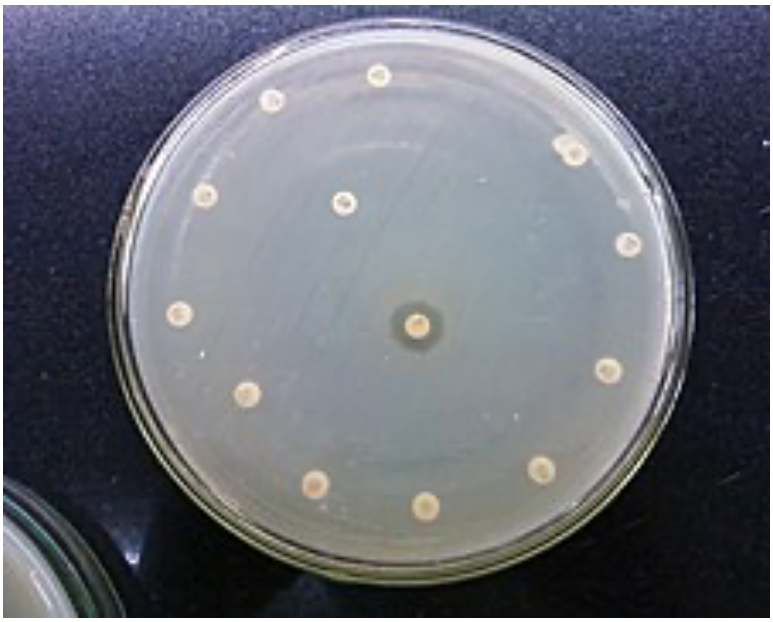
Antimicrobial Resistance Gallery

The antimicrobial resistance crisis: a history of unheeded warnings

(Felipe C. Cabello and Henry P. Godfrey)



Antibiotic susceptibility test by disk diffusion showing this "pan-resistant" bacterial strain or "superbug" to be resistant to all the tested antibiotics. (Wikimedia Commons)

The problem from its origins

Antimicrobial resistance (AMR) has emerged as a major global health threat, comparable to pandemics like COVID-19, tuberculosis, and sexually transmitted infections. The World Health Organization (WHO) warns of its devastating impact, highlighting the alarming rise of bacteria resistant to antimicrobials, lifesaving drugs that once effortlessly prevented and treated bacterial infections. This situation was suggested to happen at the birth of modern antimicrobial therapy. Many warnings regarding the danger of antimicrobial resistance for human health have been voiced by scientists developing these lifesaving therapies, and lately by the public, patients, and consumers suffering from problematic resistant infections. Unfortunately, these alerts have been repeatedly unheeded resulting in the present disastrous situation regarding the failures, complications, and increased expenses in treating bacterial infections. These infections were readily treated when antimicrobials were first introduced in the first half of the 20th century.

Paul Ehrlich (Nobel Prize in Physiology or Medicine 1908), the visionary behind the "magic bullet" concept in treating infections, encountered resistance as early as 1908. The magic of the bullet was its binding to a receptor in the parasite but absent in the host cells (the principle of selective toxicity, which guides the search for and development of antimicrobial drugs); this

binding altered the parasite's physiology and killed them. Ehrlich's synthetic arsenical dyes, effective against African sleeping sickness caused by trypanosomes, faced a formidable foe: resistant parasites. Ehrlich suggested that these "drug-proof" trypanosomes probably lacked the receptor needed for the "magic bullet" to bind and kill them. This resistance, he discovered, was:

- Permanent: passed down through generations of parasites
- Specific: targeting only the original arsenical dyes that were selected for resistance
- Quantifiable: measured by the increased drug dose needed to achieve killing
- Treatable: in some cases, through higher doses or combined drug therapy

Yet despite recognizing the potential dangers that these crops of resistant parasites posed for the treatment of disease, Dr. Ehrlich's discoveries of alternative treatments of sleeping sickness and the success of Salvarsan and Neo-Salvarsan for syphilis against a seemingly non-resistant *Treponema pallidum* overshadowed the looming specter of AMR.

