used nowadays to preserve foods such as milk.

After years of top-level research, noticing the relationship between microorganisms and infection as unequivocal and having disproved spontaneous generation, he formulated the germ theory of infectious diseases or microbial theory of disease. This overturned all previous theories and marked a medical milestone.

This theory had already been envisaged for some time but with no precision. There was mention of small beings, germs, that were passed from person to person, and flew through the air. But this was not accepted; there was no proof, even though they were right. An imbalance of the humors, or simply spontaneous generation, was thought to be the cause of all diseases, but some people, who were as scarce as they were sharp, did not see it that way.

The Roman Marco Terencio Varrón warned against tiny creatures that could not be seen but were in the air and could enter the body via the mouth or nose, causing illnesses.

Contagion was taken for granted by great medical experts like Avicenna, who also suspected the existence of organisms that were foreign to the body as the cause of illness. Centuries later, the Italian physician Girolamo Fracastoro said much the same thing, as did one or other scientists over the years, but these were all suppositions that the majority of medical professionals were not happy with.

Thus, the disease-infection relationship, although obvious, had to wait until the arrival of Pasteur and another great figure, the German Robert Koch, who consolidated the former's theory with his postulates –Koch's postulates.

Through his own hard work, Koch managed to become regarded as one of the fathers of bacteriology. After he finished his medical studies, he concentrated on research and studied anthrax and cholera. In 1882, partly thanks to the development of new microbiology techniques that he had promoted himself, he identified the cause of tuberculosis: the Mycobacterium tuberculosis bacterium. This discovery earned him the Nobel Prize in 1905.

However, it was his postulates that changed microbiology and made it take off:.

1. **The pathogenic bacterium must be isolated from diseased animals, not from healthy individuals.**
2. **The bacterium can be isolated in pure culture.**
3. **If the bacterium is inoculated into a healthy individual, it must cause the same disease.**
4. **The bacterium can be isolated again in pure culture.**

In little more than two decades, these postulates, whose validity remains virtually unchanged, made it possible to identify the majority of the most important pathogens.

Let's not forget about viruses – Pasteur and Koch focused on bacteriology-, little great pathogens that are halfway between the living and the inert and cause diseases that are difficult to fight (HIV, Zika, Ebola, etc.).

We owe their discovery to the Dutch microbiologist Martinus Willem Beijerinck. In his attempt to understand the tobacco mosaic disease, his studies, which were more focused on the plant kingdom –something that unfairly belittled hiscv work– led him to find something smaller than a bacterium. He called this «something» virus.

And that's not all, he also created new culture methods that allowed the study of microorganisms as never before. This, alongside Koch's postulates, gave microbiology a tremendous and decisive boost, modernizing and standardizing its study and thus paving the way for the development of new fields such as immunization.

A bit of history... of vaccines

Many books mention Jenner as the inventor of vaccines, but it is not entirely fair to give him all the credit. The fact of being a westerner probably made the authors of such books, also westerners, get carried away by enthusiasm and feather their own nests. The truth is that Jenner was thoroughly familiar with immunization and all he did was take the next step, the decisive one.

The true origins of vaccination are in Asia. The first inoculations to prevent smallpox –a viral illness-, were carried out in India two centuries before our era. The disease was the most accessible for such a method from a practical point of view and also one of the most tragically important infectious diseases in history. Back in the Middle Ages, inoculation was widely practiced in China where, two centuries later, in the seventeenth century, it even received government support.

It is also known to have been practiced in Africa and, most importantly, Turkey, where it probably started thanks to its relations with China. Indeed, Turkey is where Wortley Montagu, the British ambassador there, lived with his wife in the early eighteenth century.

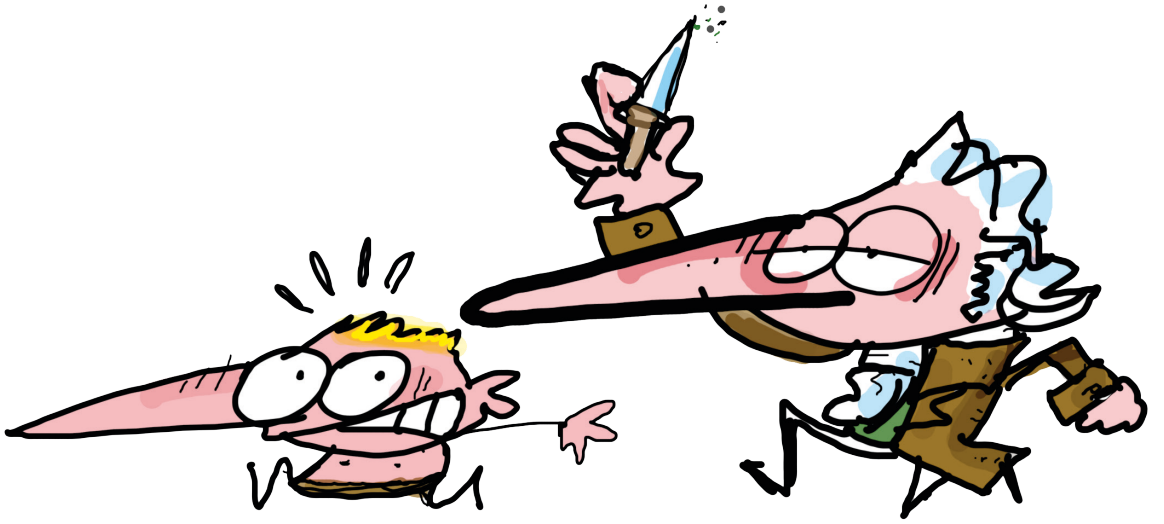
Lady Mary Montagu was an intelligent woman, a writer, ahead of her time and with an open mind, so much so that, after witnessing it in Turkey, she saw the potential of smallpox inoculation. More than one was shocked when she decided to inoculate her own children. She was the one to introduce this practice in the United Kingdom, advocating its usefulness as prophylaxis, which caused some social outrage.

The procedure was quite simple. It was enough to draw liquid from a pustule of someone with mild smallpox. Small cuts were made on the healthy person's skin, and the liquid was applied. The person would become infected and develop an also mild case of smallpox but would become immune. From time to time, one of these people would die; nevertheless, the results were good enough for the practice to become widespread.

Smallpox inoculations are reported in certain epidemics, and armies such as George Washington's Continental and even great names like Catherine the Great of Russia agreed to try the new method. In Virginia, in the budding United States of the eighteenth century, smallpox inoculation or variolation even became regulated.

So, why is Edward Jenner given so much credit? Inoculation was quite widespread, and he was clearly aware of it. The key to understanding this can be found in our friends the dairy cows.

There is a well-known tale about how Jenner observed that milkmaids who milked cowpox-infected cows and got it themselves were immune to the human variant. It turns out that this disease can also affect humans, but in a much milder way, so it was ideal to protect oneself against the second, which is more problematic even in the case of mere inoculation.



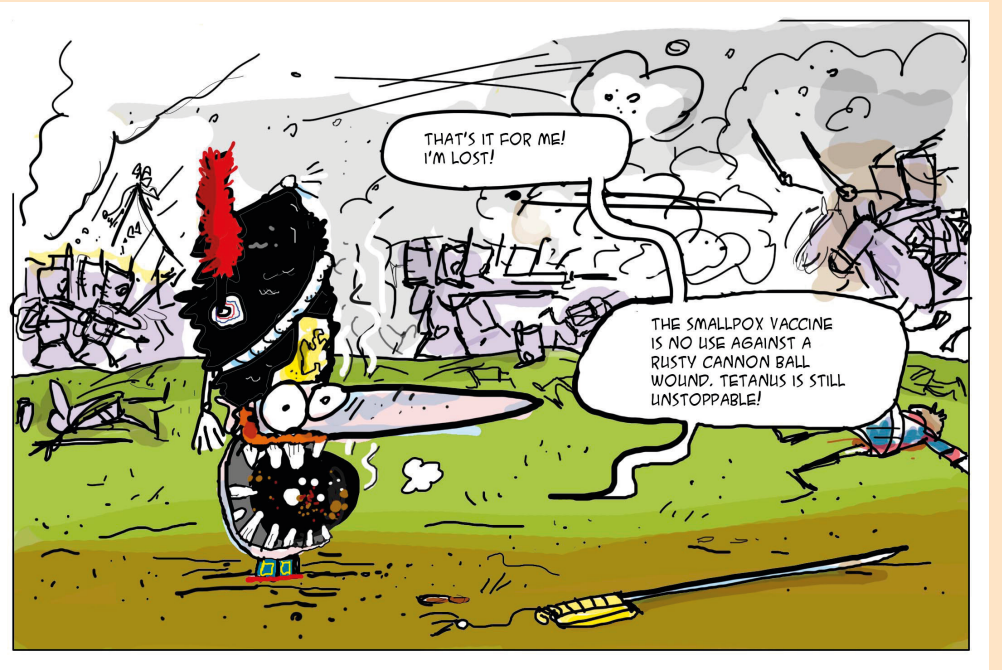
To prove his point, Jenner experimented with an eight-year-old boy called James Phipps –the son of his gardener-, inoculating him with pus from a milkmaid who had caught cowpox from a cow named Blossom. The boy had a bit of a temperature, but nothing serious. After a reasonable length of time, he did it again, but this time with smallpox, and nothing happened. The boy had become immune. This was back in 1796.

He had used mildly aggressive viruses to protect against aggressive ones. This is already a vaccine. Besides, he proved that it worked by testing it again on more people, showing that if such cowpox pus was passed from one patient to another, the protective effect still worked. Jenner was not the first to carry out experiments of this kind, but he was the best. Just one step away from glory. Jenner's vaccination was safer and, once accepted as such, replaced variolation in the mid-nineteenth century. Incidentally, the origin of the word vaccine is vacca (cow).

The discovery harnessed enormous popularity. Even Napoleon Bonaparte ordered his troops to be vaccinated. Nevertheless, the first to see the potential of vaccination at the level that it deserved were the Spanish, who thought big and organized an expedition to vaccinate the population of their overseas territories.

This feat starts with two main characters: King Charles IV, who was unfortunately familiar with the disease –his daughter Maria Teresa died from smallpox at the age of three; and the court's physician, Francisco Javier de Balmis, born in Alicante. Balmis had been keeping up to date with this topic, he knew about Jenner's research and had translated an important treatise on vaccination written by the French Jacques-Louis Moreau de la Sarthe into Spanish.

Balmis proposed and the Spanish Crown arranged. It was a tremendously ambitious project that would take several years and would bring the smallpox vaccine –already established in Spain– to America and the Philippines, also reaching Macau (under the Portuguese Crown) and China. Balmis himself would head the enterprise, currently known as the « Balmis Expedition».



The virus would be transported alongside hundreds of copies of Moreau's treatise to train the healthcare professionals of the new vaccination commissions. But a critical question arose: how to transport the virus. Well, the only possible way: alive. Therefore, sick people were needed.

Nowadays, this might seem a weird idea, but there was no other way. On the one hand, they needed to take the sick people and, on the other, the healthy who would become ill when the former started to recover from the disease. For this purpose, Balmis set sail with 22 orphan children who had never had the disease, their nurse, Isabel Zendal, her son, some physicians, and the crew.

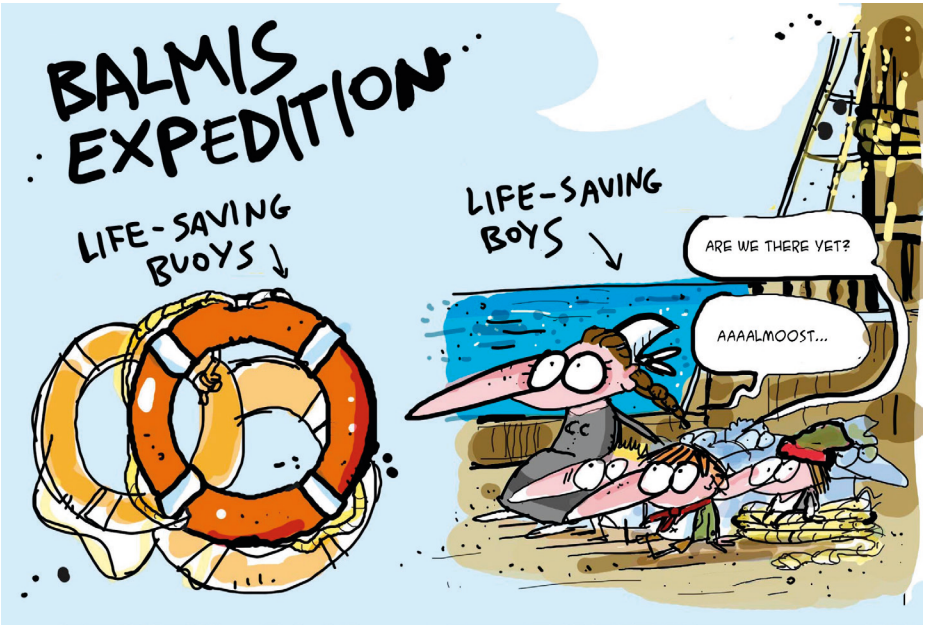
The Corvette María Pita departed from La Coruña in 1803, with a one-month stopover in the Canary Islands to vaccinate the population, eventually arriving in Puerto Rico in February 1804. To their great surprise, they found that the vaccine had already arrived from the Danish colony of Saint Thomas. The same happened in Cuba, where it had been introduced by Tomás Romay.

In Venezuela, the expedition branched and Balmis's deputy, José Salvany y Lleopart, traveled to New Granada (Colombia) and the Viceroyalty of Peru (Peru, Chile, Bolivia, and Ecuador). Salvany, who is hardly known –history tends to be unfair-, spent seven years vaccinating across the length and breadth of those lands. An adventure that would eventually cost him his life.

Balmis headed to New Spain (Mexico), he chartered a new vessel with another 22 children on board, and crossed the Pacific to the Philippines. After accomplishing his mission there, part of the expedition returned to Acapulco and Balmis made his way to China to continue his vaccination campaign with the support of the Portuguese and the English. He finally returned to Spain in the summer of 1806, and from there tried to get the children who set out from La Coruña back to Spain. His attempt was fruitless, none of them returned. The expedition was a complete success, managing to vaccinate thousands of people.

Still in the nineteenth century, let's take a leap in time and move a few decades forward, over which microbiology continued to flourish, until we find ourselves face to face with the brilliant Louis Pasteur. Most of us have surely heard about the story of the rabid dog that bit a little boy, Joseph Meister, and Pasteur's intervention with his rabies vaccine in 1885, but his passion for vaccination came from way back.

His studies had proved how to mitigate the virulence of microorganisms, which is very important in vaccine development. Moreover, before Joseph got bitten by the dog, he had already created effective vaccines for anthrax –in cattle- and cholera -in chicken. The latter was the first vaccine to be developed in a laboratory (1987).



Let's go back to rabies and we'll see Pasteur developing the vaccine using rabid rabbits. It turns out that once the virus enters the body it travels to its favorite area: the nervous system. It takes some time, but when it reaches the brain and the spinal cord there is little that can be done.

Well, Pasteur used the nervous tissue of infected rabbits and desiccated it to attenuate the pathogenic agent. This is how he prepared the vaccine to start experimenting with dogs alongside his collaborator Émile Roux. That is what they were doing when they learned about what had happened to the boy. He was going to die and there was nothing to lose, so he was given the yet experimental vaccine, and it was a complete success. Within little more than a year, it had already saved the lives of 2,500 people infected with rabies.

This was the first vaccine to be developed from a pathogen that directly caused the disease in humans –Jenner used a different virus obtained from cows- and the technique used, as well as Louis Pasteur's extremely important contributions to microbiology, paved the way for scientists who started to work following in his footsteps.

Also in 1885, the Spanish physician Jaume Ferrán developed the first vaccine against cholera in humans. He studied Pasteur's

advances and made good use of what he learned. Although he underwent criticism for this mysterious methodology, he developed several vaccines

The also Spanish PhD in Pharmacy, César Chicote, was the head of the Municipal Laboratory of Madrid from 1898 to 1932 and organized the Free Housing Disinfection Municipal Service during the typhus, cholera, diphtheria, scarlet fever, measles, and smallpox epidemics. In 1911, he also started to work on developing a vaccine against typhus.

Within only a few years, one vaccine after another started to come to light. The pace was fast and the new discoveries were crucial. Such is the case with Salmon and Smith, who, one year after the young Joseph Meister recovered, created a vaccine using killed instead of attenuated microorganisms to treat pigeons for a disease that was similar to cholera.

There was a boom. When the century was coming to its end, there were already several vaccines such as Waldemar Haffkine's against the, sadly, well-known plague. As a matter of fact, he was working at the Pasteur Institute, where he also developed another cholera vaccine. He had such faith and confidence in his work that he liked to use his own body to test on. He was his own Guinea pig.

The German Richard Pfeiffer was also one of the legendary figures. He discovered Haemophilus influenzae in 1892 and, alongside his compatriot Wilhelm Kolle, discovered the vaccine against typhoid fever, a merit shared with the British Almroth E. Wright who was also carrying out research on it but doing it his own way. Kolle also came up with a new vaccine against cholera.

We can't leave this century behind without mentioning the studies of the French Émile Roux and the Swiss Alexandre Yersin, his collaborator at the Pasteur Institute, as well as the work of the German Friedrich Loeffler. It's thanks to them that we know that diphtheria is not caused by a bacterium as such but by a toxin produced by it: the diphtheria toxin.

Yersin, who conducted most of his research in Asia, to the great glory of the Pasteur Institute, is also known for discovering the plague bacillus, named Yersinia pestis in his honor. The Japanese Kitasato also studied this bacillus, but Yersin got the credit at the time.

