ANTIBIOTIC RESISTANCE: APPROACHING THE POST-ANTIBIOTIC ERA

WRITTEN AND EDITED BY THE SAFE TEAM

SUPERBUG AWARENESS FOR EDUCATION

SAFE

INDEX OF CONTENTS:

We have all heard of **antibiotic resistance**, an increasingly serious issue in our society that influences the **prevention and treatment** of bacterial infections. These microorganisms develop mechanisms to evade the action of antibiotics.

In some cases, this inhibits, when we start an antibiotic treatment, the effect of the antibiotic on the infections we suffer, and other treatments need to be used.

Unfortunately, antibiotics are not endless, so we will not always be able to have an alternative treatment to fight the infection caused by a resistant bacterium.

Today, **multi-resistant** bacteria -resistant to various antibiotics- and **pan-resistant** -resistant to all antibiotics- have already appeared.

In this report we introduce you to the current situation of the most resistant bacteria to antibiotic treatments (**superbugs**), in order to contextualize the real impact of this problem, and the possibility that it can lead us to a **post-antibiotic era**, where we will not have any effective antibiotics to fight bacterial infections.

WHATS IS A MICROORGANISM?

A microorganism is any organism that can only be observed through a **microscope**. It includes **prokaryotes** (bacteria and archaea) and certain **eukaryotes**, such as protozoa, unicellular algae or some fungi (yeasts and molds). Viruses, virions and prions are also grouped in this category, but they don't have a cellular nature and are considered **strict parasites**.

When these microorganisms infect animals and/or plants, the treatments that allow us to prevent and treat their infections are called **antimicrobials**, which are classified as **antibacterials** (or **antibiotics**), **antivirals**, **antifungals** and **antiprotozoals**.

Each antimicrobial acts on specific characteristics of each pathogen and are **specific to each type of microorganism.** In this report we will focus on antibiotics and the 13 bacteria with the greatest ability to avoid their toxic effects, therefore, the **most resistant bacteria to antibiotic treatments**, linked with the problems that arise both in humans and the veterinary sector.

WHICH ARE THE MOST DIFFICULT BACTERIA TO TREAT?

Among the bacterial species behind the most common infections in humans, the WHO has identified the 13 species with the **highest virulence and resistance to antibiotic treatments.**

If we do not consolidate hygiene habits and responsible consumption of antibiotics, these bacteria will be the **main causes of mortality in a near future, becoming the post-antibiotic era.**

RESOURCES ON ANTIMICROBIAL RESISTANCES

Besides this report, the team behind the SAFE project (educational project funded by EIT Health, which promotes scientific vocations among youngsters and raises awareness about the Antimicrobial Resistance issues using the Learning-Service methodology). SAFE has generated informative resources to understand the problem of Antimicrobial Resistance and the interrelationship between its causes, under the concept of One Health.

For more information and resources within the framework of the project, you can enter the SAFE blog, where you will find videos, infographics, and other materials aimed at all types of audiences:

SAFEINITIATIVE.EU

WHICH ARE THE MOST COMMON ANTIBIOTICS?

*This table refers exclusively to the groups of drugs addressed in this report.

FAMILY	ANTIBIOTICS	HOW DO THEY WORK?
β-lactam	Penicillins (amoxicillin, ampicillin, meticillin) Cephalosporins (First, Second and Third generation) Carbapenems, Monobactams	Inhibition of cell wall synthesis
Aminoglycosides	Gentamicin, neomycin, tobramycin, amikracin, kanamycin, streptomycin	Inhibition of protein synthesis
Macrolides	Azithromycin, clarithromycin, erythromycin	Inhibition of protein synthesis
Polypeptids	Polymixin E (colistin), polymixin B, capreomycin	Action on the cell membrane
Quinolones	Nalidixic acid, fluoroquinolones (ciprofloxacin and levofloxacin)	Inhibition of DNA replication and its translation into proteins (Inhibition of DNA supercoiling)
Sulfonamides	Sulfametoxazol	Inhibition of nucleic acid synthesis
Tetracyclines	Tetracycline, oxitetracycline, chlortetracycline	Inhibition of protein synthesis
Fenicols	Chloramphenicol	Inhibition of protein synthesis
Azoles	Metronidazole	Inhibition of nucleic acid synthesis
Others	Rifampicin, Clindamycin, Lincomycin Linezolid Etambutol, Isoniazid Fosfomycin Glycopeptides (Vancomycin) Trimethroprim Nitrofurantoin	Inhibition of transcription, specifically RNA polymerase Inhibition of protein synthesis Antimicobacterial, Inhibition of protein synthesis Inhibition of cell wall synthesis. Used mainly in urinary tract infections Inhibition of cell wall synthesis Inhibition of DNA synthesis Damage of bacterial DNA. Used mostly in urinary tract infections

THE MOST RESISTANT SUPERBUGS

1.- Acinetobacter baumannii

DISEASES, INCIDENCE, MORTALITY AND VIRULENCE

A. baumannii is a pathogen with limited virulence. Despite this fact, **certain characteristics of this specie enhance its virulence.**

It is often found in hospitals, due to its resistance to various antibiotics and its ability to survive in inert dry objects, such as medical instruments or sheets, sinks and taps. This species can also be found in the skin microbiota of healthy health personnel, so attention should be paid to the cleanliness and hygiene of the hands of hospital staff and infrastructure.

Only in 2017, 8,500 patients hospitalized in the U.S. were infected with bacterium resistant to carbapenem, which is an antibiotic of latest generation, 700 of which died.

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

A. baumannii has **intrinsic resistance to many antibiotics**. But over the last twenty years these resistances have increased, **hindering its treatment.**

Most strains are resistant to **penicillins**, first-, second-, and third-generation **cephalosporins**, **aminoglycosides**, and **fluoroquinolones**.

Thus, today we have treatment options using **carbapenems**, **colistin** (polymyxin E) and **fluoroquinolones** in combination with **aminoglycosides** and / or **rifampicin**.

In Spain, according to the European Center for Disease Prevention and Control (ECDC), the percentage of infections caused by these resistant strains has decreased between 2013 and 2018. However, this trend does not represent an improvement in the issue or it is reflected in all European countries, since, if we take Croatia as an example, the percentage continues to increase alarmingly.

2.- Campylobacter spp.

DISEASES, INCIDENCE, MORTALITY AND VIRULENCE

Of all foodborne diseases, campylobacteriosis or *Campylobacter* spp. (different species of the genus Campylobacter), is **considerably high**.

One every 10 people is infected each year by it, meaning the loss of about 33 million years of healthy life. This value translates into **550 million cases a year**, 220 million of which affect children under five years old.

