# Bacteriophages and Bacterial Resistance: The Link

**Juan Martín Talavera-González[1], Martín Talavera-Rojas[1], Nydia Edith Reyes-Rodríguez[2], Vicente Vega-Sánchez[2]**

[1]*Universidad Autónoma del Estado de México*
[2]*Universidad Autónoma del Estado de Hidalgo*
*Email: jmtalaverag001@profesor.uaemex.mx*

**KEYWORDS**
Bacterial resistance, bacteriophages, agriculture.

**ABSTRACT**
Bacterial resistance is a public health problem that has caused the most deaths in the world; Various international organizations have launched an emergency call for attention to this problem. One of the main factors that contribute to its appearance is the inappropriate use of antibiotics, which generates the appearance of bacteria with specific genes that shield them from exposure to these drugs. In nature there are elements such as bacteriophages that have the ability to "steal" these genes from inside bacteria and transport them to other bacteria in different environments; In addition, due to their propagation, they are considered one of the links that contribute the most to the dissemination of genes, causing public and veterinary health problems as well as economic losses in different sectors such as agriculture and agriculture.

## 1. Introduction

When a person develops a disease of bacterial origin and antibiotic treatment fails, putting their health at risk, even leading to death, it may be thought that antibiotics have lost their effectiveness because the bacteria has generated resistance to these drugs.

Infections from resistant bacteria kill approximately 700,000 people per year, and it is predicted that by 2050 it will cause 10 million deaths per year, surpassing deaths caused by cancer. The World Health Organization has placed this public health problem as a priority for immediate attention (1) .

Bacteria express antibiotic resistance when they activate specific genes called "antibiotic resistance genes" (ARGs) that are integrated into their genome, which confer protection when exposed to one or more antibiotics, making it difficult to eliminate (2) them.

Through a pressure of selection and/or natural adaptation, bacteria can develop an intrinsic resistance by producing their own ARGs by modifying their genome to seek their survival, which underlines their evolutionary potential. There is also acquired resistance that consists of the transfer of genes by transduction, mediated by tempered bacteriophages that are a vehicle for the transfer of ARGs between bacteria and thus disseminate them in different environments (1) .

In this text, tempered bacteriophages and their potential in the transfer of resistance genes during the transduction process in different matrices will be examined; in addition to its involvement in the increase of bacterial resistance to antibiotics.

## 2. Bateriophages

Bacteriophages (also known as phages) are viruses that exclusively infect bacteria. They are obligate intracellular parasites as they lack their own replication machinery, so they need the bacterium's machinery to be able to replicate. They are ubiquitous, various studies position them as the most abundant entities in the biosphere (3) .

Although there are different morphologies, most phages are composed of a nucleic acid (DNA or RNA) that contains all their genetic information, a capsid (head) to protect the nucleic acid, a contractile sheath that contains a hollow stem inside where the genome will move at the time of infection, a needle to pierce the bacteria, and fibers attached to the stem that will adhere to the outer membrane of the bacterium to attach to it (4) .

In nature, two types of phages have been recognized according to their biological cycle. On the one hand, there are lithic bacteria, responsible for infecting and eliminating bacteria while maintaining an ecological balance by regulating the bacterial population of the environment; On the other hand, there are tempered bacteria, which are the protagonists of transduction that consists of "stealing" a specific (specialized transduction) or random (generalized transduction) portion of the genome of the infecting bacterium (donor bacteria) and transporting it to another bacterium (recipient bacteria). (5)