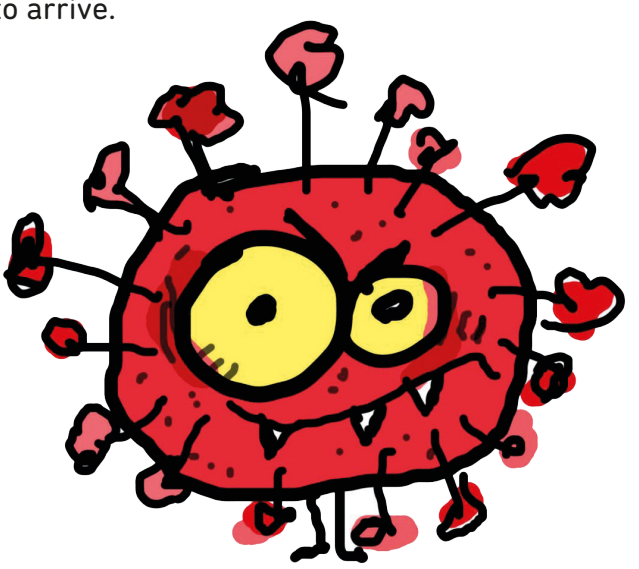
Kitasato also carried out important studies alongside the German Emil von Behring, leading to the discovery of the tetanus antitoxin. They would use the blood serum of previously infected animals once they verified that the antitoxin had appeared in their blood.

When this serum was administered to another patient, it cured them. Behring, who also gained prominence by identifying a diphtheria antitoxin, was awarded the first Nobel Prize in Medicine in 1901.

But, of course, obtaining large amounts of serum required a very large animal. This is where Jim appears, a horse bought by Hermann Biggs, a member of the New York department of Health. Biggs had become acquainted with Behring's work, learning that he used horses to obtain a large amount of blood serum, and decided to import the technique to the United States. Jim may not have been the first serum-producing horse in the world but was definitely the first in that country and, most certainly, the most famous. Jim stopped pulling a milk-wagon to become a provider of serum with diphtheria antitoxin, thus saving many lives.

This brings us to the twentieth century, which is neither so full of anecdotes nor so legendary as the others as regards immunology. Amidst a full-blown research frenzy, with much activity and little emotion, hordes of researchers spent their working days searching for new vaccines, putting in endless hours of methodical scientific work; they absolutely achieved their goal.

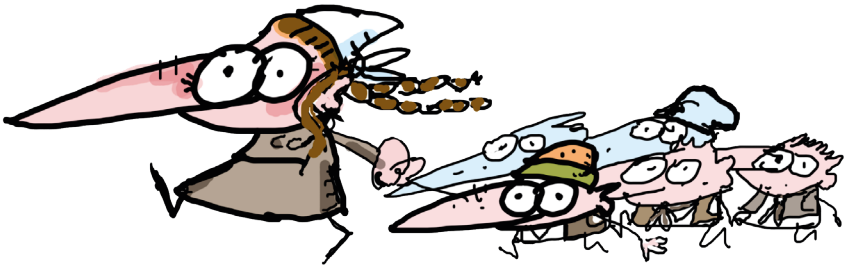
The new methods, modern equipment, the beginning of the industrial production of vaccines in the nineteenth century, and qualified staff, all resulting from the efforts of the microbiology and immunology pioneers, facilitated the creation of numerous research teams across the world, whose results did not take long to arrive.



The world of infectious diseases and vaccines also gained relevance in the mass media. As well as informing about scientific advances, they described cases such as that of the woman known asTyphoid Mary in 1909. To the delight of the yellow press, she managed to infect around fifty people with typhoid fever, which she was not affected by because she was a healthy carrier of the pathogen. She worked as a cook for several families and infected members of all of them until she was discovered to be the source. In fact, she was the first person to be identified as an asymptomatic carrier.

Another case that fed the insatiable appetite of the press was the wrongly named Spanish flu (1918), which had little to do with Spain. While across the rest of Europe fighting was taking place in the trenches –World War One- and there was control over the press, neutral Spain did report on this pandemic. Since it was the only country to do so, it became the main source of information, and hence the name given to the disease.

The fight against these diseases continued. In the 1920s, once again in the Pasteur Institute, the French Albert Calmette and Jean-Marie Camille Guérin successfully worked on a method



to attenuate the tuberculosis bacillus, making it grow in an unfavorable culture environment that enabled the creation of a vaccine. This attenuated bacillus and its vaccine are known as BCG in their honor (Bacillus Calmette-Guérin)

In the same decade, the French Gaston Ramon made huge progress by inactivating the diphtheria and tetanus toxins using formaldehyde, thus obtaining their toxoids which, to put it simply, are a version of the toxin that is not toxic because it does not attach to the cells, but it still immunizes. Hence, vaccination with the toxoid instead of the toxin began, which was a big step forward.

In the 1930s, there was a breakthrough in the fight against influenza. Patrick Laidlaw and his colleagues isolated the virus to subsequently test a vaccine on soldiers, and the first vaccine was already approved in the 1940s.

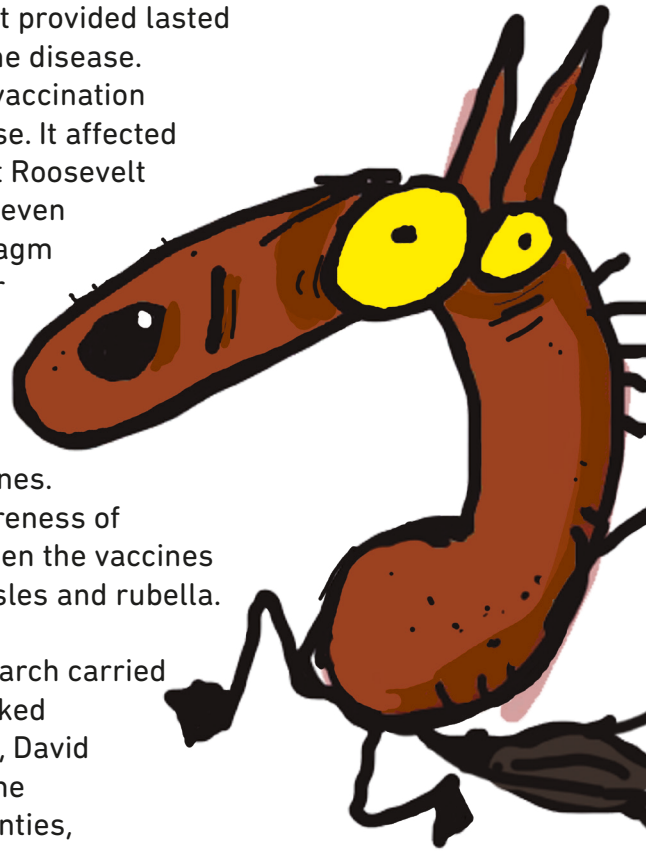
Also in the 1930s, the South African Max Theiler developed a vaccine against yellow fever using live attenuated viruses. This is where a crucial novelty appears: they were cultured in chicken embryos, a technique pioneered by the North American Goodpasture.

The culture medium is very important. Shortly after, already in the late 1940s, the North Americans John Enders, Thomas Weller, and Frederick Robbins were also conducting tests using embryos and discovered that the polio virus could be grown in cultures of certain types of embryonic tissue. Until then, scientists had thought that it could only grow in nerve tissue, for which they used live monkeys. The breakthrough, as well as saving the monkeys suffering, made the method easier and cheaper, speeding up the advance of polio research. They paved the way for the fight against poliomyelitis.

In the 1950s, several polio vaccines emerged from the work of North American researchers: Koprowski, Salk, and Sabin. Hilary Koprowski began to test an attenuated oral vaccine on humans; it was rather controversial, but not as much as those of Salk or Sabin.

Jonas Salk's vaccine consisted of inactivated virus strains that had to be injected, and, during its testing phase, which began in 1954 in the United States, more than a million children were vaccinated. Apart from its route of administration, there was another problem: one could be a carrier of the virus even though vaccinated

On the other hand, Albert Sabin developed an oral vaccine based on live attenuated viruses. Its administration was easy, the immunity it provided lasted longer, and the vaccinated individual wouldn't be a carrier of the disease. This was clearly better and led to the launching of successful vaccination campaigns. Society was worried about the spread of the disease. It affected many children who suffered from life-long paralysis. President Roosevelt himself had it and ended up needing a wheelchair. There were even more dramatic cases. Muscle paralysis could affect the diaphragm making it impossible to breathe. The grisly iron lung, a cylinder with air pressure control in which the patient was laid to be kept alive, gave the disease gloomy visibility.



In the 1970s, global vaccine campaigns increased. No one was any longer in doubt about the safety and effectiveness of vaccines. Governments became involved and the population gained awareness of the importance of getting vaccinated. These were the years when the vaccines against two well-known diseases were finally developed: measles and rubella.

The measles vaccine was approved in 1963 after years of research carried out by John Enders and his team. One of the samples they worked with had been taken years earlier from a thirteen-year-old boy, David Edmonston, and that is the sample from which they obtained the vaccine, the so-called « Edmonston-B strain». By the mid-seventies, around twenty million doses had already been administered.

When success in defeating measles was beginning –although nowadays it's emerging again among anti-vaccine groups-, the vaccine against rubella was on its way. The virus that caused it had been isolated barely a few years earlier

by Thomas Weller and Franklin Neva in the United States. Following in their steps, Maurice Hilleman, Paul Parkman, and Harry Meyer came up with the vaccine.

Thinking of Hilleman as an inquisitive scientist is an understatement, far more than an understatement. We must also thank him for the mumps vaccine and, since its approval by the FDA in 1967, 11 million doses of the vaccine were distributed over five years only in the United States. This is unquestionably impressive, but what's more, working in the laboratories of a well-known pharmaceutical company, he and his research team also developed vaccines against chickenpox, hepatitis A, hepatitis B, meningitis, Haemophilus influenzae, and pneumonia.
He used a sample taken from his daughter Jeryl Lynn when she came down with the mumps (parotiditis) to cultivate the virus, using it to develop the vaccine. The strain is still used today and is known as the «Jeryl Lynn strain».

In the 1970s, the measles, mumps, and rubella vaccines began to be administered together as one. It is known as the triple viral or MMR vaccine and is possibly the most important of all. It induces immunity in a very high percentage of patients, and it could be said that it changed the epidemiology scenario on a global scale.

The son of the Japanese Michiaki Takahashi caught chickenpox at the age of three while they were living in the United States. Takahashi, who had a wealth of research experience in the field of immunology, decided to find a vaccine against the disease, encouraged by the bitter experience of seeing his sick son. And he finally came up with it, although, in some countries, its use took long to catch on.

In the 1980s, the introduction of vaccination was complete, infectious diseases were controlled and even eradicated (smallpox), and new vaccines were gradually emerging. Although it might seem that the battle has been won, it has not. New infectious diseases will always appear. At the time, when HIV, which causes acquired immune deficiency syndrome (AIDS), became known, it triggered immense concern and social alarm.

Not yet recovered from the scare, and with no vaccine against HIV, although we're close, as we are to seeing one against malaria, vaccines continue to emerge: rotavirus, a cutting-edge vaccine against pneumococcus, COVID-19, new ones against meningitis, etc.
Despite all this, certain diseases come to the fore again because of a decrease in vaccination rates, adding to the new fronts that are being fought on (Zika, chikungunya, Ebola, dengue fever, Lyme disease...). This means that tireless research is required and vaccination must continue.

Many of these researchers to whom we owe so much were Nobel Prize winners. Others were not, but their role was equally important even though their names have almost fallen into oblivion, as have the people who, sometimes without realizing it, helped them. The history of vaccination is not only interesting but also heroic and, best of all, it's still being written.

Women and vaccines

After learning about Jenner and Pasteur's work in the field of vaccination, it's only fair to take a closer look at the women who carried out pioneering work in this area.

Lady Mary Wortley Montagu
1689 - 1762

Lady Mary Wortley Montagu challenged the foundations of the scientific society by **introducing smallpox inoculation** in western medicine. While she was visiting the Ottoman Empire, upon learning about the practice of inoculating smallpox that was carried out in Turkey, Lady Mary decided that she wanted to prevent her own children from catching the disease. In 1718, her son Edward was inoculated with smallpox and when they returned to London she promoted the procedure, challenging the medical society of the time.

Isabel Zendal Gómez
1771 - ¿?

Isabel Zendal was a Spanish nurse and rectoress of the Hospital de la Caridad in La Coruña. In 1950, the WHO recognized her as the first nurse in history to take part in an international mission. She participated in the **Royal Philanthropic Vaccine Expedition led by Francisco Xavier Balmis**. She was in charge of taking care of the 22 children (aged 3 to 9) from the Casa de Expósitos de La Coruña orphanage who left for America in 1803. Her son Benito Vélez was among them. Later, she also took care of the 22 children who were taken to the Philippines and continued during the 10 years that the expedition to take the smallpox vaccine and conduct vaccination campaigns in Spain's overseas territories lasted.

Dr Anna Wessels Williams
1863 - 1954

Anna Wessels Williams was an American pathologist who worked in the first municipal diagnostic laboratory in the United States. She managed to **isolate a diphtheria strain** in 1894 which was used to develop the first diphtheria antitoxin and later the diphtheria vaccine. She shared the credit for this breakthrough with William H. Park, so it was named the Park-Williams strain. She was also the first woman to be elected president of the laboratory section of the American Public Health Association and in 1914, she was also elected president of the Women's Medical Society of New York.

Drs Pearl Kendrick and Grace Eldering
1890-1980 | 1900-1988

Eldering and Kendrick researched **whooping cough** (pertussis). They first tested the vaccine on themselves and subsequently conducted a successful clinical trial, despite a great deal of resistance and lack of funding for their research. Working in their laboratory, they combined three vaccines (diphtheria, pertussis, and tetanus) in a single dose in 1943. This vaccine, currently known as DPT, was widely used in the United States during the 1940s.

Dr Margaret Pittman
1901-1995

Among her achievements, Pittman is known for her research on the Haemophilus influenzae bacterium. She identified six types of Haemophilus influenzae, labeling them from "a" to "f". Type b (Hib) is the most important and dangerous, as it causes meningitis and other serious infections. Her work led to the development of vaccines against Hib.

In 1958, Pittman went down in history as the first woman to head a laboratory at the National Institute of Health (NIH). She held the position of Chief of the Laboratory of Bacterial Products until she retired in 1971.

Dr Isabel Morgan
1911-1996

Throughout the 1940s, Morgan worked with a team of virologists at Johns Hopkins University in the USA. Together with her team, and aiming to improve what was at the time known as the polio virus, they were the first to prove that an inactive or "killed" virus could provide immunity in monkeys, thus invalidating the belief that only live viruses could do so.

Her work was key in the chain of research on developing Jonas Salk's **poliomyelitis vaccine** in 1955. She was also the only woman represented in the 17-person Polio Hall of Fame in Warm Springs, Georgia, USA. Later, four organizations were included thanks to their contributions to the eradication of polio: Rotary International, the WHO, UNICEF, and the Centers for Disease Control and Prevention.

Dr Dorothy Horstmann
1911-2001

Dr Horstmann was a pediatrician, epidemiologist, and virologist who proved that the **poliovirus** reaches the brain by way of the blood. Her epidemiological discovery of the places in the human body where the poliovirus could be stopped, blood and the gastrointestinal tract, contributed to the development of a vaccine.

In addition to being recognized for her work in the areas of education, clinical practice, and research, she became the first woman to receive a position as a full professor at the Yale School of Medicine and also the first woman to serve as president of the Infectious Disease Society of America (IDSA) in 1971.

Dr Anne Szarewski
1959-2014

In the 1990s, Dr Szarewski and her fellow researchers proved the association of the **human papillomavirus (HPV)** with cervical cancer. Over the ten years that followed this breakthrough, a vaccine against HPV was developed, allowing the prevention of most cervical cancers.

Dr Rachel Schneerson
1932 -

Dr Scheerson and her colleagues developed the first **vaccine against Haemophilus influenza b (Hib)**, which causes many cases of pneumonia and meningitis. It was approved in 1989 and was the first "conjugated" vaccine, with a novel design for the safe protection of younger children.

Dr Ruth Bishop
1933 - 2022

Ruth Bishop was an Australian virologist who led the research team that, in 1973, discovered the **rotavirus**, one of the main causes of severe diarrhea in children across the world. The discovery, made using intestinal biopsies that were examined by electron-microscopy, and which Bishop describes as a "combination of calculated medical research and luck", has had a huge impact on the control of rotavirus-associated diarrhea in children.

Dr Katalin Karikó
1933 - 2022

Katalin Karikó is a Hungarian biochemist who specializes in RNA-mediated mechanisms. In 2023, she was awarded the Nobel Prize in Physiology and Medicine. This award, shared with the immunologist Drew Weissman, acknowledges their sudies on mRNA, which were key to developing the vaccines to contain the COVID-19 pandemic.

The team made by Uğur Şahin and Özlem Türeci had been studying messenger RNA as a therapeutic tool for over two decades when the COVID-19 pandemic started. Together they founded BioNTech (short for Biopharmaceutical New Technologies), a company whose purpose was to develop individualized vaccines that could train the body to fight cancer. We now know that mRNA technology is not only useful for developing **COVID-19 vaccines** but has a much broader impact.

Katalin Karikó, Drew Weissman, Philip Felgner, Uğur Şahin, Özlem Türeci, Derrick Rossi and Sarah Gilbert were granted the 2021 Princess of Asturias Award for Technical and Scientific Research in recognition of their contribution to the development of some of the COVID-19 vaccines.

How do vaccines work?

Better the devil you know... immunological memory

The origins of preventive vaccination are directly related to immunological memory. The aim of vaccination is that the immune system can recognize the infectious agent in the future and trigger a response to destroy it.