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

The resistance of *Campylobacter* spp. is very different between the US and the EU, especially in the percentage of **fluoroquinolone** resistance (higher in the EU), due to the use of this antibiotic to treat poultry.

Currently, a report published by the ECDC states that there are very high percentages of resistance to **ciprofloxacin**.

However, **fluoroquinolones** can be used with **macrolides** where the resistance is relatively low.

3.- Enterococcus faecium

DISEASES, INCIDENCE, MORTALITY AND VIRULENCE

This bacterium has the ability to colonize and form **biofilms** in hospital material (catheters, mechanical ventilation devices...).

The bacterium transfers itself from the colonialized material to the patients by forming biofilms in the intestines. It does this thanks to its surface proteins.

It usually acts as an **opportunistic pathogen** in elderly or immunocompromised patients and the prognosis is usually not very good.

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

This bacterium has recently increased resistance to multiple antimicrobials.

Most strains are resistant to **vancomycin, ampicillin, cephalosporins, clindamycin, cotrimoxazole (trimethoprim + sulfamethoxazole) and aminoglycosides.**

4.- Escherichia coli

DISEASES, INCIDENCE, MORTALITY AND VIRULENCE

Most strains of *E. coli* are harmless, but some can cause serious illness by secreting **Shiga toxin**.

This toxin triggers hemorrhagic colitis that usually resolves after 10 days, except in **young children and the elderly** where the infection is **life-threatening** as a result of progressing to **hemolytic-uremic syndrome (HUS)**.

HUS occurs when the blood vessels in the kidneys become inflamed, leading to kidney failure and even death. The **lethality rate of HUS is 3-5%.**

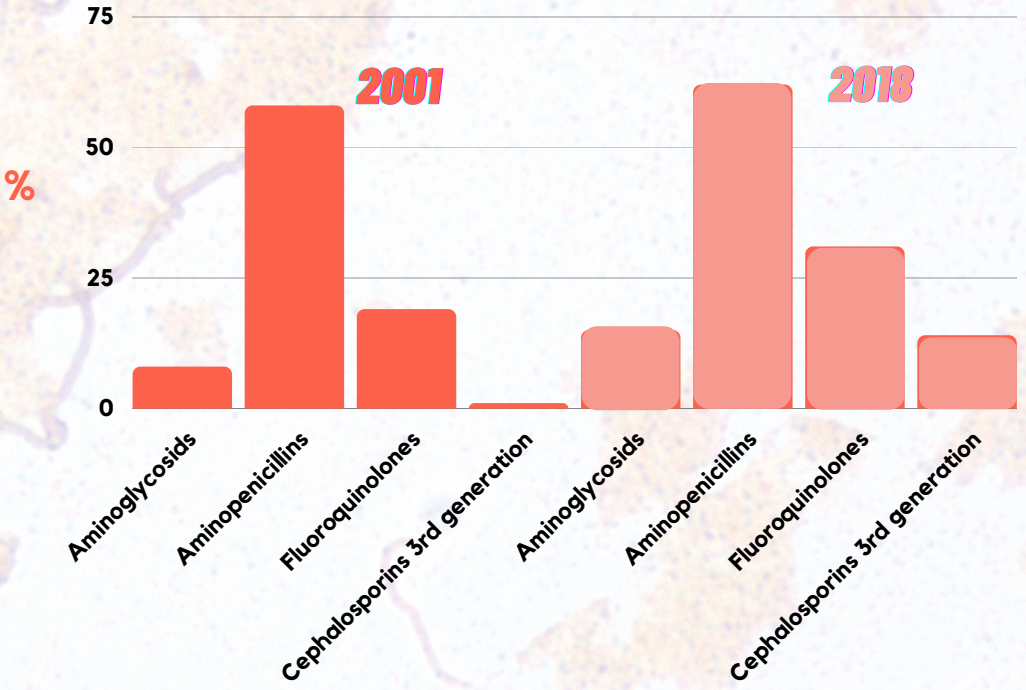
WHAT RESISTANCES DOES THIS BACTERIA HAVE?

E. coli has become highly resistant to **penicillins**, **cephalosporins**, and **tetracyclines**. **Graph 1** shows the increase in antibiotic resistance of this species over the last decades in Spain.

There is an increase in resistance to third generation **fluoroquinolones** and **cephalosporins**.

Currently, the antibiotics that have a **low percentage of resistance** are **carbapenems**, **phosphomycin** and **nitrofurantoin**, which could change if they are not used responsibly.

GRAPH 1. EVOLUTION OF ANTIBIOTIC RESISTANCES OF *Escherichia coli* (ECDC)



5.- *Haemophilus influenzae*

DISEASES, INCIDENCE, MORTALITY AND VIRULENCE

Two main categories of *H. influenzae* are defined: strains with capsule and strains without capsule.

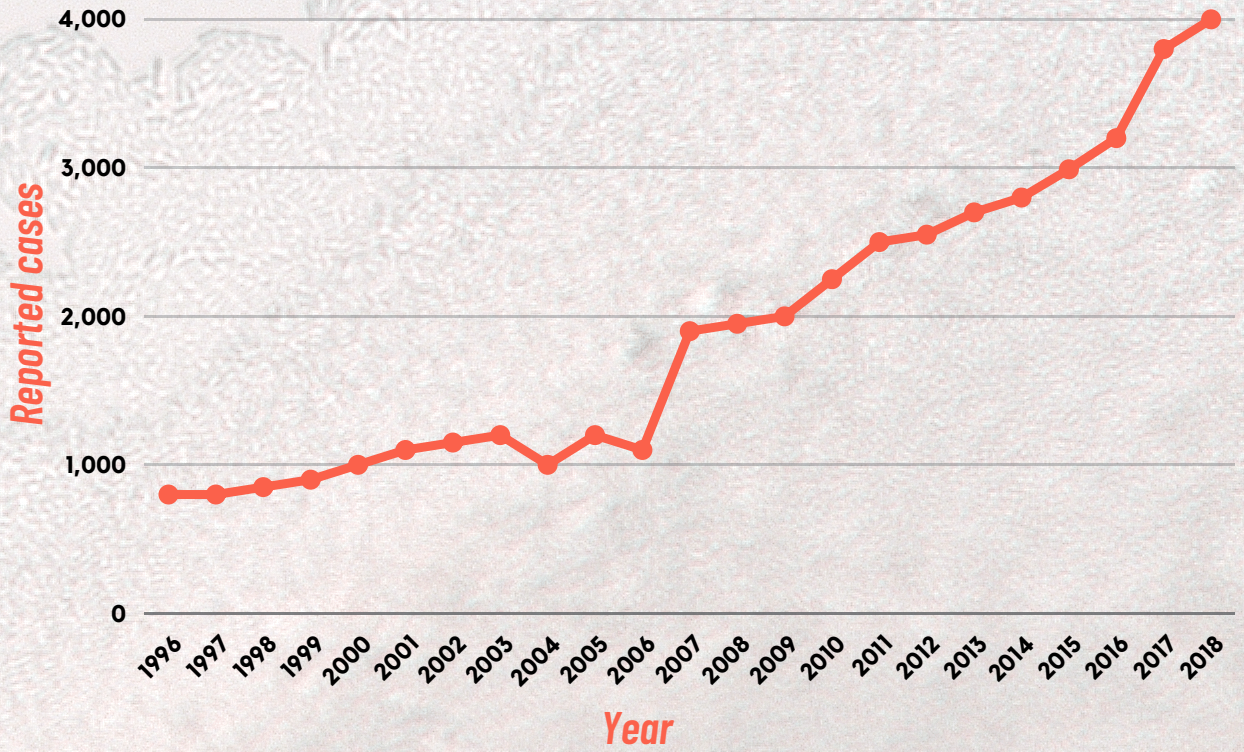
The **capsule is the main factor providing the virulence** of this species, as it increases its ability to evade the immune system.