Paul Ehrlich and his collaborator Sahachiro Sata. (Wikimedia Commons)

A legacy of warnings unheeded

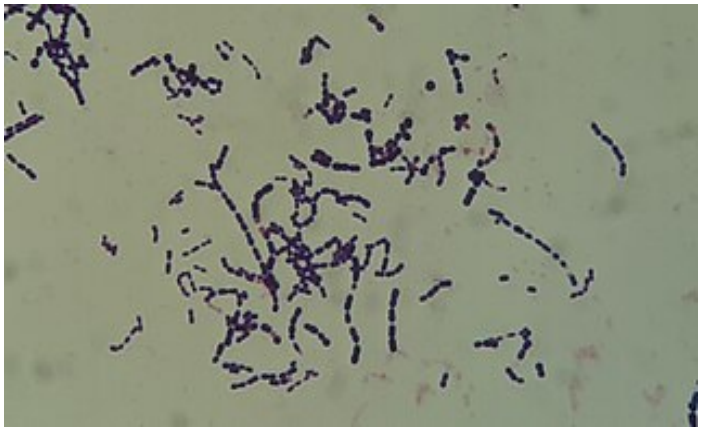
Unfortunately, the alarm bells rung by Dr. Ehrlich and other early pioneers went largely unheeded. The widespread and often misuse of antibiotics in subsequent decades fueled the evolution of resistant bacteria. The success and convenience of these wonder drugs blinded us to the long-term consequences, leading to:

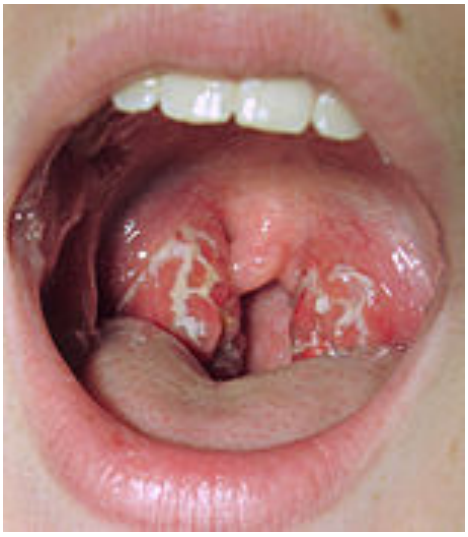
- Treatment failures: once-treatable infections now pose serious challenges
- Complications: longer hospital stays, higher treatment costs, and increased risk of death

- Limited options: a dwindling arsenal of effective antibiotics leaves us vulnerable to future outbreaks of bacterial infections

From sulfanilamide to penicillin: A dawn of triumph, soon mired in resistance

Ehrlich's "magic bullets" paved the way for further discoveries. In 1935, Gerhard Domagk's discovery of Prontosil (Nobel Prize in Physiology or Medicine 1939), converted in the body to the active drug sulfanilamide, revolutionized the treatment of infections by Gram-positive bacteria such as sore throats, pneumonia, and meningitis. A wave of synthetic "sulfa" derivatives followed, boasting miraculous results in the treatment of infections by Gram-positive and Gram-negative bacteria. Unfortunately, by the early 1940s, whispers of resistance to sulfas emerged. World War II battlefields and post-war hospitals witnessed its rise, prompting warnings such as that of Case Western University's Richard M. Krause: "... without penicillin, we'd face untreatable sulfa-resistant streptococci epidemics." In 1955, Maxwell Finland of Harvard University summarized the growing concern that overuse and misuse by doctors and individuals was fueling resistance and therapeutic failures. He advocated the education of physicians and the public as a key weapon against this burgeoning threat.