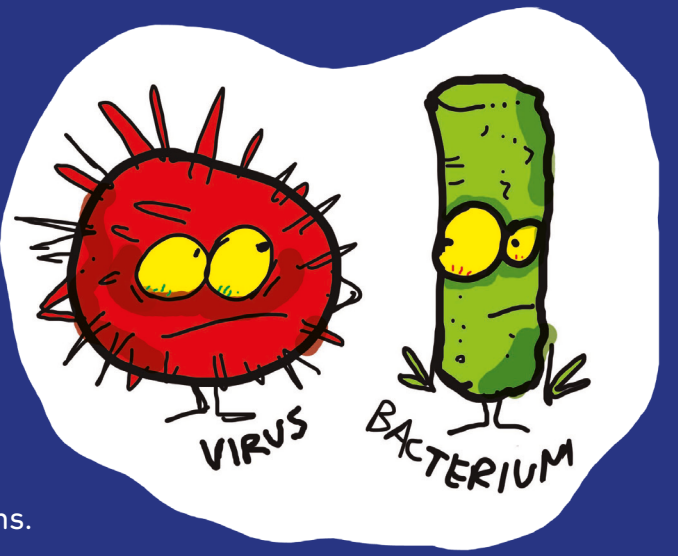
A very important characteristic of the immune system is that the very first time it recognizes a pathogen (virus or bacterium) it develops a **primary adaptive response.** Once the specific cells called B and T are activated, they start to proliferate through a process called clonal selection to form specific cells called effectors and antibodies. A small number of these effector cells will subsequently become **memory cells**. Thus, if the same pathogen attacks again, a **secondary adaptive response** (or memory response) is generated that is much faster and more effective than the primary response.

With vaccination, the immune system is taught to specifically fight a disease, creating antibodies that recognize its pathogens. Vaccines sometimes just "train the system" to recognize a part of the virus or bacterium, triggering the desired long-term response so that, if exposed to the disease, the immune system can defend itself and not develop it. This is called **immunity.**

And how long does immunity last?

Many vaccines provide lifelong immunity whereas others such as those against whooping cough (*Bordetella pertussis*) and tetanus require booster doses after a certain number of years. This is why booster doses for whooping cough, together with tetanus and diphtheria are scheduled for teenagers and adults to prevent outbreaks.

In 2012, approximately 50,000 cases of whooping cough were reported in the USA.



Vaccine classification

Vaccines can be developed from viruses, bacteria, or toxins. Depending on the manufacturing technology they can be **recombinant or traditional.** Recombinant vaccines are produced by genetic recombination, using genetically modified yeasts to synthesize the targeted antigenic proteins. The human papillomavirus (HPV) vaccine is an example of this type.

On the other hand, attenuation in traditional vaccines is obtained through the purification of pathogen-infected cultures.

KILLED OR INACTIVATED VACCINES

Killed vaccines –also called inactivated– contain **whole pathogens** (viruses or bacteria) that have been treated using either chemical processes or heat, or certain proteins or other small fragments taken from the relevant pathogen (subunit vaccines).

This process destroys the microorganism's capacity to replicate within the patient's body to cause the disease, but the characteristics that allow the person's immune system to identify it as a pathogen and, therefore, generate a protective response through antibodies, remain intact.

This type of vaccine generally produces a weaker immune response, which means that several **booster doses** will be required to reach protective levels and maintain immunity over time.

	Immune response	Vaccine examples
Killed or inactivated	Require boosters. The immune response is not as thorough.	Rabies, influenza, intravenous polio, hepatitis A.
Live or attenuated	Most provide long-term immunity. Strong immune respons.	Measles, mumps and rubella (MMR vaccine), rotavirus, smallpox, chickenpox, yellow fever, mpox.

LIVE OR ATTENUATED VACCINES

Live vaccines, also known as attenuated, contain antigens that have been **weakened** through manufacturing processes by which the virus that causes the disease is "cultured" in animal cells or embryos (e.g., chicken). The methods involved in passing a virus through a non-human host yield a version of the virus that the human immune system can still recognize but which **can't replicate** properly in a human host, so they are not capable of causing infection.

These vaccines are able to trigger an immune response that is **very similar to that of the natural infection** and should not be administered to immunosuppressed individuals. They provide long-term protection.

Apart from COVID-19 vaccines, which are a new type of vaccine (mRNA), most of those that are currently commercialized are **polyvalent or combined**; in other words, they contain various antigens, preventing several diseases in a single dose, and they are usually combinations of different types, among which are the following:

Toxoids

Some bacteria depend on toxins to cause the disease, as is the case with tetanus or diphtheria. The toxin can be deactivated and formulated to stimulate the production of antibodies that may effectively "disarm" the bacteria. The inactivated toxin is called a "toxoid".

Subunits

A subunit vaccine contains known antigenic parts of a pathogen that stimulate the immune response. Although subunits can be purified molecules of the original pathogen, they currently tend to be of recombinant origin. These vaccines are very safe, but their profile is not as immunogenic as that of attenuated or inactivated versions, requiring a much more powerful adjuvant. The recently developed vaccine against human papillomavirus (HPV) is an example of this type.

Conjugate Vaccines

Many bacteria are protected by an outer polysaccharide layer. These protein-type coatings of bacteria are good targets for the immune system, although they are generally weak immunogenic components. However, if they attach to and conjugate with a carrier protein, they can have a powerful stimulating effect on the immune system.

As examples, we might mention the vaccines against Haemophilus type b, meningitis C, or the pneumococcal vaccine

AND WHAT MORE IS THERE? LET'S TAKE A LOOK AT THEIR COMPOSITION

To obtain safer vaccines that continue to generate the necessary cell immunity, adjuvants have been gradually added to the formulas (the word comes from the Latin "*adyuvare*", which means "to help"). They include substances such as **aluminum**, water in oil or oil in water emulsions (Freund's adjuvant), **monophosphoryl lipid A** (MPL), or even **virosomes** (spherical vesicles that contain viral envelope proteins), which, when combined with the antigen, trigger a stronger response than the one achieved with the antigen alone.

The quantities of aluminum in a vaccine are smaller than those ingested by babies through follow-on formula.

Adjuvants influence our immune system's response in different ways:

- Reducing the antigen dose required to obtain a satisfactory response. This reduces costs as well as the number of booster doses needed.
- Increasing the immunogenicity of the antigens. Indeed, this is essential for patients with an immature immune response.
- Increasing the speed and duration of immune responses.

Besides, vaccine formulations include **preservatives,** such as phenol and phenoxyethanol, whose function is to maintain stability at extreme temperatures or prevent any potential bacterial contamination, which is the role of the small amounts of antibiotics (e.g., neomycin) that are included in some vaccines.

Other compounds that are present are the **residues** that, as is the case with other drugs, inevitably linger after the manufacturing process. One such residue is **formaldehyde**, which is used to inactivate viruses.

The human body naturally produces more formaldehyde than the amount that can be found in a vaccine. Not to mention pears, which are rich in formaldehyde.

IMMUNIZATION SCHEDULES

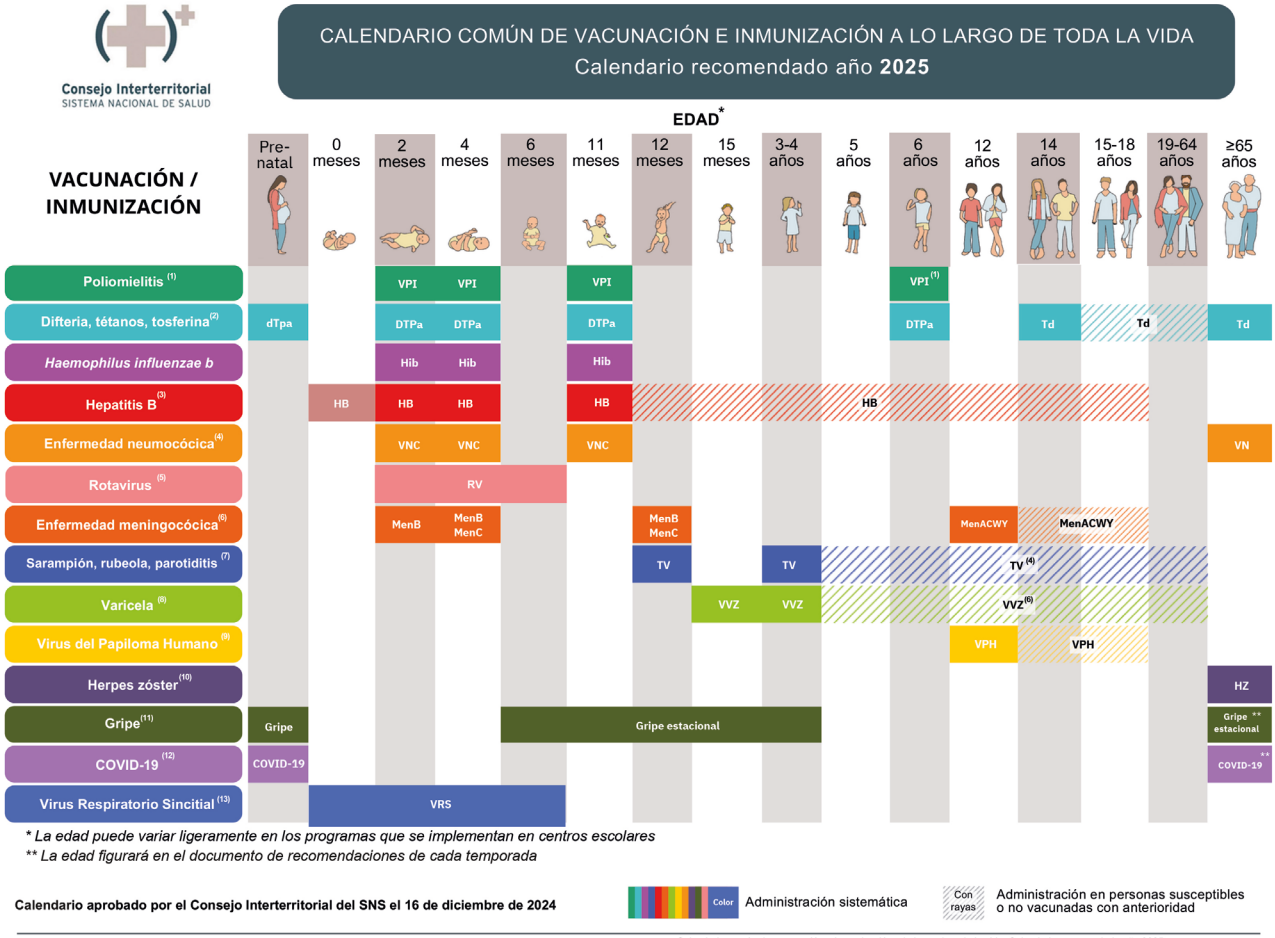
As regards their schedule of administration, which is defined by the health policy of the corresponding country, vaccines are classified as follows:

Systematic: Vaccines that are administered to the entire population, unless there is a medical contraindication, to achieve group or herd immunity. An example of these is the vaccines listed on the vaccination schedules of each autonomous community.

"Herd effect. Vaccinating 95% of the population not only prevents the spread of the disease but, by curbing transmission, it protects those who need it most: those who cannot get vaccinated".

Non-systematic: They are individually administered to risk groups according to lifestyle or personal or environmental circumstances. An example is the vaccines that are administered to travelers. All the vaccines included in the vaccination schedule are funded by the National Health System.

Commercialized vaccines that do not appear on the schedule are regarded as optional and can be obtained



from community pharmacies upon medical indication/ prescription. Scientific societies have issued standard recommendations for these types of vaccines.

In chapter 5 we'll deal with the diseases that we protect ourselves against by using systematic vaccines. In November 2018, the common immunization schedule established in agreement with the autonomous communities was presented in Spain.

It is a lifelong schedule that provides protection even before birth, as it includes the vaccines that are indicated during pregnancy. It is one of the most comprehensive and advanced in the world.

The schedule is regularly updated and also includes vaccine recommendations associated with certain diseases and risk conditions that are more prevalent, such as immunodeficiency, cardiovascular and respiratory diseases, diabetes, and liver diseases.

Why is it so hard to make vaccines?

Because...

...vaccines are biological products. They are made from live organisms. They must also meet the highest quality and safety standards. And what's more, their production always requires extreme precautions. They must be developed in a controlled atmosphere and under aseptic conditions.

Manufacturing a vaccine is a complex process that consists of several phases that are strictly controlled from beginning to end.

Controls are continuous and implemented throughout the entire production chain to guarantee the quality of the raw materials, the equipment, the procedures, and the final products. Systematic analyses of purity, effectiveness, microbiological safety, and harmlessness are carried out for each of the produced vaccine batches. If a batch does not meet the quality standards, it is not distributed, with no exceptions. Certain vaccines undergo more than 50 analyses throughout the manufacturing process.

When the production process ends, samples of each batch are sent to the relevant healthcare authorities, who test them again. Their distribution can only begin after they are approved.

Considering all the controls involved, it takes between **6 and 22 months** to produce a vaccine. For example, 6 months for the influenza vaccine and 22 for the one against poliomyelitis.

WHAT ABOUT RESEARCH?

Research on vaccines is a long, complex, and costly process. Because they are biological products that are made using live microorganisms, their development cycle is quite different from that of pharmaceutical products:

- **Exploratory phase:** understanding the disease, its epidemiological data, and the proteins (antigens) that must be used to prevent it.

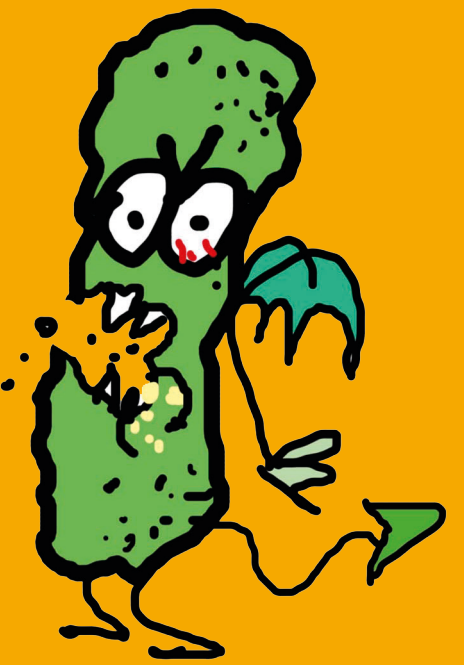
- **Pre-clinical phase:** assessing the safety of the antigens and selecting the best candidate vaccine.

- **Clinical development:** samples of between 10 (phase 1) and 1,000 (phase 3) individuals participate in clinical trials and the first vaccine batches are produced (clinical batches and industrial batches for compliance purposes).

- **Regulatory approval:** all the data gathered in previous phases are sent for approval by the corresponding health authorities.

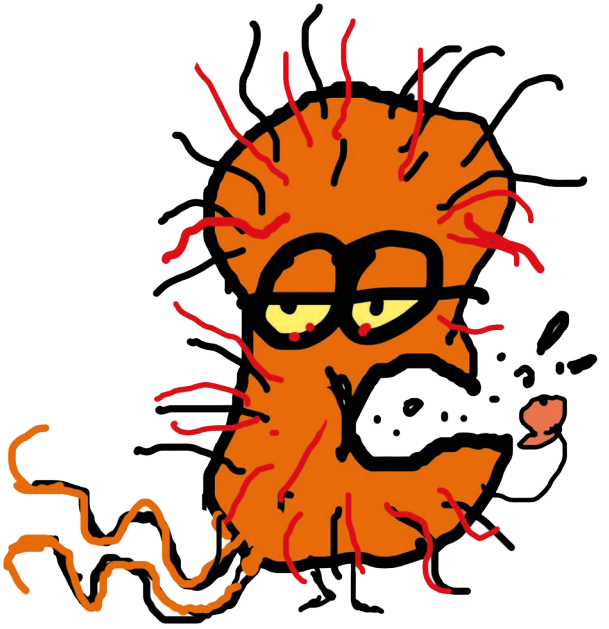
- **Manufacturing process:** it takes up to 22 months to produce a single batch of vaccines.

- **Quality control:** around 70% of the production time is devoted to quality control.



WHAT ABOUT SUPPLY SHORTAGES?

Increased demand or stockout?



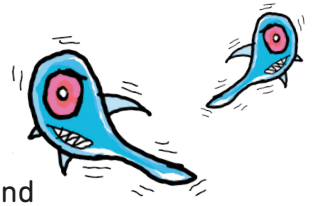
In recent months there have been issues with the supply of certain vaccines such as those for diphtheria, whooping cough, tetanus, hepatitis A, hepatitis B, pneumococcal disease, or meningitis B.

As we saw before, a long time is required to complete the manufacturing process, and this is the main reason for supply shortages or stockouts, alongside increased demand in certain countries and the fact that certain combinations that used to exist are no longer manufactured.

It is also true that vaccine manufacturing and distribution are concentrated in the hands of a **few global companies**, which means that any production issues they might have leave the recipient countries with few alternatives to meet the demand. This is the case when a vaccine that is made by only a few companies is affected by manufacturing problems, forcing Health Authorities to **establish priorities** for vaccinating the population (e.g., when there were whooping cough vaccine shortages, pregnant women were given priority over children who needed booster doses) or to provide different administration guidelines (such as when there was a shortage of Hepatitis B vaccines for adults, which was temporarily remedied by administering two doses of the vaccine for children).

Diseases that we protect ourselves against

We are now going to learn about some diseases that, although many **think of as distant**, are actually **close by**. Fortunately, there is a vaccine for each of them.



TETANUS

Tetanus is an acute infectious disease of the nervous system. It is not contagious and is caused by a strong toxin that is released by the spores of the *Clostridium tetani bacterium*.

The spores can be found anywhere in the environment, especially in soil, ash, the intestinal tracts and feces of animals and humans, and also on the surfaces of skin and rusty tools like nails, needles, barbed wire, etc. The **spores** are very resistant to heat and most antiseptics, and they can **survive for years.**

Anyone can get tetanus, but the disease is particularly common and **serious** in newborns and pregnant women who haven't been sufficiently immunized.