This bacterium enters the body through the airways -aerosols or direct contact, which accelerates its spread.

Since 1996, there has been a **growing trend** in the European Economic Area (EEA) for *H. influenzae* **infections** (**Graph 2**): from 632 cases in 1996 to 3982 in 2018.

Of these, 253 died in 2018 patients as a result of the infection, while in 1996 only there there were 119 dead.

GRAPH 2. INVASIVE INFECTIONS BY *Haemophilus influenzae* IN EEA (4)



WHAT RESISTANCES DOES THIS BACTERIA HAVE?

In Spain, there is resistance to **ampicillin** and **amoxicillin** (25% of cases) and **cephalosporins** (15% of cases).

6.- Helicobacter pylori

DISEASES, INCIDENCE AND MORTALITY

These bacteria often cause **chronic infections** in global southern countries. In global northern countries, infection is more common with increasing age.

Due to infection by this bacterium, patients are 3 to 6 times more likely to develop **gastric cancer**, defining the species as **one of the most important risk factors** for this variety of cancer, and the seventh leading cause of death. for cancer in Europe; the third in the world.

This species causes one of the most common bacterial infections in humans and is estimated to be **present in half of the world's population**.

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

Over the last 20 years, antibiotic resistance in *Helicobacter pylori* has doubled. These resistances include **clarithromycin**, **levofloxacin**, and **metronidazole**.

7.- Klebsiella pneumoniae

DISEASES, INCIDENCE AND MORTALITY

K. pneumoniae infections are uncommon, but have a relatively high mortality rate. It is responsible for **3-5% of community-acquired pneumonia and 12% of hospital-acquired pneumonia worldwide.**

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

This bacterial species is resistant to **penicillins** and **cephalosporins**. Over the last few years, carbapenemase-producing strains, resistant to **beta-lactam** antibiotics, have emerged.

8.- Mycobacterium tuberculosis

DISEASES, INCIDENCE AND MORTALITY

According to the WHO, in 2018, **10 million cases of tuberculosis were confirmed worldwide and 1.5 million deaths.**

The mortality it causes is soaring in those HIV-infected patients, where the likelihood of developing tuberculosis is 19 times higher than in HIV-negative people. In 2018, of 862,000 diagnosed cases of tuberculosis and HIV on the African continent, 251,000 died from *M. tuberculosis* infection.

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

According to the antibiotic resistance of the strains, we can distinguish two types: **multiple drug resistance** (MDR) and **extensively drug resistance bacteria** (XDR). MDRs are bacteria resistant to **rifampicin** and **isoniazid** (first-line antibiotics), while XDRs are resistant to these two antibiotics, and to **fluoroquinolones** and second-line injectables such as **amikacin, kanamycin or capreomycin**.

9.- Pseudomonas aeruginosa

DISEASES, INCIDENCE AND MORTALITY

This bacterium causes **bacteremia, pneumonia associated with mechanical ventilation, and severe community-acquired pneumonia.**

It is considered the **fifth leading cause of global infections and the second leading cause of nosocomial pneumonia**.

Cases of mortality and morbidity caused by this species have increased due to its combined ability to form **biofilms** and to increase in **multidrug-resistant strains.**

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

It has an intrinsic resistance to **aminopenicillins, amoxicillin / clavulanic acid** and first, second and even third generation of **cephalosporins**.

10.- Neisseria gonorrhoeae

DISEASES, INCIDENCE AND MORTALITY

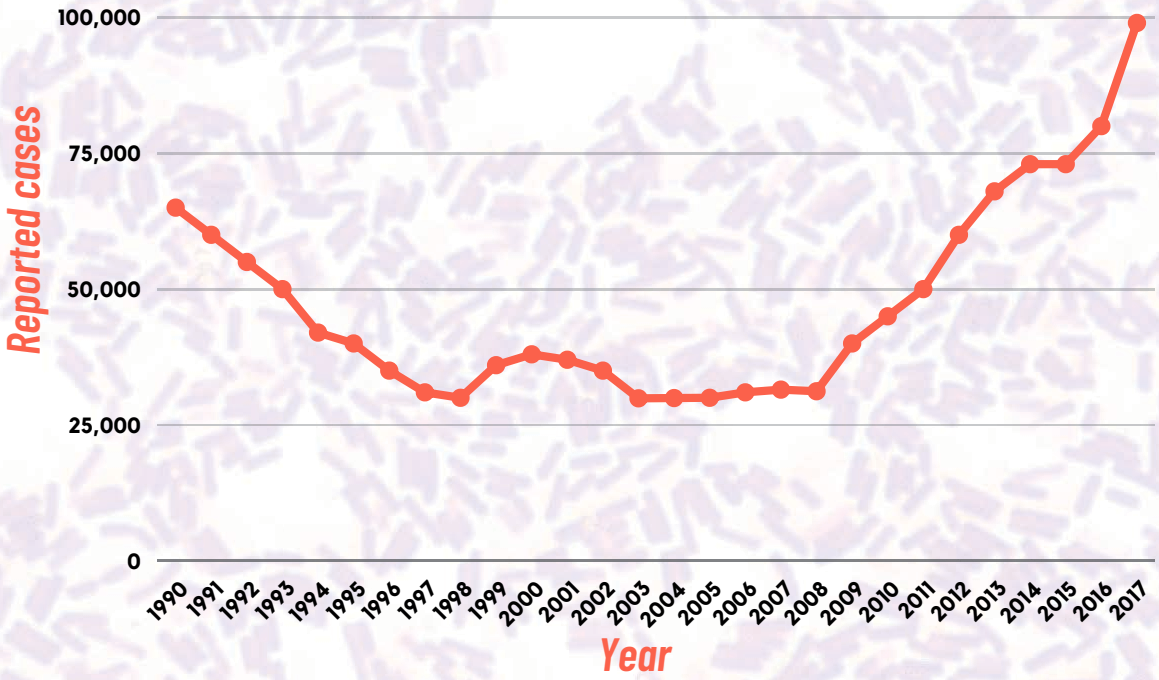
Gonococcal infection is currently the **second most prevalent sexually transmitted infection of bacterial origin** after that caused by *Chlamydia trachomatis*.