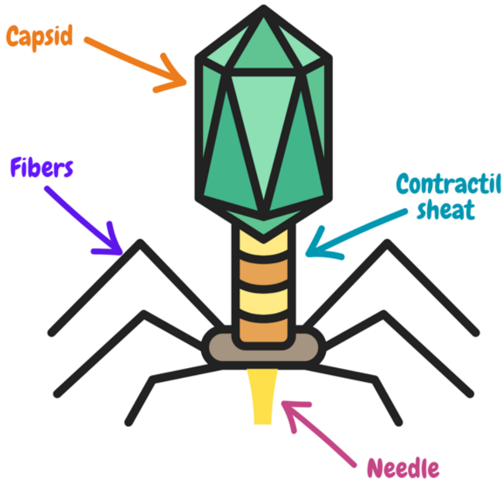


Figure 1. Parts of the bacteriophage

## 3. What is transduction?

Transduction begins when the phage, by means of specialized proteins in the fibers attached to the stem, recognizes and anchors to specific receptors located in the wall of the bacterium. Later it is the injection of their genetic information; The phage will make a hole in the bacterial wall and simulating a syringe, it introduces its nucleic acid, at which time it is called a prophage, which can remain inside the bacterium and its offspring. Then, the prophage will detect the bacterial SOS response (alarm of the presence of an antibiotic, stress, etc.) indicating that the bacterium is about to die, so it will detach from the bacterial genome to begin the assembly and formation of new virions; in the detachment, genes are "stolen" from the bacterium that may include ARGs. Now, newly formed virions, in addition to containing viral nucleic acid, also contain bacterial nucleic acid. Then, the mature viral progeny (complete assembly) will produce and release proteins to kill the bacterium and allow its release into the extracellular space. Then, the newly released phages go in search of other bacteria to start a new cycle; on their way they can infect commensal bacteria transforming them into pathogenic bacteria, or these pathogenic bacteria potentiate their dangerousness (3) .

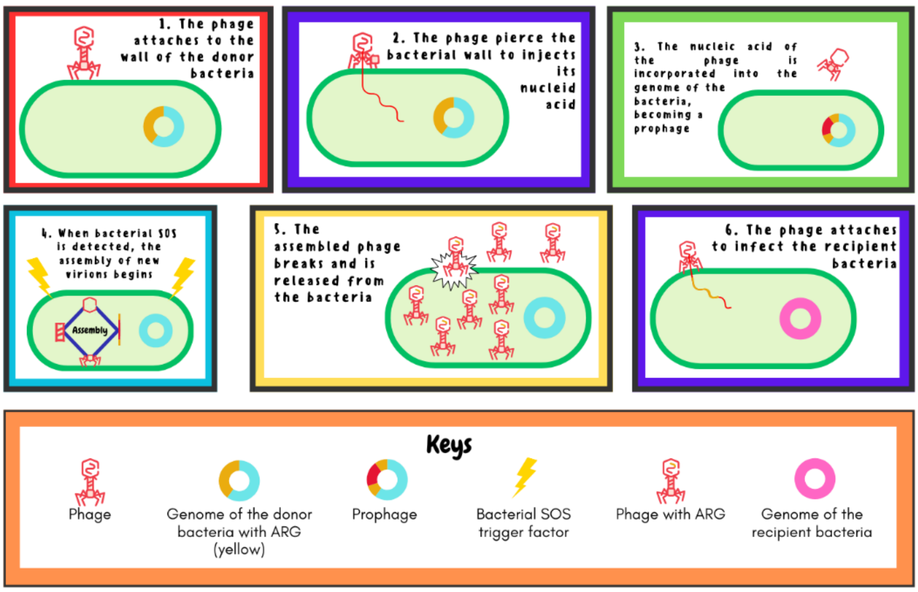


Figure 2. Resistance gene transduction process

Spread of ARGs

In recent decades, gene transfer by the transduction method has gained relevance as one of the phenomena that most contribute to the emergence of new resistant bacterial strains. Recent studies have suggested that one of the main niches (although not the only one) that favors the process of transduction of ARGs are urban wastewater treatment plants that simulate a "mixer" by combining residual waste composed of resistant bacteria and tempered phages accompanied by remnants of antibiotics of human origin (domestic and hospital). animal (pig, cattle and chicken slaughterhouses) and agricultural (soils fertilized with animal manure). In addition, it has been reported that after these sites are subjected to treatment with chlorination and ultraviolet irradiation, a high density of tempered phages possessing multiple ARGs manages to survive (1) .

The surviving phages will accelerate the spread of antibiotic resistance by transferring ARGs when, through water discharges, they can reach agricultural crops through irrigation. A study carried out in Spain found in soil samples collected from greenhouses, gardens and crop fields, phages that contained genes that confer resistance to antibiotics of the group of beta-lactams, sulfonamides and quinolones, as well as samples of ready-to-eat vegetables such as lettuce, spinach and cucumbers (6) . Similarly, another aspect that has to be considered is the type of water that is used for the irrigation of agricultural crops since, if it is contaminated by feces, the probability of transfer of ARGs increases; various studies confirm that in this type of organic waste there is an abundance of a wide variety of bacteria resistant to antibiotics and mobilizing elements such as bacteriophages (7) . Some scientists point out that the application of livestock manure on agricultural crops is proportional to the abundance of ARGs (6) .