Symptoms and treatment

The incubation period of tetanus can range from 3 to 21 days after infection. Most cases occur within 14 days of it.

Symptoms can include jaw cramping or inability to open the mouth, muscle spasms, difficulty swallowing, convulsions, headache, fever, and sweating.

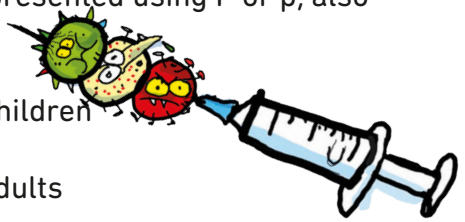
The symptoms of neonatal tetanus include muscle spasms that are often preceded by the newborn's inability to suckle or breastfeed and excessive crying.

Tetanus is a **medical emergency** that requires **hospital care** so that immediate treatment with human tetanus immune globulin and drugs to control muscle spasms can begin.

People who recover from tetanus don't have natural immunity and **can be infected again**, so they should get vaccinated.

Vaccination

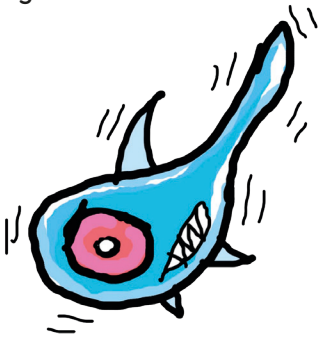
There are many types of vaccines to protect against tetanus. In Spain, combined vaccines against tetanus, diphtheria (represented using letters D or d, depending on whether it is the dose for children or adults, respectively) and whooping cough, also called peretussis (represented using P or p, also according to who the dose is intended for) are used:



- Vaccines against diphtheria and tetanus (DT) for children
- Vaccines against diphtheria, tetanus and whooping cough (DTaP) for children
- Vaccines against tetanus and diphtheria (Td) for adults
- Vaccines against tetanus, diphtheria and whooping cough (Tdap) for adults

In Spain, the ones that appear on the immunization schedule are penta- and hexavalent, which include the above combinations in a single shot, as several doses are required to achieve protection against these diseases.

Anti-tetanus prophylaxis should be provided when there are wounds that are regarded as tetanus-prone, such as:

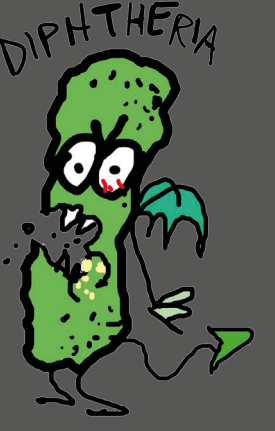


- Puncture wounds caused by sharp objects or tattoos.
- Wounds contaminated with dirt, dust, saliva, or feces.
- Wounds with tissue loss or caused by explosions.
- Frostbite wounds.
- Wounds with evidence of sepsis.
- Extensive burns or those which have gone untreated for over 6 hours.
- Surgery where there is risk of fecal contamination.

*As of April 2024, there were still **10 countries where the elimination of maternal and neonatal tetanus had not been achieved**. In the South-East Asia Region, maternal and neonatal tetanus were eliminated in 2016. This region, where one-fourth of the world's population live, is, alongside the European Region, the second of the six WHO regions to succeed in the elimination of maternal and neonatal tetanus.*

DIPHTHERIA

Diphtheria is a disease caused by *Corynebacterium diphtheriae*, which is a Gram-positive bacterium whose only reservoir is the human body and which produces a toxin that causes the condition. Respiratory diphtheria is an acute, potentially deadly disease that can spread from person to person with systemic effects mediated by a powerful exotoxin. In the pre-vaccination era, it was a major cause of infant death, but after vaccines containing diphtheria toxoid were introduced in the 1940s, its incidence rate fell steeply in developed countries. However, it still has a strong presence in certain countries such as India, where 3,850 cases of diphtheria were reported in 2024.



Symptoms and treatment

Diphtheria starts when the bacillus enters the body through the nose or mouth, colonizing the respiratory mucous membrane. In its pharyngeal form, the disease begins with loss of appetite, general malaise, mild fever, and a sore throat. After one or two days, white-grayish membranes that firmly stick to the pharynx and tonsils and may bleed appear. They can extend by contiguity palate, uvula, larynx, and trachea worsening the medical condition. Children over the age of 6 are particularly prone to swelling and enlargement of the submaxillary and cervical lymph nodes, occasionally with edema. The toxin induces multiorgan damage affecting the heart, nervous system, kidneys, etc. and its mortality rate is high.

Vaccination

The fact that there are still diphtheria-endemic countries (Pakistan, Haiti, the Dominican Republic, or India) entails the possibility of importing cases; therefore, travelers must be up to date with the recommended vaccination series that corresponds to their age, undergoing accelerated vaccination schemes where necessary. In the first year of life, at least 90% coverage with 3 doses of the vaccine (usually the pentavalent or hexavalent combinations) is required to guarantee the control of the disease. Declines in vaccination coverage may entail a real risk of re-emergence of the disease in a population.

RUBELLA

Rubella virus is a togavirus of the genus *Rubivirus*.

The virus is transmitted **by the respiratory route** and replicates in the nasopharyngeal mucosa and the local lymph nodes. Humans are its only known reservoir.

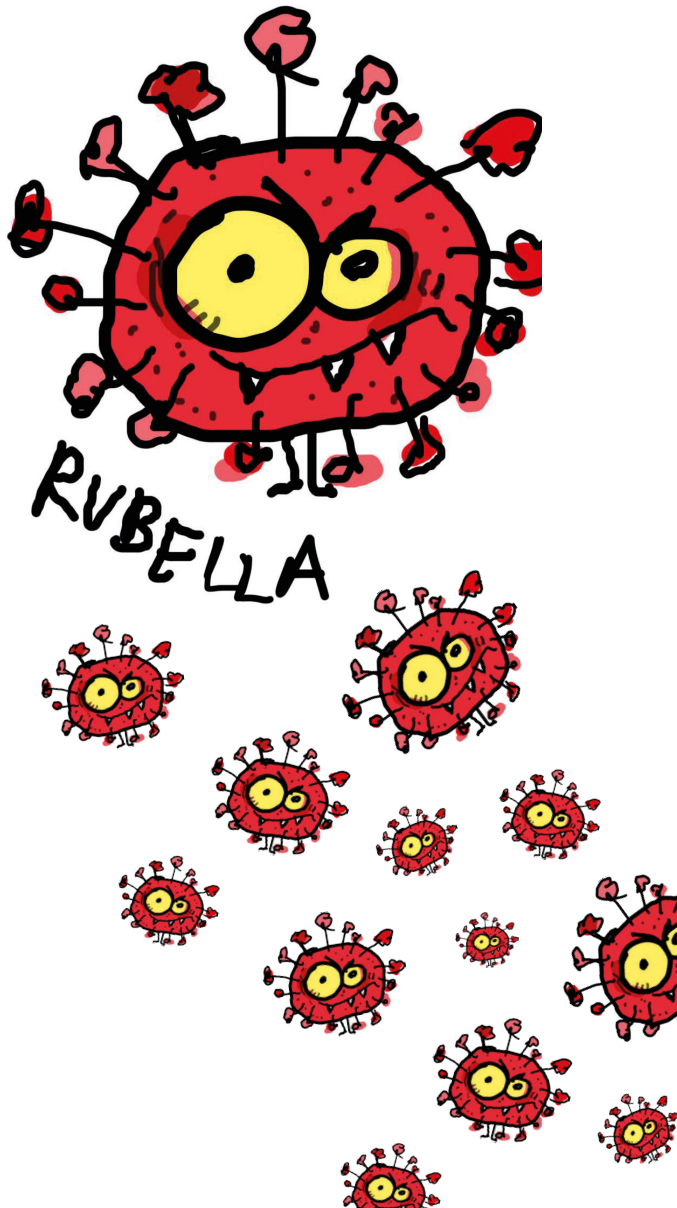
Symptoms and treatment

Rubella symptoms are characterized by being transient and include **skin rash,** conjunctivitis, pruritus, enlarged lymph nodes, low-grade fever, and nausea. Arthralgias and arthritis are not common in children, but affect more than 70% of adults, particularly women. Bleeding problems, Guillain-Barré syndrome, and encephalitis are rare.

Becoming infected during **pregnancy** has **serious** consequences for the fetus, including congenital heart disease, cataracts, and intellectual disability. Infection during early pregnancy can cause **congenital rubella syndrome** (CRS) or lead to fetal death.

Vaccination

Vaccination against the disease appears in the immunization schedule under the **triple viral vaccine.** Likewise, it is common to vaccinate **girls of childbearing age** who haven't been vaccinated or had the disease.



HEPATITIS B

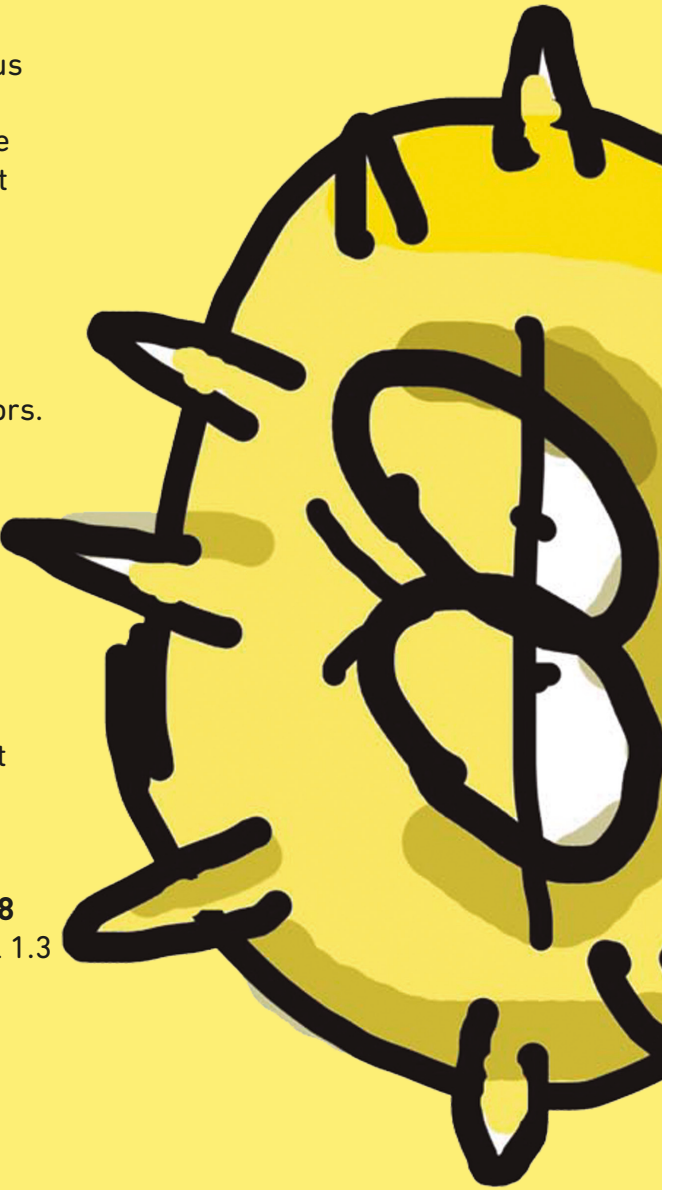
Hepatitis B is a liver disease caused by the hepatitis B virus (HBV), which belongs to the *Hepadnaviridae* family. The virus causes **liver damage** and alters the liver's function. A small percentage of infected people never manage to eliminate the virus and the infection becomes chronic. These people are at greater risk of dying from hepatic cirrhosis or liver cancer.

HBV is spread by **contact with the blood or bodily fluids** of infected people, the same as the human immunodeficiency virus (HIV). However, HBV is around **50 to 100 times more infectious than HIV**. There are no animal reservoirs or vectors.

The main paths of HBV transmission are:
- Perinatal (from mother to child at birth).
- Injections and contaminated transfusions.
- Unprotected sex.
- Acupuncture.
- Tattoos and piercings.

Before the implementation of systematic vaccination against hepatitis B, almost all children in developing countries got infected.

- In 2024, hepatitis B was responsible for approximately **1.08 million deaths globally,** which accounts for 83% of the total 1.3 million deaths caused by viral hepatitis.
- Hepatitis B represents a serious **occupational hazard** for health professionals



Symptoms and treatment

Most people don't experience any symptoms during the acute stage of infection, although some may develop yellowing of the skin and eyes (**jaundice**), dark urine, exhaustion, nausea, vomiting, or abdominal pain. A small number of people with acute hepatitis may develop **acute liver failure**, which can be fatal.

There is no specific treatment for acute hepatitis B. Therefore, care is focused on maintaining well-being and a healthy, balanced diet, especially as regards the reposition of liquids lost through vomiting and diarrhea.

C**hronic hepatitis B infection** can be treated with medication such as **oral antiviral drugs**. Treatment can slow down the advance of cirrhosis, reduce the incidence of liver cancer, and improve long-term survival.

However, in most people, treatment does not cure the infection but only suppresses the replication of the virus. Therefore, when hepatitis B treatment is started, it must be continued **for life.**

Vaccination

The vaccine against hepatitis B is very safe and effective and, since 1982, more than **one billion doses** have been administered across the world. The vaccine has 95% efficacy in preventing this chronic disease and provides protection for at least 20 years.

At present, the WHO does not recommend booster shots.

POLIOMYELITIS

Poliomyelitis is a highly contagious disease caused by three types of polioviruses 1, 2, and 3 (three enteroviruses from the *Picornaviridae* family). The virus is transmitted by person-to-person spread, mainly through the fecal-oral route or, less frequently by a common vehicle, such as contaminated water or food, and multiplies in the intestine. If the virus invades the nervous system, it can cause paralysis in a matter of hours.

Symptoms and treatment

Initial symptoms are fever, tiredness, headache, vomiting, stiffness of the neck, and pain in the limbs. Once the virus has entered through the mouth, the intestine is the main site of infection, although it may also be found in the pharynx. Depending on the capacity of the virus to affect the central nervous system, which is known as **neurovirulence**, a major illness may occur where viruses spread to the spinal cord and, finally, the brain.

The paralysis it causes is permanent, despite the possibility of a certain degree of function recovery. Poliomyelitis mainly affects children under 5 years old. There is no cure.

Vaccination

The polio vaccine that is currently used in Spain is an injectable inactivated polio vaccine (IPV) of the combination type. The one that used to be used before was a live-virus oral vaccine or OPV, which is cheaper and still the choice in countries where the wild polio virus circulates. When the full vaccination scheme is administered, the vaccine against poliomyelitis can provide lifelong protection.

At the global level, since the **Global Polio Eradication Initiative** (GPEI) was launched in 1988, the number of cases has decreased by over 99%, from an estimated 350,000 cases annually to just two endemic countries: **Afghanistan** and **Pakistan**. In exceptional cases, the wild virus is imported into a country causing cases of poliomyelitis. This possibility can be prevented by maintaining high vaccination coverage. The last case of poliomyelitis caused by the wild virus that was reported in Spain took place in 1989.

HAEMOPHILUS INFLUENZAE TYPE B

Haemophilus influenzae (Hib) is a pleomorphic bacterium that spreads through respiratory droplets. It was described in 1892 and given its name because it was thought to be responsible for an influenza outbreak. *H. influenzae* type b (Hib) causes 95% of severe invasive infections in children among the unvaccinated population.

Older children and adults are more likely to host the microorganism and can act as **primary reservoirs** for the transmission of Hib to susceptible individuals.

Symptoms and treatment

Hib causes **invasive infections** such as pneumonia, bloodstream infections or sepsis, meningitis, epiglottitis, septic arthritis, cellulitis, purulent pericarditis, and, less frequently, others such as endocarditis and osteomyelitis.

Hib is the most common cause of sporadic (non-epidemic) **bacterial meningitis** in children aged between 4 and 18 months and is frequently associated with **neurological sequelae** even if the right antibiotic treatment is quickly provided. Hib infections are clinically indistinguishable from those caused by other bacteria such as pneumococcus (can also cause otitis media, sinusitis, meningitis, or sepsis) or meningococcus (causes sepsis and meningitis) and symptoms include fever, headache, photophobia, vomiting, stiff neck, and altered mental state. In severe cases, there can be hypotonia, convulsions, and coma.

Death caused by Hib meningitis ranges between 5% in developed countries and 40% in developing countries. There is a high risk of sequelae, which affect 10 to 15% of survivors and include cerebral palsy, epilepsy, hydrocephalus, blindness, and sensorineural hearing loss. Other less severe sequelae are partial hearing loss, speech problems, behavioral disorders, and learning disorders.

Vaccination

Before the introduction of the vaccine against this bacterium in all childhood immunization schedules, Hib was the **second cause of pneumonia, sepsis, and bacterial meningitis** in children under the age of 5. In the Spanish immunization schedule, it is currently administered in a **combination vaccine** (hexavalent) that also includes protection against other diseases.

WHOOPING COUGH

It is a disease that primarily affects children and is caused by the *Bordetella pertussis* bacterium.

Symptoms and treatment

Its clinical course is around 6 weeks long and consists of a first catarrhal phase, after which **paroxysmal coughing** starts, which can be followed by inspiratory stridor (the whoop), or vomiting. Sneezing fits are characteristic in infants of breast-feeding age. These fits may progress to **apneic episodes and cyanosis**.

Treatment consists of the use of antibiotics such as erythromycin or other macrolides, bronchodilators, secretion fluidifiers, proper nutrition, and environmental measures.

Vaccination

Currently, the vaccine of choice against diphtheria, tetanus and whooping cough on the childhood immunization schedule in Spain is the one that combines diphtheria and tetanus toxoids and an acellular component against pertussis (DTaP).