Between 1990 and 2018, there has been a growing trend in the number of cases of gonorrhea in the European Economic Area (**Graph 3**).

Most infections throughout 2018 occurred in patients between the ages of 15 and 34, mostly men.

Although not a deadly disease, it does have serious consequences such as **infertility, ectopic pregnancy and chronic pelvic pain**. In addition, it **facilitates the transmission of HIV**.

GRAPH 3. INFECTIONS BY *Neisseria gonorrhoeae* IN EEA (4)



WHAT RESISTANCES DOES THIS BACTERIA HAVE?

Over the last few decades, strains resistant to **fluoroquinolones, penicillins, macrolides, sulfonamides, and tetracyclines have increased.**

11.- Salmonella enterica

DISEASES, INCIDENCE AND MORTALITY

Salmonella spp. is the most common bacterial agent behind **foodborne outbreaks**, being a threat to public health. Its virulence depends on genetic **pathogenicity islands**, that is, sets of **genes that make it more virulent**, and which can transmit from bacterium to bacterium the ability to form **biofilms and antibiotic resistance**. The incidence of the disease is highest in **children under 5 years of age and adults over 60 years**.

Certain *Salmonella enterica* serotypes - Typhi and Paratyph serotypes- cause the **typhoid fever**.

Typhoid fever is a serious disease with a mortality rate of 12-30% in patients who do not follow treatment.

An estimated 21 million people are affected by this disease each year. Most deaths occur in malnourished patients, infants or the elderly.

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

This species has worrying levels of resistance to **cephalosporins (ceftriaxone), azithromycin, sulfonamides, chloramphenicol, tetracycline, ampicillin, streptomycin, and fluoroquinolones (ciprofloxacin).**

12.- *Staphylococcus aureus*

DISEASES, INCIDENCE AND MORTALITY

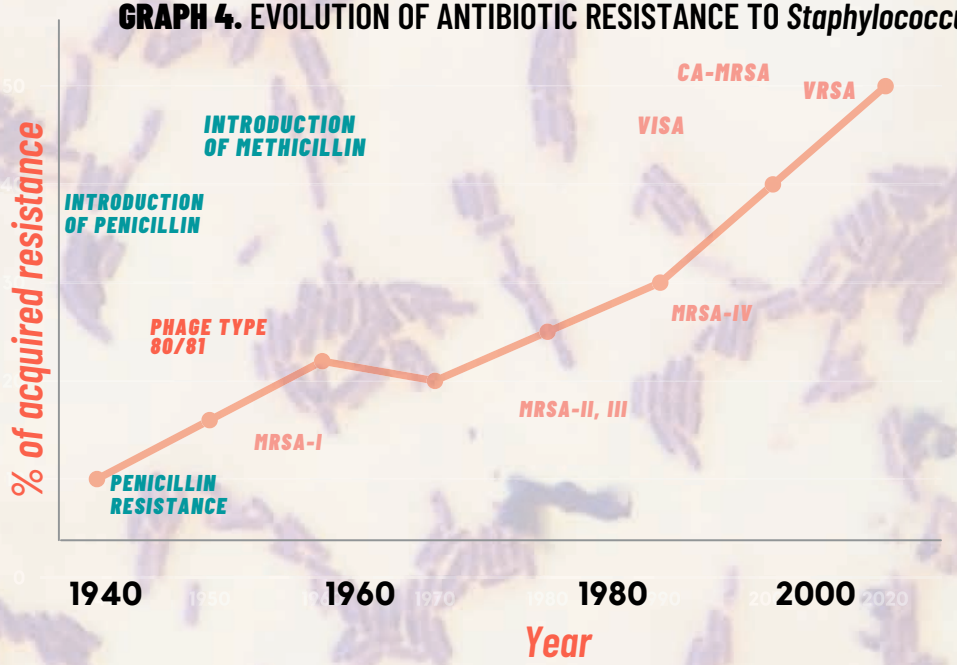
This bacterium can become very virulent due to the **high synthesis of different toxins and enzymes** that help it invade the tissues. It is estimated that in the United States in 2019 there were more than 323,000 infections by **methicillin-resistant** *Staphylococcus aureus* (**MRSA**), where more than 10,000 people died. Globally, invasive infections caused by MRSA are estimated at 20%.

WHAT RESISTANCES DOES THIS BACTERIA HAVE?

The emergence of antibiotic-resistant bacterial strains, in the case of *S. aureus*, has skyrocketed. So much so that when penicillin was approved in 1941, treatment-resistant strains were found a year later. The same has happened with antibiotics such as **vancomycin** (VRSA) and **methicillin** (MRSA), which were introduced to the market in 1958 and 1959, and the first resistances were detected in 2002 and 1960, respectively (**Graph 4**).

They also have resistance in 30-50% of cases to **methicillin, naphthylline, oxacillin and dicloxacillin**. Currently, MRSA is resistant to all **β-lactams**. There are new treatments such as **linezolid**, but resistance to this antibiotic has also been described.

GRAPH 4. EVOLUTION OF ANTIBIOTIC RESISTANCE TO *Staphylococcus aureus* **(39)**



MRSA *(methicillin-resistant S.aureus),* ***VISA*** *(vancomycin average resistance of S. aureus),* ***VRSA*** *(vancomycin-resistant S. aureus),* ***and CA-MRSA*** *(community-acquired MRSA).*

13.- Streptococcus pneumoniae

DISEASES, INCIDENCE AND MORTALITY

These bacteria cause 30 to 40% of acute otitis, 40% of acute sinusitis, and 50% of community-acquired bacterial pneumonia.