Another industry in which bacteriophages with ARGs are frequently reported are agricultural activities, for example, in livestock fairgrounds, shed floors and animal farms, where the soil and wastewater contain animal fecal matter (5) .

Similarly, this type of phage has been detected in sausages (ham and mortadella) even though they have undergone treatment for their production; likewise, in minced pork, chicken and beef from retail premises that met the correct microbiological parameters (6) . Experts highlight a latent risk for the human food chain since many of these products are sold ready to eat. In relation to the above, the phage Ø734, specialized in transporting the stx2 gene (coding for the Shiga toxin) and capable of infecting commensal bacteria, was isolated in samples from several nine-year-old children who developed hemolytic uremic syndrome, when ingesting contaminated food (8) .

Bacteriophages with multiple genes that confer resistance to various groups of antibiotics (beta-lactams and quinolones) have been detected in wastewater of hospital origin, specifically in the emergency services area and the inpatient area (5) . Similarly, research revealed that both healthy individuals and patients with cystic fibrosis harbor abundant ARG-positive phages in the lungs. The concern is latent, since being a potential reservoir of resistance genes and acting as efficient vehicles in their transfer can contribute to the colonization of commensal bacteria and make treatment difficult (9)

In 2021, a group of Mexican researchers isolated, from migratory birds positioned in wetlands adjacent to livestock and agricultural activities, bacteriophages possessing genes that confer resistance to tetracyclines, beta-lactams, sulfonamides and quinolones, and were also able to transduce these genes in vitro to intact ARG bacteria from chickens and ducks, highlighting that, due to the speed with which migratory birds move, They can disseminate and exchange these genes among a wide variety of animal species. Several authors agree that freshwater niches are sites of high ecological risk due to the large number of industrial wastewater discharges and livestock farms. (10) .

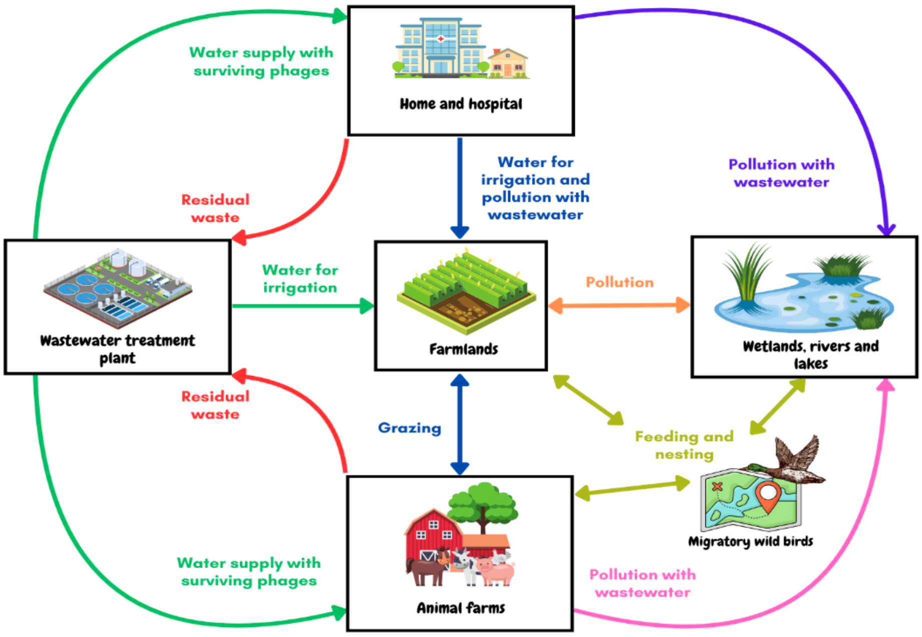


Figure 3. Dissemination of ARGs in contaminated environments

## 4. Conclusions

The improper use of antibiotics leads to the appearance and development of new ARGs, which can be transported by tempered bacteriophages to multiple matrices despite being exposed to different inactivation factors and disinfectants. To reduce the appearance of multidrug-resistant bacteria, it is recommended that antibiotics be used responsibly and under the advice of appropriate personnel.

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