The Spanish Association of Pediatrics (AEP) recommends Tdap vaccination for all adults who are regularly in contact with younger children, that is, kindergarten and nursery school staff, health professionals, and also pregnant women, as they are at-risk groups.

Vaccination against whooping cough during pregnancy protects newborns for 3 months after birth until they receive their own vaccine.

MEASLES

The measles virus belongs to the *Rubulavirinae* genus of the *Paramyxoviridae* family. Humans are the only known reservoir for the measles virus. It spreads by **direct contact** or through airborne **droplets** from the upper respiratory tract that are expelled by infected individuals. Each infected person would, on average, spread the virus to 12-18 other people.

Measles is **extremely contagious**. If an infected person interacts with others, up to **90% of unvaccinated individuals** who are close to them can also become infected. In the USA, Texas is currently experiencing its worst measles outbreak in 20 years. As of March 2025, the outbreak has reached **309 cases**, with one reported death and 40 hospitalizations.

Symptoms and treatment

The disease caused by the measles virus is **highly contagious**. Symptoms include high fever, cough, and a **generalized rash** of between **7 and 10 days** of evolution that can lead to more or less severe complications such as otitis media, pneumonias, brain damage and, in some cases, severe neurological sequelae.

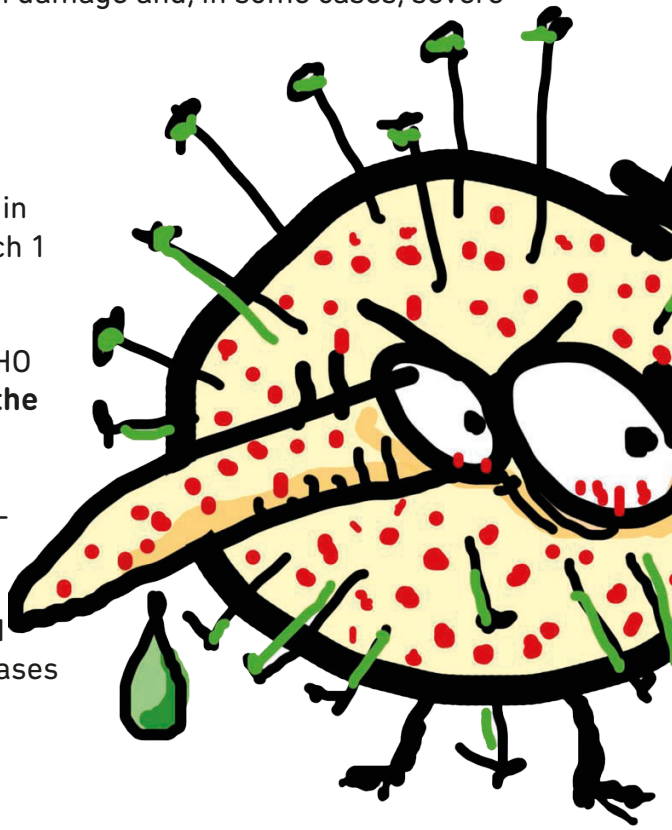
Vaccination

As of today, measles continues to be a major cause of death in developing countries (49 million cases in children out of which 1 million die) that can be prevented through vaccination.

A large number of international health bodies such as the WHO believe that measles **could be eradicated worldwide** when **the rate of vaccinated population reaches 95%**.

In 2016, the Region of the Americas became the first WHO region to have eliminated measles.

The ultimate goal of the **MMR vaccine** (measles, mumps and rubella, abbreviated as MMR) is the eradication of these diseases and it is included in the childhood immunization schedule.



PNEUMOCOCCAL DISEASE

The *Streptococcus pneumoniae* bacteria, also known as pneumococcus, causes many types of infection among which are **pneumonia, septicemia, meningitis, and otitis media**. There are more than 90 serotypes of S. *pneumoniae* that can cause infections.

Children under the age of 2 and the elderly population are more likely to suffer from them. Nasopharyngeal colonization is the only reservoir of the pneumococcus.

Symptoms and treatment

In adults, death is mainly caused by **pneumonia**, and in children by meningitis, especially in developing countries. Treatment relies primarily on antibiotics, although there are increasingly high rates of resistance to them.

Vaccination

Currently, to adapt the serotypes to our country's epidemiological profile, there is a pure **polysaccharide** vaccine (PPSV23) and 2 **conjugate** vaccines: the **13-valent** (PCV13) for children and the **20-valent** (PCV20) for adults over 65 years.

Over the last years, since the vaccine was included in the immunization schedules, there has been a significant drop in the number of cases of **invasive pneumococcal disease** (IPD) and pneumonia-associated hospital admissions caused by the vaccination serotypes. Besides, there has been a reduction in meningitis cases due to highly antibiotic-resistant strains (cefotaxime-resistant) such as serotype 19A.

CHICKENPOX AND SHINGLES

Chickenpox, which is caused by the **varicella zoster virus (VZV)**, a member of the *Herpesviridae* family, is an exanthematous, highly contagious, childhood disease. Its main symptoms are mild fever and a characteristic **skin rash** that evolves from **papules** t**o blisters**, which eventually scab over and cause intense itching. Its potential **complications** include pneumonia, sepsis, osteoarticular infections, and encephalitis.

It is an **airborne disease** that can also be spread **by direct contact** with respiratory secretions, as well as the skin blister fluid of infected individuals. It is also transmitted through skin lesions and **objects that have been recently contaminated** with blister and mucous secretions.

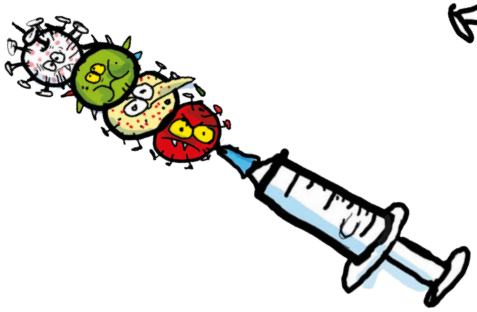
Symptoms and treatment

It can be spread from 1 to 2 days before the rash appears until all its lesions have crusted over. After the initial infection, which involves mild fever and cold-like symptoms, the **exanthema phase** develops with its characteristic skin lesions (blisters or papules), the **virus remains l**atent in dorsal root ganglia (spinal ganglia) and cranial nerve ganglia, where it can become reactivated at any age causing shingles (herpes zoster).

Herpes zoster, also known as shingles, is a recurrent reactivation of the virus that mainly affects adults over the age of 50 and immunocompromised individuals.

It is usually a benign condition and only the symptoms are treated, although **complications** are frequent, especially in immunocompromised children.

Vaccination



It is currently included in the immunization schedule and there are specific vaccines against varicella, one against shingles, and a **combination vaccine** that also protects against measles, rubella and mumps (known as **MMRV** or tetra-viral). All of them are attenuated viral vaccines.

MUMPS

Also known as **epidemic parotitis**, it is a disease caused by a highly contagious myxovirus that mainly affects the **salivary glands**, hence one of its names, because the largest of these glands are called parotid glands and are just in front of the ears, under the jaw.

Symptoms and treatment

Mumps infections are painful and cause **enlargement of the salivary glands**, fever, headache and sometimes hearing loss and lymphocytic meningitis, also known as mumps meningitis. There can also be a risk of **infertility** in adolescents in whom the disease has caused testicular inflammation (orchitis).

Vaccination

It is recommended that children get two doses of **MMR vaccine**, which includes measles, mumps and rubella.

FLU

Seasonal influenza (flu) is an **acute viral infection** that circulates worldwide involving viruses of **type A** (subtypes H1N1 and H3N2), **B, and C** (which causes milder illness).

Type A viruses cause most **seasonal epidemics** and type B most **regional outbreaks**. The influenza virus evolves rapidly, changing its antigenic characteristics, which is why vaccines need to be modified every year to be effective against the strains that circulate in the corresponding season and hemisphere.

It is mainly transmitted via the **dissemination of respiratory droplets** from unprotected coughs and sneezes. Short-distance air transmission of the virus takes place, especially, in **enclosed and crowded spaces**. Other common ways of spreading are contamination as a result of contact with the hands of infected individuals and direct inoculation of the virus.

Symptoms and treatment

Seasonal flu is characterized by a **sudden fever onset**, coughing (generally dry), muscle and articular pain, headache, a sore throat, severe **physical discomfort, and a runny nose.** Coughing may be intense and last for 2 weeks or longer. When infected people cough or sneeze, they release **infectious droplets** (containing the virus) into the air at distances that can reach 1 meter, thus infecting those who are nearby and breathe in the droplets.

In most cases, fever and the rest of symptoms tend to disappear within a week with no need for medical care. Nevertheless, for **high-risk individuals**, influenza can be a serious, even life-threatening, disease. The most common **secondary diseases** that are associated with influenza are pneumonia, bronchitis, sinusitis or otitis, and the worsening of pre-existing chronic conditions. Severe infections may cause heart problems, meningitis, encephalitis, or meningoencephalitis.

Every year, up to 650,000 people in the world die from seasonal flu and influenza-related respiratory diseases. This figure shows the high disease burden of influenza and its **high social and economic cost.**

Vaccination

Annual vaccination against influenza is regarded as one of the most effective measures to prevent infection and its complications. The WHO and the European Union **recommend a 75% vaccination coverage rate.**

Every year, a different vaccine must be developed to adapt to the mutation of the virus and its **circulating strains.**

The WHO recommends yearly vaccination for the following groups:

- pregnant women;
- children aged 6 months to 5 years;
- people aged over 65;
- patients with chronic medical conditions;
- healthcare professionals, as their exposure to patients places them at high risk of infection with influenza viruses and of transmitting them, especially to vulnerable people;
- travelers, especially those visiting the opposite hemisphere during the flu season;
- people at greater risk for severe illness or complications which include pregnant women, children under 59 months old, the elderly population, and patients with chronic conditions (cardiovascular, pulmonary, renal, metabolic, neurologic, hepatic, or hematologic disorders) or immunosuppression (caused by HIV/AIDS, chemotherapy, corticoid treatment or malignant neoplasm).

In Spain, vaccination is recommended for people aged 65 and over, and inactivated vaccines are available in all their formulations: whole, fractioned, or subunit. The ones that are currently available are trivalent vaccines (two type A and one type B components) and quadrivalent vaccines (two type A and two type B components).

Recommendations also mention when to get the vaccine, indicating that getting the flu shot in **late Octobe**r could improve the effectiveness of vaccination.

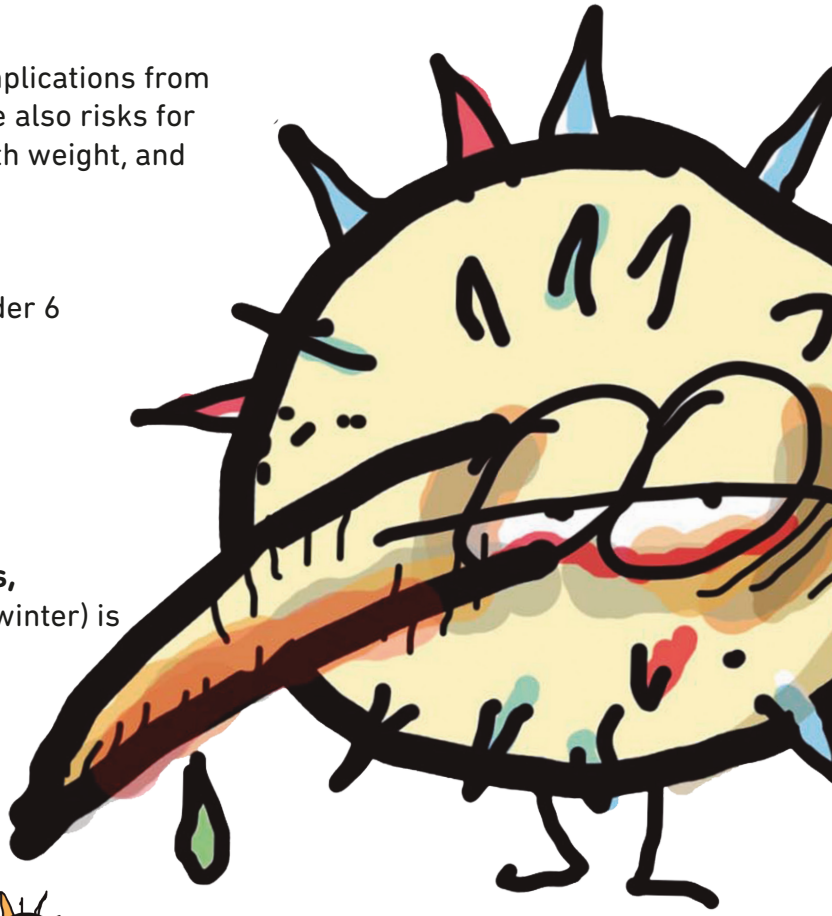
In a world as **globalized** as today's, with regular plane **travels**, crew members may be passive influenza carriers and can pass the disease on to passengers; therefore, certain countries such as France recommend their vaccination.

Did you know that, under certain conditions, a person traveling by plane who is infected with the flu virus can transmit it to up to 70% of the passengers?

Pregnant women are more likely to develop complications from the flu that may require hospitalization. There are also risks for the **fetus**, which include premature birth, low birth weight, and an increase in perinatal mortality.

Respiratory syncytial virus (RSV)
In 2024, RSV immunization started for babies under 6 months of age.

It is **passive immunization**, as it isn't a vaccine but consists of a monoclonal antibody that is administered to infants under 6 months old in a single dose before the beginning and during the RSV season. Since this illness is a **seasonal virus,** immunization before the maximum risk season (winter) is recommended.



PAPILLOMAVIRUS

The human papillomavirus (HPV), or just **papillomavirus**, is a virus from the *Papillomaviridae* family that is spread by **sexual intercourse.**

Symptoms and treatment

Diseases caused by HPV include cancer of the cervix, vagina, vulva, penis, and anus, as well as condylomata acuminata and recurrent respiratory papillomatosis. It is estimated that these viruses affect more than half of the people who have sex, although most of them suffer no problems and overcome the genital infection symptom-free.

Some of these HPV viruses are of the so-called "**high-risk**" kind that can turn normal cells into abnormal cells. Over time, these abnormal cells can develop into cancer. High-risk HPV typically affects cervical cells but is also responsible for genital warts.

Genital warts are very common but not dangerous and do not develop into cancer. Therefore, HPV types that cause genital warts are known as "low-risk". However, they can cause irritation and discomfort and are a vector for the spread of HPV to other people by sexual contact.

Vaccination

The vaccine is effective especially when the individual has not been infected, which can only be assured before first sexual intercourse has taken place. This is why preadolescents and adolescents benefit the most from the preventive effects of the vaccine, which is already included in the immunization schedule as one dose for all boys and girls between the ages of 12 and 18 (both inclusive).

There are currently two commercially available vaccines that protect against papillomavirus infection. One of them covers the four types of HPV (HPV 16, 18, 6, and 11) that most frequently develop into cancer and the other includes the two types (HPV 16 and 18) that are associated with cancer and genital warts. Vaccinated people develop defenses that prevent infection by these viruses in case of contact, although it must be borne in mind that not all the viruses involved in tumors triggered by this virus are in the currently available vaccines.

MENINGITIS

Neisseria meningitidis (meningococo) is the bacterium that causes **meningitis and sepsis.** This bacterium only infects humans.

Symptoms and treatment

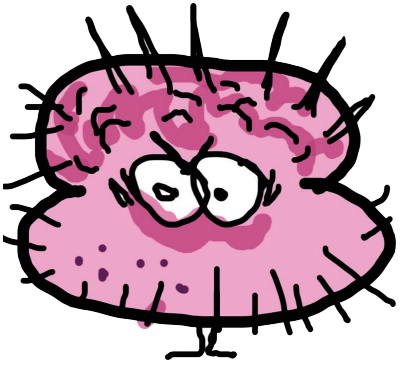
The most common symptoms are neck stiffness, high fever, photophobia, confusion, headache, and vomiting. Even when it is diagnosed early and adequate treatment is provided, around 5-10% of patients die, generally within the first **24 to 48 hours after the onset of the symptoms**. Bacterial meningitis can result in **permanent sequelae**, such as brain damage, deafness, or learning disabilities in 10 to 20% of survivors. A less frequent but even more severe form of meningococcal disease is **meningococcal septicemia**, which is characterized by a hemorrhagic skin rash and fast circulatory collapse.

Most infections **do not develop into clinical disease**, which means that most people **carry the bacteria in their throat**, acting as **reservoirs and sources of infection for others**. It is transmitted by direct person-to-person contact. There is no animal vector or reservoir. Meningococcal disease can be deadly and must always be considered a **medical emergency.** Susceptibility to it decreases with age, but after early childhood, there is a slight increase in cases in adolescence. It requires hospitalization and prompt antibiotic treatment.

Vaccination

Before the introduction of the vaccine against meningococcal group C, most cases of meningococcal disease were caused by this serotype. There are currently polysaccharide-based bivalent (**groups A and C**), trivalent (**groups A, C, and W**), and quadrivalent (**groups A, C, Y, and W135**), as well as a meningococcal B conjugate vaccine.