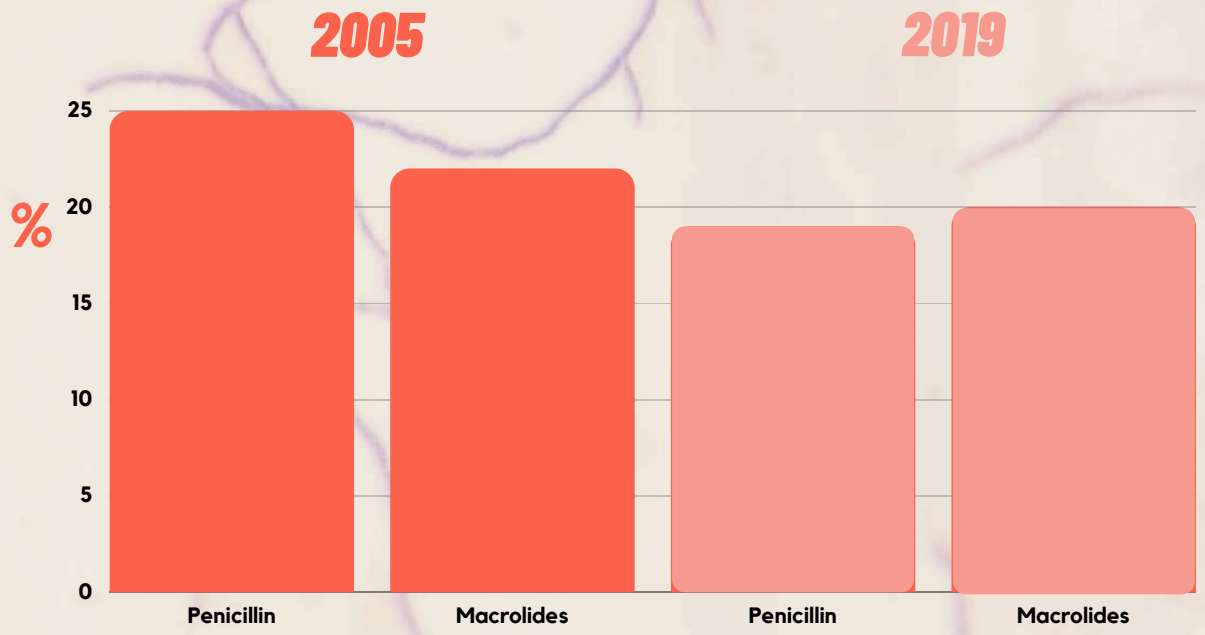
In terms of mortality, the WHO estimates that 1,200,000 children die worldwide per year for pneumococcal pneumonia, mostly in the countries on the global south.

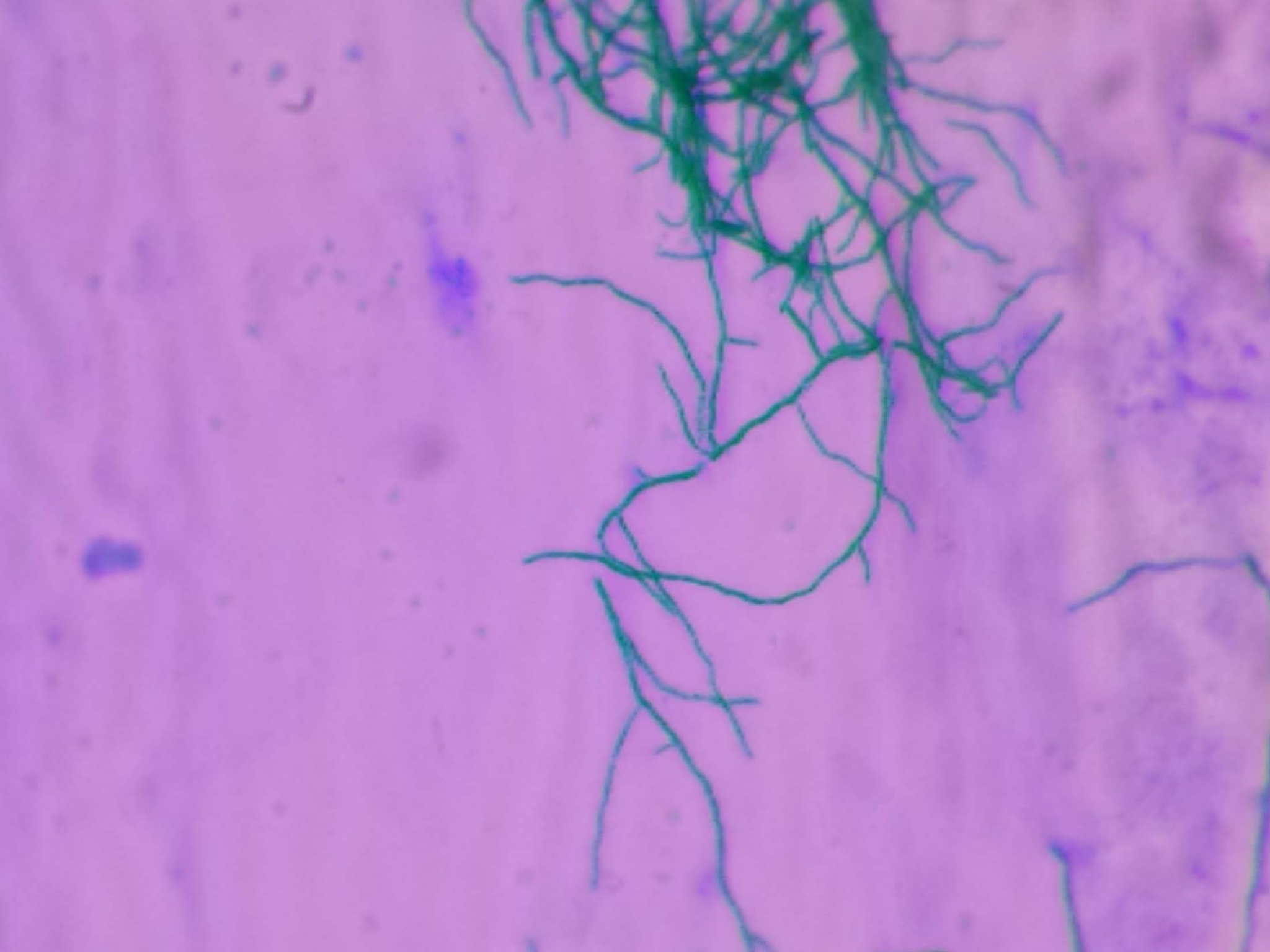
WHAT RESISTANCES DOES THIS BACTERIA HAVE?

Graph 5 shows the percentages of infections caused by antibiotic-resistant strains of *Streptococcus pneumoniae*, regarding the total number of infections by this bacterial species in Spain, according to the ECDC. The percentages have remained relatively stable since 2005, but there are still concerns about the evolution of resistance to **fluoroquinolones**, **macrolides**, **penicillins** and other **β-lactams**.

Although vaccination against this infection is indicated and administered in children under 2 years of age, limited access to vaccines in global southern countries contributes to high infant mortality.

GRAPH 5. EVOLUTION OF ANTIBIOTIC RESISTANCE BY *Streptococcus pneumoniae* (ECDC)





WHAT IMPACT DOES THE USE OF ANTIBIOTICS HAVE ON THE AGRI-FOOD AND VETERINARY SECTORS?

Unfortunately, we also find antibiotic resistance in pets and grazing animals. It should be remembered that **it is the bacteria that become resistant to antibiotics, not the animals or people receiving the treatment**.

Acinetobacter baumannii

A. baumannii causes infections in **dogs, cats, horses, birds** and other animals.

Image credits: CDC/ Matthew J. Arduino, Courtesy: Public Health Image Library

72% of isolated strains are **multidrug-resistant**, meaning they exhibit resistance in at least three different families of antibiotics.

Campylobacter spp.

The species of *Campylobacter* spp. are found in most **warm-blooded animals**, especially animals for human **consumption**; in addition to **pets** and even **seafood**. Despite being widely distributed in the animal world, they rarely cause diseases.

Image credits: CDC phil.cdc.gov/Details.aspx?pid=16870

Enterococcus faecium

Enterococcus faecium is present in **farm animals**. There has been a trend towards resistance to **aminoglycosides** as well as **cotrimoxazole**, as detected in humans. In a study of **cats** and **dogs** in Japan, of all the strains obtained, more than 40% were resistant to **kanamycin** and almost 30% to **erythromycin** and **lincomycin**.

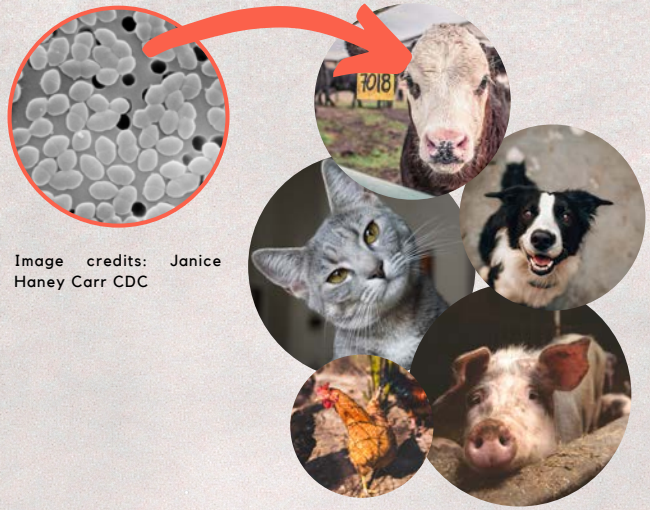


Image credits: Janice Haney Carr CDC

Escherichia coli

In *Escherichia coli*'s case, the vast majority of strains are resistant to **penicillins**, **macrolides** (**erythromycin** and **azithromycin**) and **cotrimoxazole**.

Image credits: NIH NIAID, www.flickr.com/photos/niaid/16578744517/

Staphylococcus aureus

Staphylococcus aureus is resistant to **methicillin** (MRSA), being a major threat to human health. In animals, MRSA has established itself as a veterinary pathogen in **pets** and **horses**; it concerns **ivestock** health, as a reservoir that can infect humans and as a source of resistance gene transfer.

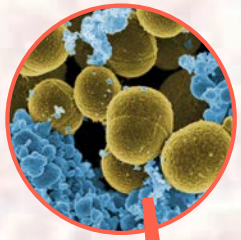


Image credits: NIH NIAID www.flickr.com/photos/niaid/51487 10483

Salmonella spp.

Salmonella spp. is considered one of the major **foodborne pathogens** and is commonly associated with the consumption of **eggs**, **meat** and **chicken intestines**, as well as other animal products.

Multiresistant *Salmonella* (**MDR**) strains are highly adaptive and are responsible for several foodborne disease outbreaks.

One study found that isolated strains of intestines and chicken eggs were resistant to **sulfamethoxazole**, **ceftriaxone** (third-generation **cephalosporin**), **nalidixic acid**, **cefazolin, and amoxicillin.**

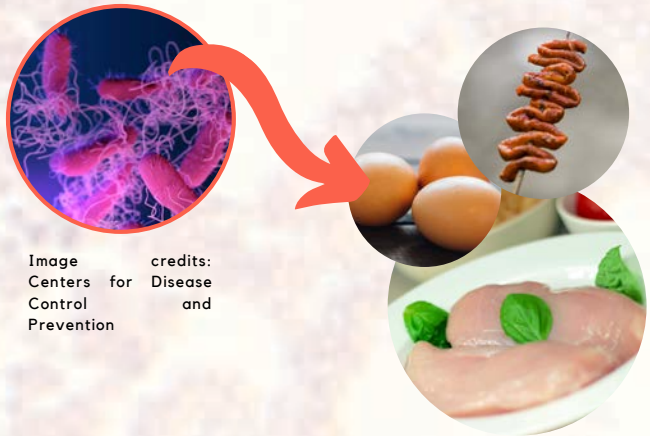
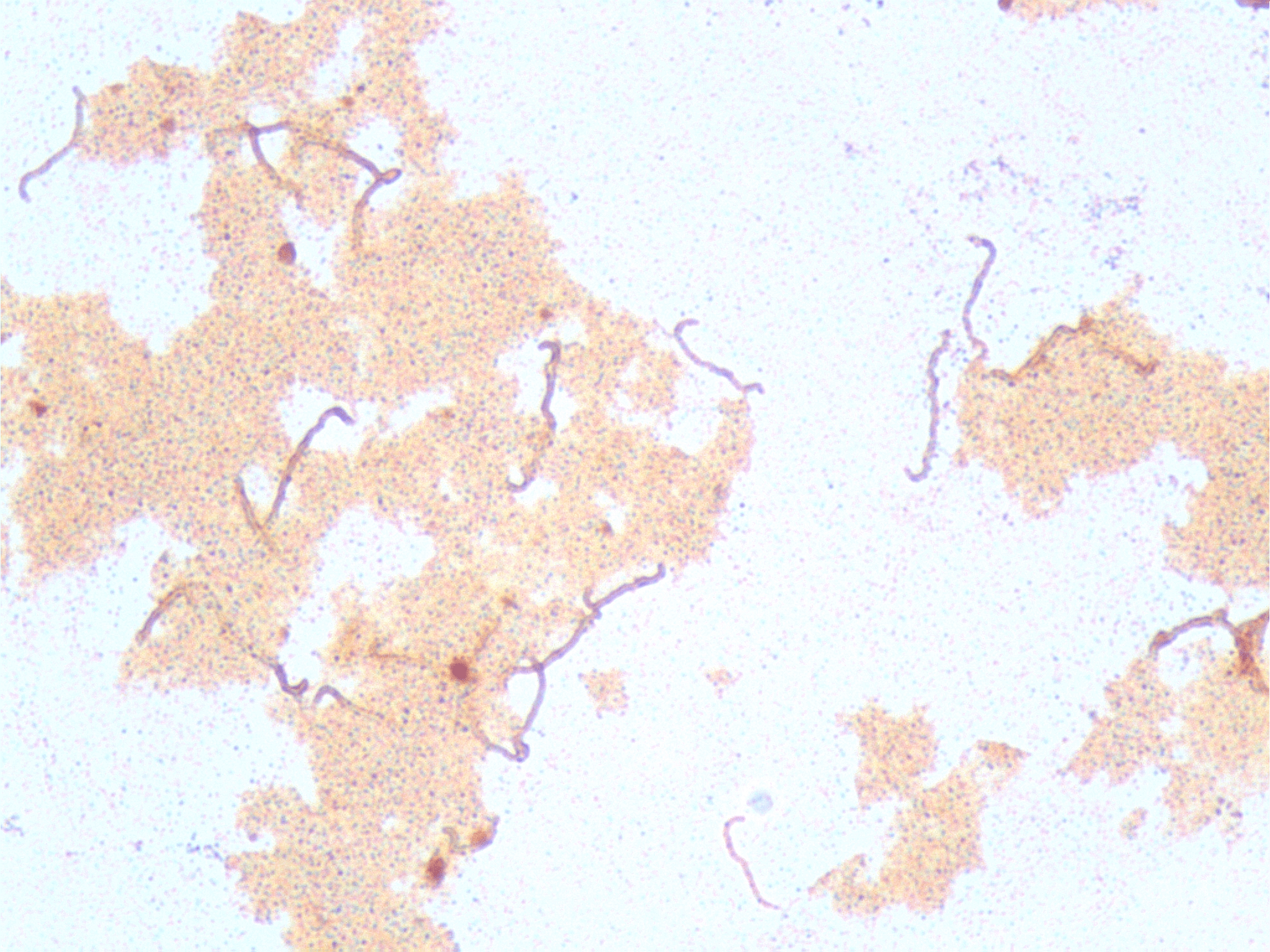