Since the **meningitis A** vaccine was introduced in **Africa** in December 2020, mass vaccination campaigns have allowed control of this deadly disease, drawing closer to its eradication in 26 African countries of the so-called «meningitis belt»

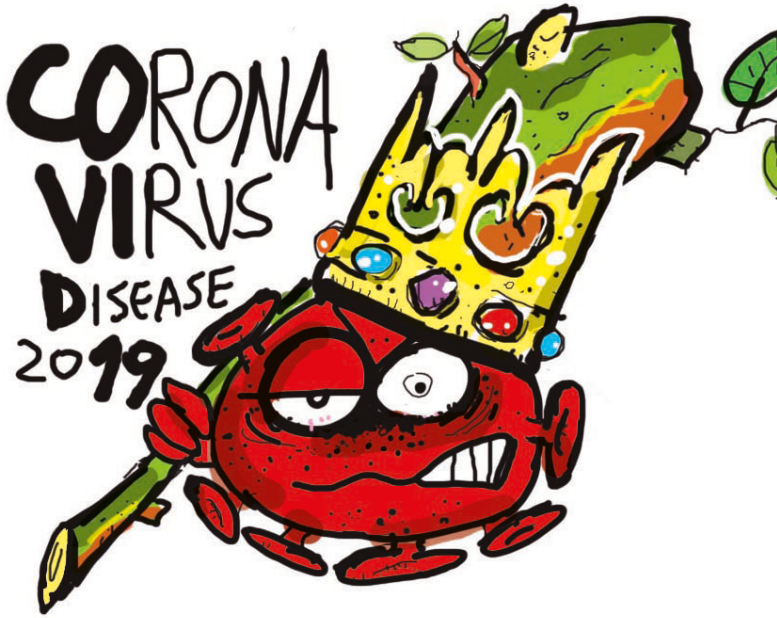


COVID-19

What is SARS-CoV-2?

Coronaviruses are a family of viruses that can cause illnesses such as the common cold, severe acute respiratory syndrome (SARS), or the Middle East respiratory syndrome (MERS). In 2019, a new coronavirus was identified as the cause of a disease outbreak that started in China and developed into a pandemic that lasted several years.

Let's talk about COVID-19 vaccines



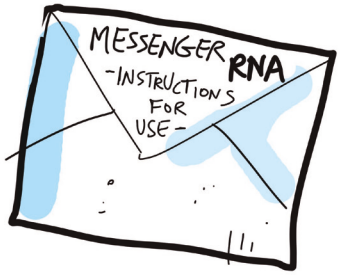
What do COVID-19 vaccines have in common?

The new vaccines make our defenses act against a protein of the virus called protein S, which is key for it to attach to human cells.

As with all vaccines, the aim is to obtain an immune response without causing the disease. There are four types of vaccines against COVID-19:

INACTIVED VACCINES
The virus is weakened (or killed) through a manufacturing process that makes it unable to cause infection.

MESSENGER RNA (mRNA)
This is a new vaccine development technique. Messenger RNA (mRNA) is genetic material of the virus that provides instructions that our cells use to make proteins. Most of the vaccines used durin the pandemic were of the mRNA type.



VIRAL VECTOR

A harmless virus (which cannot cause the disease) is used as a vector to carry a piece of the coronavirus, as a delivery system.

PROTEIN-BASED

In this case, the immune response is triggered by pieces of certain components of the virus (proteins).

In general, vaccines against COVID-19 are very effective in preventing severe disease, hospitalization, and death caused by all the current variants of the virus. Thousands of scientists around the globe are conducting research to better understand how the new mutations and variants of the virus affect the effectiveness of the different vaccines against this disease.

Given that no vaccine is 100% effective, a small percentage of people will still become sick with COVID-19 despite being vaccinated. Nevertheless, if someone becomes infected after having been vaccinated, the symptoms are likely to be milder.

Vaccination can help to protect the people around us, as it is less probable that the vaccinated population can catch and transmit the virus. This, alongside hygiene measures, the proper use of masks, and social distance has allowed us to emerge from the pandemic.

COVID-19 has proven a more serious and dangerous disease among older adults, those who suffer from chronic diseases, and people who are overweight. Hence, immunization campaigns first gave priority to healthcare workers (physicians, nurses, pharmacists, dentists,...), the elderly, transplant patients, or people with chronic cardiovascular, neurologic, or respiratory diseases.

In the future, there will be new variants of the virus and vaccines will be adapted. Strategies that include annual immunization campaigns for the effective protection of the groups most at risk have already been implemented in some countries.

Immunization Agenda 2030

The continuation of the WHO's 2020 vaccination agenda is the Immunization Agenda 2030 (IA2030). This new global strategy, adopted in 2020, sets out an ambitious vision and plan for vaccines and immunization for the 2021-2030 period.

WHAT ARE THE GOALS OF THE GLOBAL VACCINE ACTION PLAN?

EIn 1974, when the WHO first launched the **Expanded Programme on Immunization,** only 5% of newborns in developed countries were receiving adequate vaccination against the six main childhood diseases: tuberculosis,poliomyelitis, diphtheria, whooping cough, tetanus, and measles.

In May 2017, the health ministers of 194 countries endorsed a new resolution aimed at strengthening vaccination to achieve the goals of the Global Vaccine Action Plan. This resolution urged the different countries to prove their leadership and strengthen tracking and monitoring systems to ensure that updated data were used to guide strategic decisions to optimize the performance and impact of immunization.

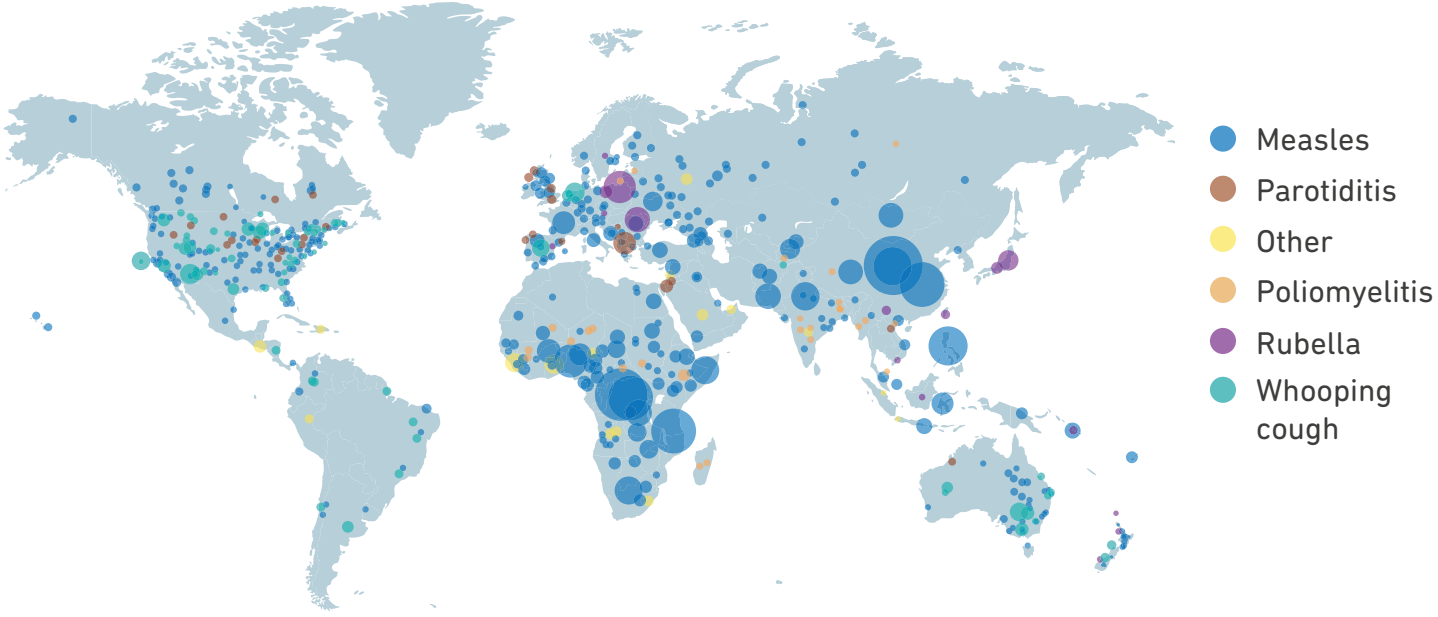
The goals include the following targets:
Reduce mortality and morbidity: Decrease deaths and illnesses preventable by vaccination across all life stages.
Increase equity in vaccine access: Ensure everyone, regardless of location or socioeconomic status, has access to vaccines.
Strengthen immunization programs: Integrate vaccination into primary health care and contribute to universal health coverage.
Improve outbreak and emergency response: Enhance the ability to respond to public health emergencies and disease outbreaks.
Promote research and innovation: Encourage the development of new vaccines and improve existing ones to combat infectious diseases.

Diseases are prioritized according to the significance of their impact on global health, especially in vulnerable populations. The key **priority diseases for IA2030** are measles, polio, pneumococcal diseases, diarrheal diseases, cervical cancer, meningitis, malaria, and COVID-19.

Every year, during the last week of April, the WHO and its associate members celebrate World Immunization Week, aimed at promoting the use of vaccines to protect people of all ages against disease. Immunization saves millions of lives and is globally recognized as one of the **most cost-effective and successful health interventions.**

Each Euro invested in vaccines saves between 4 and 5 Euros of external costs avoided.

The main goal of the 2025 campaign, whose theme is "Immunization for All is Humanly Possible" is to highlight the role that we can all play in this effort, both sponsors and the rest of society. The hashtag **#VaccinesWork** is still used on social media platforms.



VACCINATING AROUND THE WORLD...

Several of our fellow European countries have **different immunization policies** that have evolved over time. Let's look at some of them:

FRANCE

Until January 2018, vaccination against diphtheria, tetanus, and poliomyelitis was mandatory in France. However, the **rubella epidemic** that took place between 2008 and 2014, with more than 23,000 reported cases, 30 cases of encephalitis, and 10 officially notified deaths, as well as the **measles outbreak** with more than 2,500 reported cases only within the first months of 2018, including three **deaths and high hospitalization rates**, proved the inadequacy of the vaccination coverage.

Today, there are 11 mandatory vaccines for children to be able to attend school (kindergarten and school): diphtheria, tetanus, poliomyelitis, whooping cough, *Haemophilus influenza* b, hepatitis B, meningococcal (ACWY and B serogroups), pneumococcal, rubella, mumps, and measles.

Except for cases of recognized medical contraindication, parents or legal guardians of children who have not received the mandatory vaccines may be subject to **criminal procedures**.

Likewise, to improve flu vaccination coverage data, in several Departments of France, community pharmacists are administering the vaccine, thus reaching a larger number of people without burdening the system with extra costs.

This system was introduced years ago in the USA and Canada and in several European countries such as France, Ireland, and Portugal.

PORTUGAL

Vaccines included in the national immunization plan are free. While most vaccines are not mandatory, there are two that are effectively compulsory: **diphtheria and tetanus**. So far, parents who didn't want to get their children vaccinated with one or another of the vaccines listed in the state immunization program had to sign a responsibility form acknowledging the possible consequences that their decision could have for their children and the general population.

BELGIUM

The Belgian vaccination policy only includes **one mandatory vaccine**: polio. It must be administered before the child is 18 months old, after which a **certificate** that is to be submitted to the competent authorities is issued.

ITALY

In Italy, only **four vaccines used to be mandatory**. The measles vaccine was not one of them. However, in 2017, there were almost 5,000 cases of measles and four deaths caused by it. As a response to the outbreak, Italian authorities extended the number of mandatory immunizations to 10 for children under the age of 6. This came into force at the beginning of the 2017-18 school year.

According to the Lorenzin Law, children must receive a range of mandatory immunizations before attending school. This law added Italy to the number of European countries where childhood vaccines are mandatory: Bulgaria, Croatia, Slovakia, France, Hungary, Poland, and the Czech Republic.

GERMANY

Vaccination in Germany was already mandatory to be able to send children to school. The only recent change is that education centers (Kindergartens) must notify **the competent authorities** if parents do not submit documentary evidence of compliance with their children's immunization schedule.

UNITED KINGDOM

Apart from the routine vaccines on the childhood immunization schedule, the United Kingdom's National Health System (NHS) funds a nasal spray flu vaccine for children. It's offered to children aged 2 to 3 years, school-age children (Reception to Year 11) and children with certain long-term health conditions.

Mandatory vaccination is also controversial outside Europe. Despite scientific advice about vaccination, there are no clear guidelines regarding the improvement of coverage rates or the reduction of "antivaccine movements".

JAPAN

Japan's immunization schedule is **included in the national health system,** even though it plays an important role in most developed countries. The Japanese Government funds 11 vaccines including **Japanese encephalitis**, which are provided **free of charge**. This explains why the country's vaccination coverage rates are high and similar to those of European countries. In the case of measles and rubella, the rates achieved are even higher.

One of the particularities of Japan is that it's the **only country in the world** where instead of the triple viral vaccine (MMR), a combination of measles and rubella vaccine (MR) is administered, which makes the mumps vaccine optional.

UNITED STATES

In the USA, vaccination is **required by law** for children to attend school, although there are many states where **exceptions** are made for the children of parents who have religious or philosophical objections, as well as if there are medical contraindications. It is well known that there is opposition to vaccines in strong communities such as the Amish and in states like Texas and California, where a vaccine skepticism trend has become established.

The **Vaccines for Children (VFC**) program provides free vaccines for children who do not have private insurance coverage, those covered by the Medicaid program, Native Americans, and Alaska natives. By increasing vaccination coverage, the VFC Program helps protect communities from outbreaks of vaccine-preventable diseases.

AUSTRALIA

Since 2016, the **No Jab No Pay** legislation requires parents who want to receive *Family Assistance Payments* to ensure that their children's immunization records are up to date until they are 19 years old. No objections are accepted, unless medically justified. The immunization program in Australia is **free**. The policy has been effective in increasing vaccination rates across Australia

WHAT ABOUT SPAIN, WHAT APPLIES?

As a general rule, Spain favors vaccine recommendation rather than making it mandatory like most European countries.
Even so, there are bodies such as the Spanish Bioethics Committee that believe that "mandatory vaccination could be implemented, for instance, when vaccination coverage rates drop so low as to lose herd immunity, without the need to wait for an epidemic or, even, a mere outbreak to occur".

As regards diseases whose vaccination coverage is below the recommended, as is the case with seasonal flu, the Update and Reflection Document on **Influenza Vaccination** in Spain opts for studying the possibility of "increasing the supply of influenza vaccination for the general population in authorized pharmacies", which, as we have seen, is already underway through programs implemented in the community pharmacies of several countries in our vicinity.

There are currently new and increasingly effective vaccines. Given that vaccine accessibility is not an impediment to immunization in Spain, the public administration should continue working on other very important measures, such as the inclusion of new vaccines in adult immunization schedules, a task that progressively converged towards the **common immunization calendar** that was implemented in 2019. Besides, emphasis must be placed on the adoption of information mechanisms to prevent scientifically unfounded health alerts or fake news regarding vaccines. The increase in the number of parents who are against childhood vaccination is very concerning. There is a pressing need to raise awareness and involve health personnel (physicians, nurses, and pharmacists) as information agents so that they get their shots and recommend vaccination for the general population.

In short, there must be **transparency** of health issues so that people have access to **reliable and accurate information**, such as this book and the informative traveling exhibition that is based on it, as well as the educational card game, which we hope will serve as a dissemination tool.

CHALLENGES FOR THE VACCINES OF THE FUTURE

Despite research efforts, there are still many diseases against which there is **no vaccine**, such as **HIV/AIDS**, **Lyme disease, malaria, or leishmaniasis**.

Other diseases that are still pending development of the corresponding vaccines are the respiratory syncytial virus; diarrheas caused by 'Cryptosporidium', 'Campylobacter', 'Escherichia coli', 'Shigella' or 'Salmonella'; or **forgotten tropical diseases** such as leprosy, trachoma, filariasis, Chagas disease, malaria... There are also diseases, such as tuberculosis, for which better vaccines are needed.

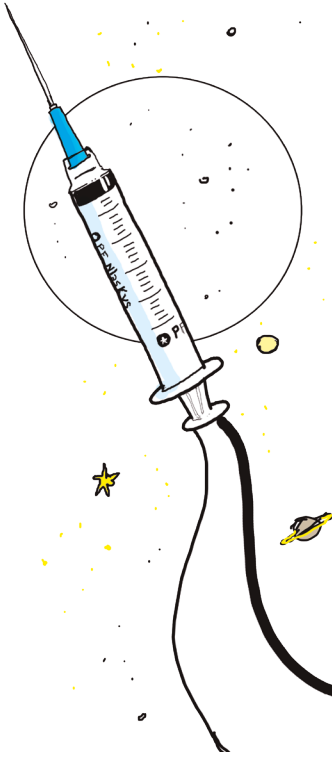
In recent years, **dengue, Zika, and chikungunya**, three arbovirus diseases that are transmitted by Aedes mosquitoes, have rapidly spread in various regions around the world, especially in tropical areas, where their vectors, *Aedes aegypti and Aedes albopictus*, continue to multiply. Mosquito control actions are part of the "One Health" approach to address vector-borne infectious diseases, acknowledging the human, animal, and environmental health connection. In Europe and the USA, a vaccine against chikungunya is already available for people over the age of 18. Pediatric clinical trials are yet to be carried out to be able to extend the possibility to children.

There are currently two commercially available vaccines for **dengue**: a quadrivalent recombinant vaccine with four serotypes of the virus and a live attenuated vaccine.

There is still no vaccine against **Zika**, although there are clinical tests underway with several candidate vaccines based on DNA and mRNA. It is one of the priority diseases that will benefit from the **WHO's strategic plan.**

As regards chikungunya, there is a single-dose vaccine for people over the age of 18.

Ebola remains a worrying issue in Africa. Currently, there are available vaccines, but it is important to use **ring vaccination** to contain outbreaks. This strategy involves vaccinating the contacts of confirmed cases and people who are in close contact with those contacts. In Europe, there are **two approved vaccines** that can be administered 8 weeks apart but would not be as useful in the case of epidemic outbreaks.



Knowledge about new concepts regarding the immunity and effectiveness of current vaccines, alongside the possibilities afforded by recombinant DNA technology, has favored the development of new types of antigens, such as recombinant proteins, viral vectors, virus-like particles, DNA vaccines, and synthetic peptides vaccines, that are currently in the research phase. There are high hopes for DNA vaccines, as they are very stable and easy to produce, or for programmable vaccines that can be customized for different pathogens through the use of nanoparticles as carriers for ARN (for example, Ebola virus, H1N1 flu, and Toxoplasma gondii vaccines).