Image credits: Centers for Disease Control and Prevention



CONCLUSIONS

The antimicrobial resistance is a **global health problem** (**One Health**). Resistant bacteria are rapidly increasing and, in turn, amplify the ability to spread the different types of resistance to other bacteria and everywhere. If the trend continues like this, **pan-resistance and multi-resistance will be a reality for most bacteria.** This will mean that we will not be able to use antibiotics to treat infections and therefore the death from bacterial infections will heavily inrease.

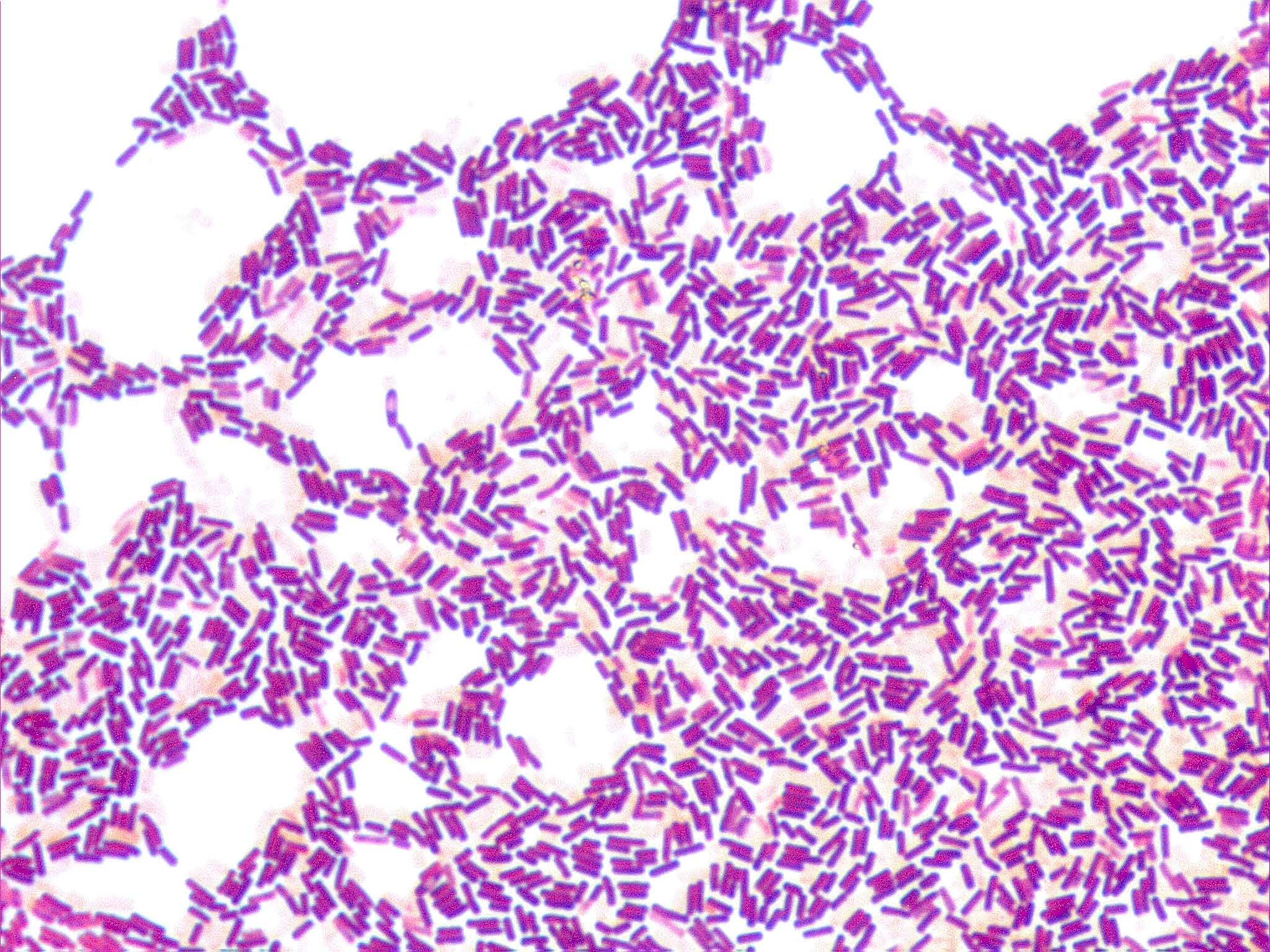
The development of new antibiotic treatments is a very long and costly process, and unfortunately not enough resources are allocated to achieve this.

Therefore, our responsibility lies in **regulating the consumption of antibiotics**, both in humans and animals. In this sense, a few years ago several regulative **laws** were introduced to forbid the use of antibiotics to promote the growth of livestock, or against the use of antibiotics as a preventive treatment.

We must also be aware of how to follow antibiotic treatments. They should only be taken against **existing bacterial infections**, not viral ones.

Moreover, following an antibiotic treatment requires to follow it up until the end of treatment, according to prescription, even if we no longer have symptoms.

If we don't, we can promote the emergence of resistance. These habits -together with **hygiene and prevention habits** such as washing your hands often, throwing the remaining antibiotics in the **specialized disposal points** in your pharmacy, **not carrying out activities at risk of exposure** to bacterial infections, or following the vaccination schedule-, are some of the actions we must all take over to prevent the accelerated increase of antimicrobial resistance, **which is already a reality** that could take us, in a few decades, to the **post-antibiotic era**, where modern medicine as we know it today will no longer be available.



RELEVANT CONCEPTS

BACTEREMIA

Presence of bacteria in the blood of the infected person or animal.

BIOFILMS

Groupings of bacteria in arrays adhered to surfaces.

ECDC

European Center for Disease Control. It is the main agency responsible for monitoring, advising governments and promoting programs for the control of infectious diseases in the European Union.

GENERATIONS OF ANTIBIOTICS

Classification of antibiotics according to their antimicrobial characteristics. Within the same family of antibiotics, antibiotics of later generations are those that have been generated by chemical modification of the original structures in response to the development of resistance to these antibiotics. If we always resort to the latest generation of antibiotics, we are blocking their future use to treat new infections.

HOST

Organism that hosts another organism, and generally provides protection and food.

MICROBIOTA

Set of microorganisms in a given habitat (multicellular living things), such as the human body or part of it.

GLOBAL SOUTH COUNTRIES

Term used in postcolonial and transnational studies to refer to the non-geographical south / north, also relocated within each country, where the South is subordinate to the North in terms of economy, access to health, etc.

STRICT PARASITES

Microorganisms that need specific growth factors, so they can only live on one particular host (species).

PATHOGEN

Biological infectious agent that causes diseases or disorders in its host.

RESISTANCE PERCENTAGES

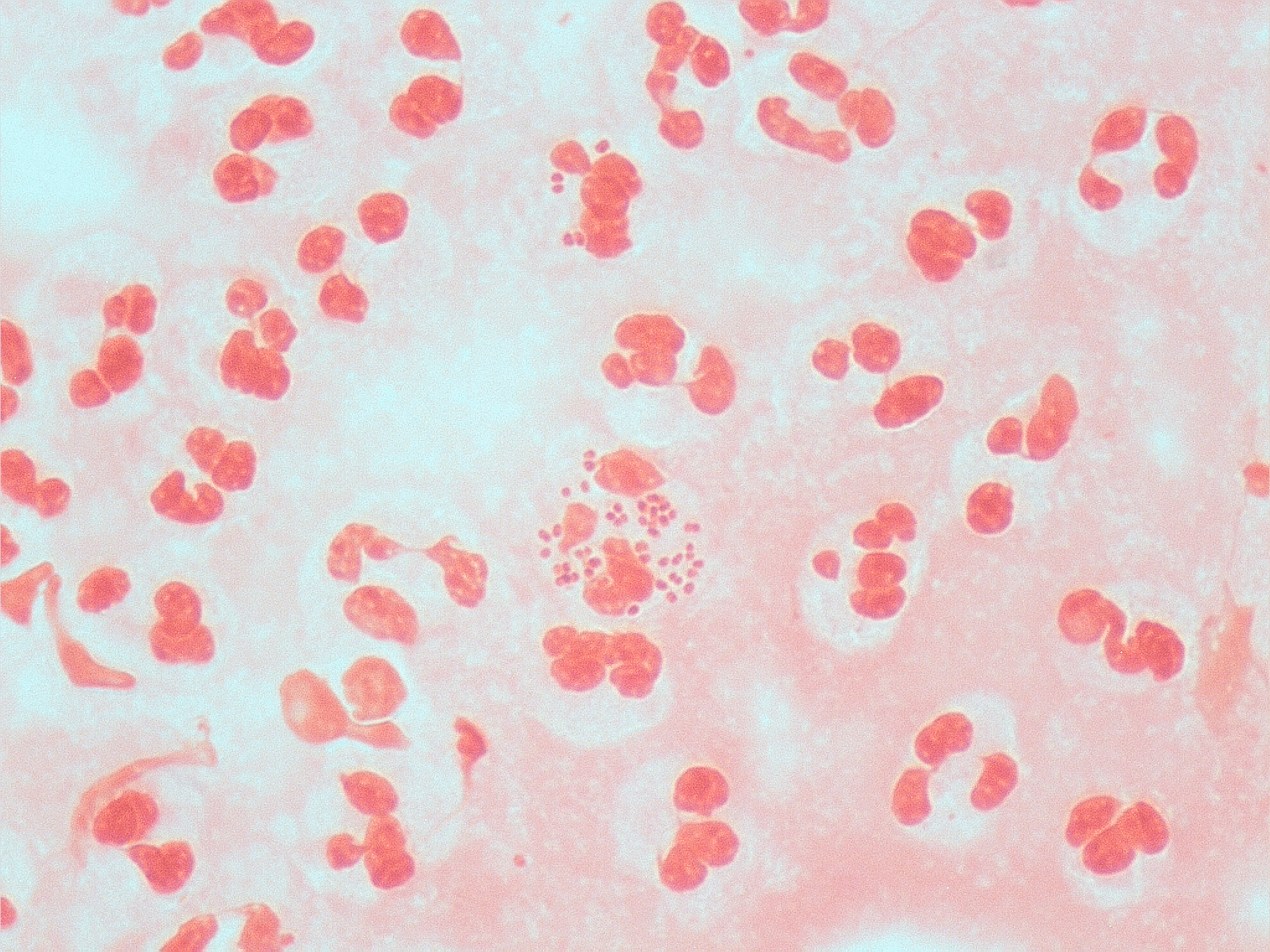
Number of bacterial strains that are resistant to antibiotics. A low percentage of resistance (less than 5%, for example) means that the number of strains that are not resistant to this antibiotic is significantly higher than the number of bacterial strains that are resistant.

PLASMID

Prokaryotic double-stranded circular DNA molecule, which can exist and replicate independently of the chromosome or be integrated into it.

BACTERIAL STRAIN

A strain is a genetically uniform population of cells. Thus, a bacterial strain is a set of genetically identical bacteria descended from the same cell, which, in their offspring, can undergo mutations.



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THIS REPORT HAS BEEN WRITTEN BY THE SAFE TEAM, BARCELONA NODE, WITH THE SUPPORT OF THE EUROPEAN EIT HEALTH PROGRAM

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EIT Health is supported by the EIT, a body of the European Union

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