Not to forget the famous mRNA vaccines during the COVID-19 pandemic.The goal is to create more powerful and versatile RNA vaccines that can be quickly adapted to new pathogens.

The advantage of these experimental vaccines is that they can be manufactured very fast, so they can be almost immediately used to combat sudden outbreaks or implement modifications and improvements. However, the main impediment for access continues to be the high cost of manufacturing.

As regards the vaccine against malaria, Manuel Elkin Patarroyo and his team at the Fundación Instituto de Inmunología de Colombia (Fidic) worked for a long time on its development. It is a synthetic vaccine (basically proteins) to protect the population with costs that are far below those of other current vaccines and Patarroyo's work laid the foundation for further research in malaria vaccines.

Reducing manufacturing time and costs of vaccines is still a short-term goal. Thus, as a fast and simple alternative to the current bioreactors that are used by the pharmaceutical industry, cabbage looper moth chrysalises are being used as biological factories (at present only for veterinary vaccine development, e.g., the vaccine against the new variant of the virus that causes rabbit hemorrhagic disease).

It has a much faster activation potential which makes it very useful in the event of pandemics, mainly because it does not rely on the supply of eggs and is not limited by the selection of the viruses for the vaccine that must be adapted for culture in eggs either.

Indeed, during its lifecycle, the caterpillar is the perfect ally. The procedure consists of isolating a type of gene (hemagglutinin gene or "HA") from a recommended virus of the vaccine that is subsequently recombined with parts of another virus that grow in insect cells. The virus of the "recombined" vaccine is then mixed with insect cells and left to replicate. Next, the HA influenza protein is harvested from these cells and purified. Thus, proteins are obtained 12 times faster than using mammal cells, and escalating insect production is as easy as adding more trays with chrysalises.

Recombinant flu vaccines are created synthetically by obtaining the gene that contains the genetic instructions for making the hemagglutinin (HA) protein. This method allows for efficient. production of flu vaccines without relying on traditional egg-based processes.

HIGH-IMPACT DISEASES IN CURRENT CLINICAL PRACTICE

Some diseases are ever more difficult to treat and would benefit from a future vaccination strategy. Let's see some examples...

Staphylococcus aureus infections are a real **healthcare challenge worldwide**. A five-antigen *Staphylococcus aureus* vaccine is currently in phase II clinical trials.

C**ytomegalovirus** is a common infection that most people have been infected with. It is especially important to evaluate when there is a primary infection during pregnancy since the newborn could be affected by congenital defects, and attention must also be paid in the case of liver transplants.

There is evidence that immune response plays a role in controlling cytomegalovirus infection and, therefore, developing a vaccine is a desirable and long-sought goal.

Other possible vaccines that could be interesting would be against *Klebsiella pneumoniae* (which causes pneumonia and bloodstream and urinary tract infections) and *Clostridium difficile* (which causes diarrheal diseases).

ANTIBIOTIC RESISTANCE, A PUBLIC HEALTH PROBLEM

We must not forget that vaccines can protect us against diseases that are ever more **difficult to treat** using the available antibiotics due to the emergence of resistance. For example, there is an alarming spread of **multidrug-resistant tuberculosis** for which there are very few treatment alternatives. Moreover, certain sexually transmitted diseases such as gonorrhea are also at risk for developing antibiotic resistance.

According to the WHO, if all children across the world were vaccinated against *Streptococcus pneumoniae* (a bacterium that can cause pneumonia, meningitis, and middle ear infections), 11 million days of antibiotic treatment could be prevented every year.

Vaccines in special populations: immunocompromised and chronic patients

Antibiotic overuse or misuse is a major public health problem. The development of new vaccines would help to reduce antibiotic resistance.

Most of these patients must follow the official recommendations of their autonomous community.

Immunosuppression severity varies according to the underlying condition and the therapy that is being received, thus conditioning the choice of immunization strategy.

There are many diseases that are linked to **immunosuppression** (including the one resulting from HIV infection, from medication, or being the recipient of a hematopoietic or solid organ transplant, both hematopoietic and solid organ). It may also be associated with anti-tumor immunosuppressive therapies or long-term steroid treatment.

Age is the main risk factor for diseases such as shingles, added to concomitance with other illnesses, particularly those affecting the immune system, as is the case with COPD or diabetes.

Shingles is a disease caused by the varicella zoster virus that can affect any part of the body, causing skin rash, blistering, and pain. It often has disabling complications and sequelae, including postherpetic neuralgia, which is the most common complication and causes intense pain in the rash areas.

The first vaccine against shingles was approved in the USA in 2006 and already has a long history of use in several countries. Vaccination in Spain is recommended for adults aged 65, with two doses administered at least 8 weeks apart. Besides, it will gradually be extended to people aged 66 to 80, starting with those who turn 80.

As regards **pneumococcal disease**, in almost every autonomous community vaccination is aimed at adults aged over 60 and people with risk factors. Among such factors are, apart from humoral or cellular immune deficiencies, lymphoma, multiple myeloma, Hodgkin's disease and other neoplasms, as well as HIV infection, chronic cardiovascular diseases, chronic lung disease, asplenia, chronic kidney failure, and diabetes mellitus.

The future development of vaccines for special populations will probably be based on the design of **personalized vaccines** according to the individual's genetic makeup.

What would the perfect vaccine be?

The panacea would be the possibility of developing **long-term-effect, low-cost, universal vaccines.** The ideal vaccine of the future should be safe, capable of generating an immune response similar to that induced by the natural infection with the virus, and able to provide **long-term** or lifelong protection against different antigens or several strains of a virus (as is the case with seasonal flu). Besides, **fast, large-scale** production under safe conditions should be viable and, something crucial in terms of costs... it should not require the cold chain for its preservation.

New ways to administer traditional vaccines are also being researched to eliminate the pain of intramuscular jabs (e.g., microneedle patches, jet injectors, inhalable or intranasal vaccines) and so they need not be given by qualified healthcare personnel, which is required for vaccines that are injected with a syringe.

Do you have any questions?

We have answers

Do vaccines really have aluminum?

YES. It is used in the formulation of certain vaccines to boost the immune response.

What if we compare it to aluminum in soil, water, plants, and food?

We are all exposed to aluminum on a daily basis, especially through food and certain drugs such as antacids. In their first 6 months of life, babies receive more aluminum through breast milk or follow-on milk formula than what they will from any vaccine.

Is mercury still in the childhood vaccines that are included in the immunization schedule?

NO. Mercury, in the form of thiomersal, was used to prevent bacterial contamination in vaccines. It is not currently in the formulation of single-dose childhood vaccines. The tiny amount of mercury that a vaccine contains is smaller than what can be found in a tuna sandwich.

Do we really need to get a flu shot?

YES. Influenza is a serious disease that kills around 300,000 to 500,000 people every year. Pregnant women, younger children, adults with health issues, and anyone with a chronic medical condition, such as heart disease or asthma, are at greater risk for developing a severe illness and dying. Vaccinating pregnant women has the extra benefit of protecting newborns, which is very important if we recall that there is no vaccine for babies aged under 6 months.

Seasonal flu vaccines have been used for over 60 years and provide immunity against the three most prevalent strains that circulate each year. Vaccination is the best form of reducing the likelihood of having the flu and transmitting it to others. Avoiding the flu means avoiding extra healthcare costs and loss of income for not going to work or to school.

What if my doctor doesn't get the vaccine?

Failure of healthcare staff to comply with immunization recommendations entails an unnecessary and avoidable risk of infection for patients.

- Recommended vaccines for all health personnel: vaccines against measles, rubella and whooping cough (triple viral), tetanus and diphtheria, hepatitis B, chickenpox, and influenza.
- Vaccines recommended when working under specific conditions: vaccines against poliomyelitis, invasive meningococcal disease, whooping cough, hepatitis A, and typhoid fever.

In addition to healthcare professionals, the group of healthcare workers or **healthcare personnel** also includes all health facility workers who are not directly exposed to patients but can be affected by infectious agents that can be spread to and from healthcare workers and patients. These workers include managers and office staff, as well as kitchen, laundry, security, maintenance, administrative, and volunteer staff.

Can you get the flu from the vaccine?

NO. Flu shots can't cause the flu because they don't contain **any live viruses.**

Should children get more than one vaccine at the same time?

Scientific evidence reveals that the administration of several vaccines at the same time has no negative effects on the child's immune system. Children are exposed to several hundreds of foreign substances that trigger immune responses every day. The simple acts of eating or playing introduce new antigens into the body, and the nose and mouth host a large number of bacteria.

What if we bear in mind that children are exposed to many more antigens when they catch a cold or have pharyngitis than when they get vaccinated?

Nowadays, there are different combination vaccines that provide protection against more than one disease, and new combinations will probably become available in the next few years. Diphtheria/tetanus/whooping cough (DTP) and measles/mumps/rubella (triple viral or MMR) are widely used combination vaccines for routine childhood vaccination. Other combination vaccines that are currently available include hepatitis A+B and hepatitis A+typhoid fever, IPV+DTP, pentavalent (IPV+- DTaP+Hib), triple viral (MMR) +varicela (MMRV or quadriviral), and hexavalent (IPV+DTaP+HepB+Hib).

The main advantage of administering several vaccines at the same time is that fewer consultations are needed, which saves time and money. Besides, giving a combination vaccine when possible (e.g., against diphtheria, tetanus and whooping cough) also reduces the number of jabs as well as the child's discomfort. Different measures can be taken to lessen the pain when the shot is given.

What is the difference between vaccine-induced immunity and immunity provided by natural infections?

Vaccines interact with the immune system triggering an immune response that is similar to the one generated by natural infections but without causing the disease or placing the immunized person at risk for its complications.

¿What if the price to pay for natural immunity was cognitive dysfunction caused by Haemophilus influenzae type b infection, congenital defects caused by rubella, liver cancer as a consequence of hepatitis B, or death as a result of measles complications?

There are very real risks associated with refusing vaccination. There are still vaccine-preventable diseases that can have serious consequences for you and your loved ones.

"Not getting vaccines is like browsing the internet using a computer with no anti-virus or traveling by car without wearing a seat belt. It is a choice that entails significant risks."

Is it true that vaccines cause autism?

NO. There is no evidence of a link between vaccination and autism. Autism symptoms usually begin during the first years of life, which is when most childhood vaccines are administered.

Autism is still an idiopathic disorder. Its cause remains unknown.

In 1998, a study regarding a possible association of the vaccine against mumps, measles and rubella with autism caused alarm.

However, the study was later confirmed to be mistaken and the journal that published it withdrew the article.

Vaccines have unknown side effects.

As with any other drug, all the side effects of vaccines are described in the fact sheet and patient information leaflet and can be obtained from the Medicine Online Information Center of AEMPS – CIMA: https://cima.aemps.es/cima/publico/home.html

What if we told you that, because of that already withdrawn article, the drop in vaccination rates has caused measles, rubella, and mumps outbreaks in Europe and the USA?

Unfortunately, the original publication had a negative impact on vaccination rates, which has indeed caused outbreaks of measles, rubella, and mumps.

Vaccines are only for children...

FALSE. The immunity provided by vaccines decreases over time and, besides, as years go by, people become more susceptible to many diseases (e.g., pneumonia or influenza) and more vulnerable to their consequences.

What if even though you're free from serious consequences you can still transmit the disease to someone more vulnerable, such as your grandchild or pregnant partner?

Many of the vaccines that are currently on the immunization schedules did not exist a few decades ago. Adult vaccination is crucial to protect vulnerable population groups against diseases such as rubella, human papillomavirus (HPV), measles, hepatitis B, influenza, pneumococcal disease, tetanus, singles, and many others.

What if some of the vaccines did not exist when you were a child?

Many of the vaccines listed on current immunization schedules did not exist before the 1970s. Check your immunization record or start a new one based on the records you have.

The Ministry of Health and the autonomous communities agreed on a **common lifelong immunization schedule** that was implemented in 2019.

All the vaccines required by the Spanish National Health System (SNS) are unified under a common immunization schedule, according to the available scientific evidence and the principles of quality, cohesion, and equity. This schedule incorporates the vaccination indications for risk groups and adults into the childhood immunization schedule.

All vaccines are dangerous during pregnancy.

FALSE. Vaccinating pregnant women has the extra benefit of protecting their newborns (this is the case with influenza, for example, as there is still no vaccine for babies aged under 6 months). The flu vaccine should be recommended for all pregnant women, after 14 weeks and when the second or third trimesters of gestation coincide with the season when the influenza virus is most likely to be circulating.

There are, however, certain vaccines that are not recommended during pregnancy, which are live attenuated vaccines such as the triple viral and those against chickenpox, human papillomavirus, shingles, yellow fever, and typhoid fever.

What if there is a high likelihood that the pregnant woman be exposed to the disease?

This must be assessed on a case-by-case basis, establishing whether the benefits outweigh the potential risks, especially when becoming infected puts both mother and fetus at risk.

What if she is breastfeeding?

Vaccines are not contraindicated while breastfeeding. Most antigens are not excreted in breast milk and those that are, such as the chickenpox antigen, are in such a small quantity that it does not pose a risk to the breastfed baby.

People with allergies cannot get vaccinated.

FALSE. Children and adults who have most food or environmental allergies, such as dust-mite or pollen allergies, can get vaccinated.

However, certain vaccine components such as gelatin, yeast, or egg protein can trigger allergic reactions. Therefore, it is important to be aware of any specific allergies and the exact nature of the allergic reaction if any.

Like any medicine, vaccines may trigger allergic reactions. Nevertheless, severe allergic reactions to vaccines are so rare that you are more likely to be struck by lightning.

If I skip a dose on the immunization schedule I must start all over again.

FALSE. This isn't necessary because the administered doses still count, even if more than the recommended time may have gone by. Consult your physician to resume immunization and meet the dates on your schedule.

Can the pentavalent and hexavalent vaccines cause sudden infant death syndrome?

NO: There is no causal link between the administration of those vaccines and sudden infant death syndrome. However, these vaccines, which protect against diseases such as diphtheria, tetanus, and whooping cough, are administered to babies at an age when they are at higher risk of suffering such syndrome, but it is something that can happen regardless of whether they are vaccinated or not.

A healthy lifestyle replaces the need to get vaccinated.

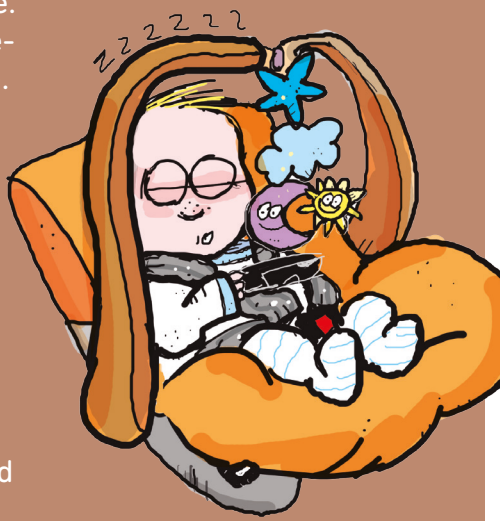
FALSE. A healthy lifestyle can help you stay healthy and prevent certain diseases, but by no means replaces the need to get vaccinated. A healthy diet, good sleeping habits, and exercise may be beneficial for your immune system but will not provide the specific protective immunity that vaccination offers.

Besides, vaccines play an essential role in combating antibiotic resistance and improving the allocation and efficiency of healthcare resources by avoiding the cost of treatment for diseases that they prevent.

My child is too small, I'd rather wait.

What if waiting exposes your child to an avoidable risk?

Babies are particularly vulnerable to certain diseases such as hepatitis B. A large number of infected people don't know that they have the disease, which can spread very easily through contact with blood or saliva. This means that we must protect children with the vaccine as soon as possible. Young children's immune systems are immature because they are still developing the defenses that they will use to combat infections in the future.



There are economic interests behind vaccines.

FALSE. In Spain, investment in vaccines is currently slightly above 1% of total pharmaceutical expenditure and around 0.30% of total healthcare expenditure, with approximately €4 spent per inhabitant.

Vaccination is, unquestionably, one of the most cost-effective tools in public health, with great economic benefits for the population's health and well-being. By preventing a considerable number of diseases and their

consequences, vaccination contributes to the sustainability of healthcare systems, reducing the number of hospitalizations, visits to health centers, and prescriptions for treatment.

Herd immunity makes vaccinating children unnecessary, as the diseases have been virtually eradicated.

FALSE. Vaccines are victims of their own success: as the diseases they prevent become **less visible**, so do the reasons to get vaccinated. However, except for smallpox, none of these diseases have disappeared. Some diseases are still common, even if we see less of them (e.g. whooping cough or hepatitis). Even diseases that have been virtually eradicated in a certain country (e.g., poliomyelitis or diphtheria) can be just one plane trip away. Epidemics can occur anywhere around the globe where people are not protected by vaccines.

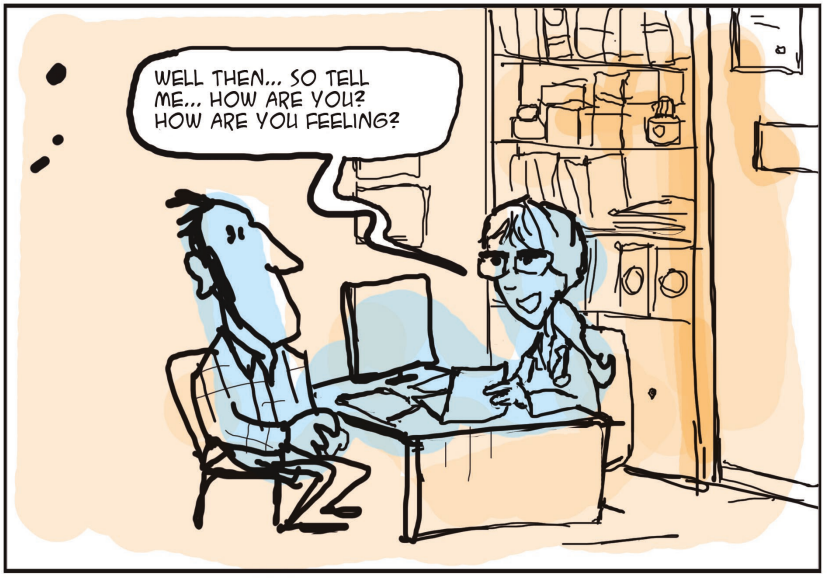
If vaccination coverage rates drop, **herd immunity** will be lost and diseases that were believed to be virtually eradicated may show up again.

Where is it recorded that I have been vaccinated?

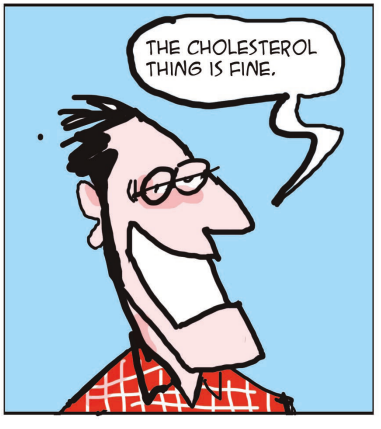
In Spain, your vaccination records are kept through the Sistema de Información de Vacunaciones e Inmunizaciones (SIVAIN). This system centralizes the data of all vaccines administered both in the National Health System and in private clinics. The autonomous communities are responsible for providing this data. You can access your vaccination history through the health services of your autonomous community or through the health folder in the electronic headquarters of the Ministry of Health. This will allow you to know all the vaccines that have been administered to you, regardless of the autonomous community where they were given to you.

Should I get vaccinated against COVID-19 every year?

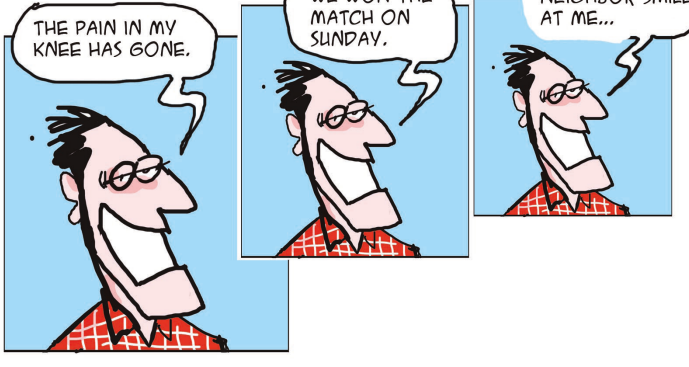
The World Health Organization (WHO) recommends that certain groups of people receive COVID-19 vaccinations approximately every 12 months. This includes older adults, people with chronic diseases, immunocompromised individuals, pregnant women, and health workers. These groups are at higher risk of severe disease and mortality from COVID-19, so annual revaccination helps maintain their protection.


WELL THEN... SO TELL ME... HOW ARE YOU? HOW ARE YOU FEELING?


GREAT!


THE CHOLESTEROL THING IS FINE.


THE URIC ACID THING'S GOING WELL TOO.


THE PAIN IN MY KNEE HAS GONE.
WE WON THE MATCH ON SUNDAY.
THE PRETTY SIXTH-FLOOR NEIGHBOR SMILED AT ME...


ALL RIGHT, ALL RIGHT, THAT'S ALL VERY GOOD, BUT...
DID YOU GET YOUR SHOTS?


SHOTS? ISN'T THAT FOR CHILDREN?
OH DEAR, YOU SILLY THING!

Authors

RAQUEL CARNERO GÓMEZ

Originally from Burgos, she graduated in Pharmacy from the University of Salamanca and completed a master's degree in the pharmaceutical industry in Madrid, a sector in which she has worked for several years holding several positions. She is currently a consultant in regulatory intelligence in healthcare. She has a diploma in Public Health from the Spanish National School of Health and also holds a Diploma in Clinical Pharmacy and a Postgraduate Degree in Health Economics and Outcomes Research. She is a member of the NGO Farmamundi, as well as its delegate for Castile and León, and she leads the Madrid chapter of the Healthcare Businesswomen's Association (HBA). She loves languages and health communication, excelling in several articles and conferences. She is co-author, with Luis Marcos, of three books: *Vacunando* (Salamanca University Press), *Antibióticos vs bacterias* (Larousse) and *Lo que no te esperas del sexo. Una cita con las infecciones de transmisión sexual (ITS)* (Menoscuarto).

LUIS MARCOS NOGALES

Born in Salamanca, he graduated in Pharmacy from the University of Salamanca and completed a master's degree in the pharmaceutical industry in Madrid, a sector in which he worked for several years. He currently works as a community pharmacist in Salamanca, with a special focus on compounding, an over century-long family tradition. He has just published *Hygeia. The Girl Who Wanted to Heal / Hygea. La niña que quería curar* (Valnera Ediciones), his first children's (and bilingual) book.

He is a board member of the Spanish Society of Individualized Medicine (LASEMI). Besides his profession, his great passions are history, comics, and scientific dissemination. He is also a delegate of the Spanish Association of Pharmacists of Letters and Arts (AEFLA), a member of the NGO Farmamundi, the Spanish Society of Clinical, Family, and Community Pharmacy (SEFAC), and a teacher.

He is the creator, along with illustrator Ansola, of the saga *Epopeya farmacéutica* (Ediciones Universidad de Salamanca), which currently has two volumes: Epopeya farmacéutica. *La farmacia en el mundo antiguo* and *Epopeya farmacéutica. La farmacia en la Edad Media.* Both authors, also with Ansola as the illustrator, have published *Antibióticos vs bacterias. De la resistencia al contraataque* (Larousse) and *Lo que no te esperas del sexo. Una cita con las infecciones de transmisión sexual (ITS)* (Menoscuarto Ediciones). Both authors are also founders of the @vacunando science outreach project, which combines the book, a free traveling exhibition, a board game, an active social media presence, and educational conferences and talks in primary and secondary schools. Currently, the @vacunando project is supported by several institutions and backed by the "la Caixa" Foundation. Raquel and Luis are also co-founders of the #DivulgaSalamanca (@DivulgaSalamanc) platform. Their work has been recognized with several awards: Academy of Pharmacy of Castilla y León, I Premio Innovación Social y ODS del Consejo General de Colegios Oficiales de Farmacéuticos, Premio INDEPF, and Winner of the IV Premios #ReConocidos del Sector Sanitario for Antibióticos vs Bacterias for their efforts in disseminating information about antibiotic resistance.

IÑIGO ANSOLA

Well known cartoonist from Laredo, Cantabria. Author of the daily cartoon in the newspaper *El Diario Montañes* since 2008. He has a sarcastic and witty sense of humour.

Project Vacunando

The *Vacunando Project* has been designed to spread an important health message among the general public: misinformation may lead to vaccine hesitancy, which is nowadays a health threat for all. Scientific dissemination is in great need to help boost our immunization programs all over the world.

Vacunando is often referred to as "an infallible vaccine against misinformation, a very contagious and sometimes even deadly disease".

The *Vacunando Project* was born as a scientific outreach initiative at a time when health education was paramount. Now, in this post-pandemic world it is more important than ever to convey the message that vaccines are essential for combating preventable diseases and to support vaccination programs for all populations: from infants to pregnant women, with special attention to adults over 65 years. This book aims to present the scientific background behind immunization programs and highlight the achievements made over the past two centuries.

Written by two pharmacists, the book *Vacunando. ¡Dos siglos y sumando!*, originally published in Spanish by Salamanca University Press in 2019, stands out with its unique approach and design, featuring visually appealing cartoons and concise, precise text. Illustrated by Ansola, a great cartoonist who brings the message to life with a touch of humour. It is uncommon for a book of this nature to include both the history of vaccines and microbiology, covering all relevant historical figures. More importantly, it dedicates an entire

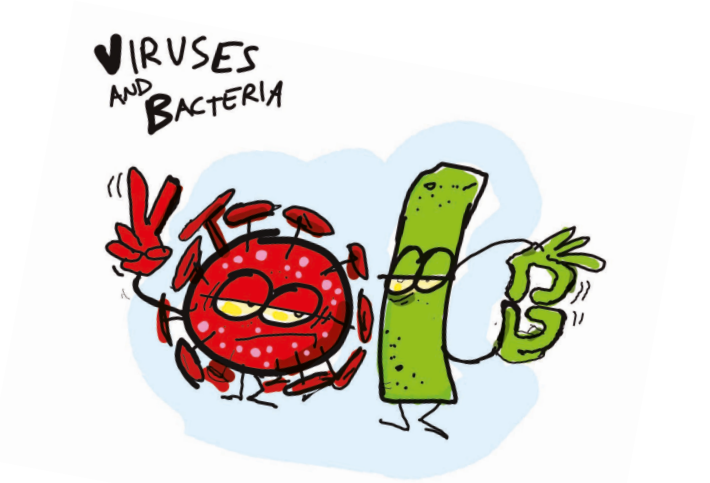
section to Women and Vaccines, highlighting their contributions to research and their milestones in vaccine development. These talented women, who did not often receive the recognition they deserved, played a crucial role in research and in advancing international immunization programs, such as the Spanish Balmis Expedition in the 19th century.

In conjunction with the publication of the illustrated book *Vacunando. ¡Dos siglos y sumando!*, an informative exhibition was installed across several faculties of the University of Salamanca (USAL). This event coincided with the celebration of the USAL's 800th anniversary.

Informative panels of the exhibition are full of important messages, covering all aspects of immunization, from the WHO 2020 Project to the common National immunization scheme (updated in this book to the 2025 schedule), with a section showing "Questions and Answers" taken from controversial topics like autism link to vaccines, vaccines components, such as aluminum or thimerosal and the questions related to seasonal influenza shots or the risks during pregnancy. All these are accompanied by the recognizable protagonists of *Vacunando* (Blossom the Cow, Jenner, Pasteur, Lady Mary Montagu). In addition to its scientific content, the book also addresses the health equity, political, and social aspects of vaccines, including international approaches to immunization programs and market access requirements across regions.

The exhibition extended beyond the University Campus to various locations throughout the city, including the CIC Center, Fonseca College, Parque Empresarial, CIALE, and the I+D+I Hub USAL, attracting hundreds of visitors. In autumn 2019 it traveled to Madrid and almost six years later, it has been installed in more than 120 places, from general hospitals and vaccination centers to city town halls, secondary and primary schools, including cultural and community centers, and even shopping malls. @vacunando is also very active on social media (X, Instagram, and Facebook). The Project has received several awards for its significant role in raising awareness and enhancing visibility at a crucial time when anti-vaccine and vaccine hesitancy movements are gaining traction across Europe via social platforms and websites.

A website and an educational card game –supported by Fundación La Caixa and the NGO Farmamundi– have been developed as a tool for educators and healthcare professionals. The game is based on the amazing microorganism created by Ansola. Both will soon be available in English, along with this updated version of the book, allowing it to reach a broader audience.



Outro

Generations born in the first half of the 20th century still remember the devastating childhood diseases that caused many to lose siblings at a young age or to witness them growing up with severe, lasting consequences. Paralysis from polio. Male infertility from mumps. Encephalitis, deafness, and immune amnesia from measles. Just to name a few.

Those old enough to remember the time before vaccines became available have seen firsthand the benefits they brought to humanity—saving the lives of children, the elderly, pregnant individuals, and the immunocompromised, while also improving overall quality of life in countries with access to vaccination. It is easy to forget these benefits when diseases no longer seem to circulate—precisely because vaccines have been so successful. However, fear of the unknown and skepticism toward vaccines have contributed to growing hesitancy. A common question arises: Why should we still vaccinate against diseases no one seems to get anymore? This is a valid concern, and that is why accurate information is essential.

People need to understand that the infectious agents causing these diseases are still present and that a certain level of herd immunity is required to break chains of transmission. Communicating about vaccines is crucial to raising awareness that vaccination not only protects the individual receiving it but also those around them. By getting vaccinated, you help safeguard your neighbor—someone who may be immunocompromised and for whom vaccines may not work as effectively.

Vaccination is not just an act of self-care; it is an act of compassion. Correct information is essential to reassuring concerned parents that vaccines are safe and will protect their children.

Beyond individual and public health benefits, vaccination has an economic impact: it is far cheaper to prevent disease through vaccination than to treat people in hospitals. Effective vaccination programs reduce the burden on healthcare systems worldwide, preventing strain during outbreaks and ultimately saving lives and resources.

Since the rollout of the first vaccines, vaccine misinformation has left many people worried, making them and their children vulnerable to vaccine-preventable diseases for the wrong reasons. This is precisely why initiatives like Project Vacunando are so important.

Through this book, its social media presence, and other initiatives, Project Vacunando serves as an invitation for more dialogue between those who are skeptical about vaccines, those who have questions, and those who are vaccine advocates. This book provides an overview of the history of vaccines, highlighting key aspects and influential figures from the past, present, and future of vaccinology.

A deeper understanding of the history of vaccination may also inspire the next generation of vaccinologists -those we will rely on to develop vaccines against diseases for which no protection currently exists. The potential impact of Project Vacunando in raising vaccine awareness should not be underestimated.

Michael Schotsaert
Associate Professor at the Icahn School of Medicine at Mount Sinai (NY)

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Interesting websites:

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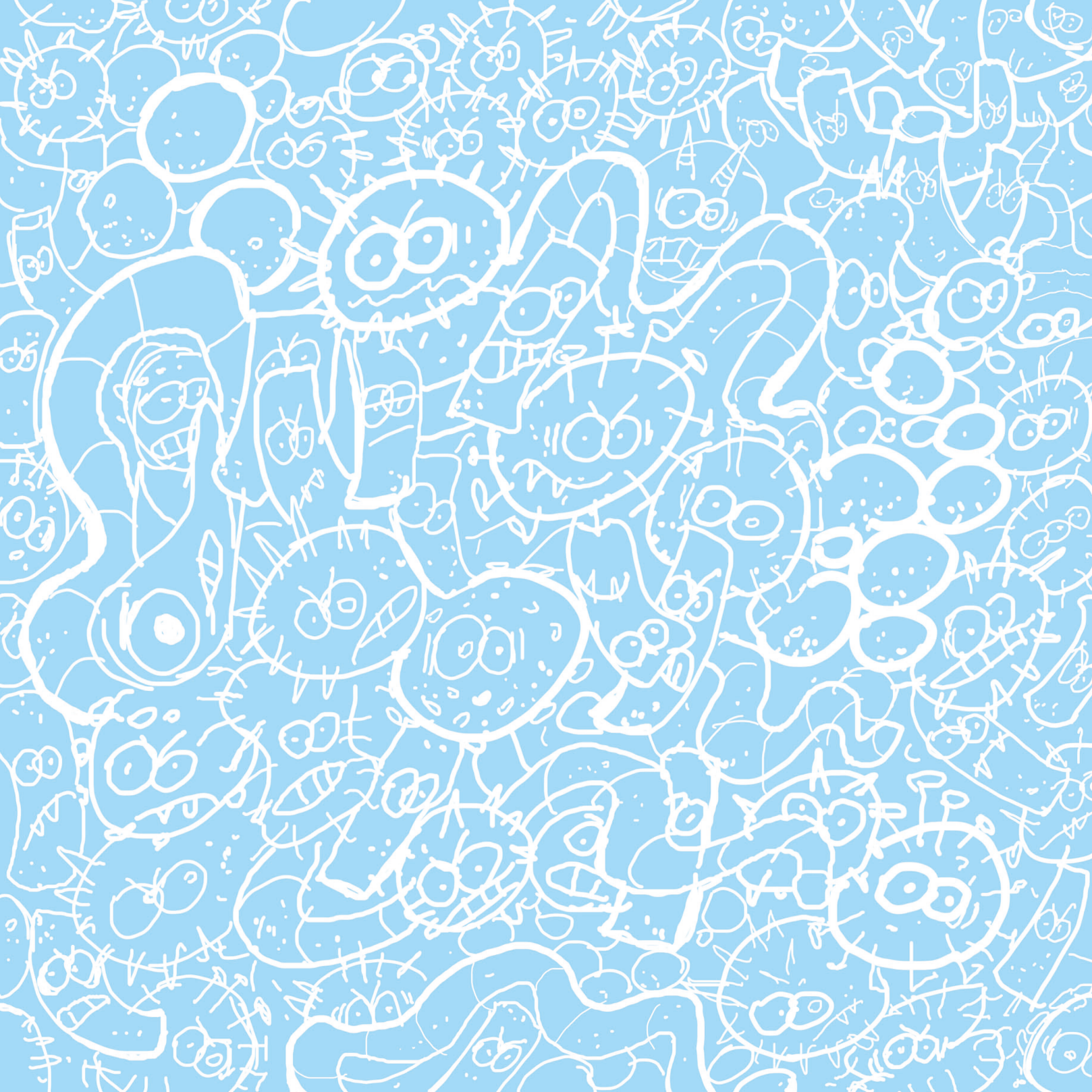

If "Blossom," the cow that gave its name to vaccines, were to raise its horns, it wouldn't believe that in the 21st century there are still doubts about their safety. Edward Jenner's gardener's son and the intrepid Isabel Zendal would pull their hair out, and Louis Pasteur himself would die of rage. And if we've been vaccinating for two centuries, what are these doubts? What are vaccines? What is their history? What are their components? What diseases do they protect us from? Are they effective? Should we get vaccinated throughout our lives or only in childhood? Who should take special care? Who should we ask? What is herd immunity? Are the anti-vaxxers right?

Here you have all the answers in black and white (and some color). A book that is an infallible vaccine against misinformation, a highly contagious and sometimes even deadly disease.

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