Streptococcus pyogenes, the cause of streptococcal sore throat. (Wikimedia Commons)

Penicillin and *Staphylococcus aureus*

The 1940s ushered in another era with the arrival of penicillin, Alexander Fleming's gift from a fungus (Nobel Prize in Physiology or Medicine 1945). Unlike sulfas, it lacked frequent side effects and targeted Gram-positive bacteria, especially *Staph. aureus*. But, by the decade's end, Mary Barber in the United Kingdom sounded the alarm: "Widespread, often careless use of penicillin...threatens its future." Her work, alongside that of Richard Novick and Mark H. Richmond, revealed an unsettling truth - genes for penicillinase, an enzyme deactivating

penicillin, resided on plasmids, portable genetic elements bacteria could readily share. The specter of easily transferrable resistance genes raised alarm bells across the scientific community.

Chemical modifications yielded penicillin derivatives like methicillin, ampicillin, and pheneticillin, expanding the antibacterial spectrum and offering options for oral, rather than injection, administration of antibiotics. Yet, resistance reared its ugly head once more. *Staph. aureus* and others readily adapted, leaving us scrambling for alternatives. Moreover, Gladys Hobby, Joseph W. Bigger, and Walsh McDermott in the 40s and 50s further revealed another lurking danger - bacterial populations exposed to antimicrobials harbored small numbers of tolerant cells, capable of persisting, causing relapses, and facilitating mutations to full-blown resistance.

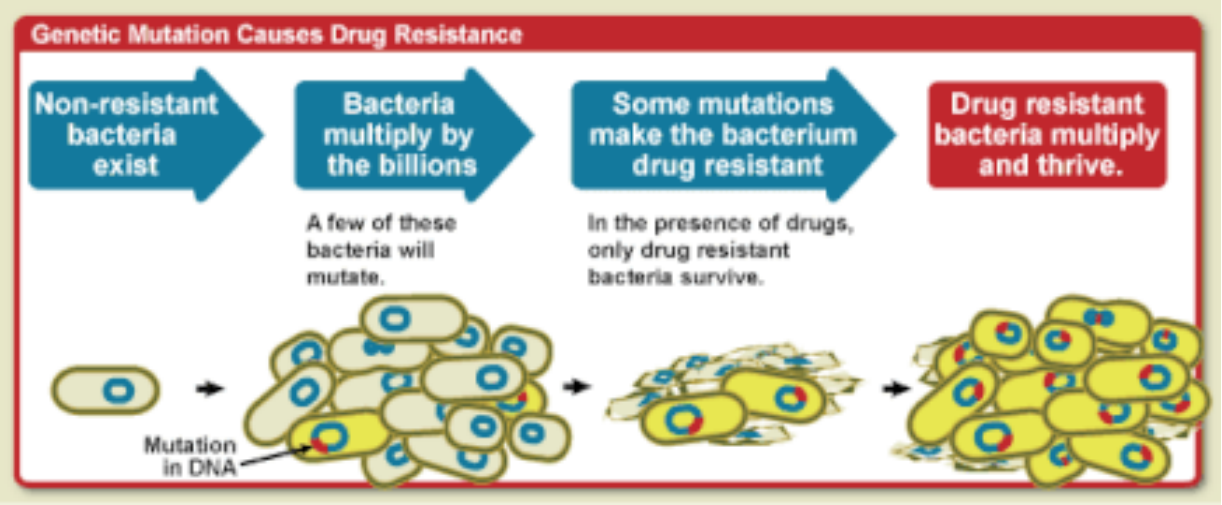
Alexander Fleming receives the Nobel Medal and Diploma. (Wikimedia Commons)

From Dubos' warnings to widespread resistance and its mechanisms

René Dubos, the "father of antibiotics," understood the precarious dance between our wonder drugs and bacterial adaptation. He cautioned that widespread use could breed "training" in bacteria and lead to resistance. His insight proved prophetic. As sulfas, streptomycin tetracyclines, and chloramphenicol graced the medical scene in the 1950s, so did resistance, echoing the concerns of Tuft University's Louis Weinstein about the threat of this resistance to treatment.

The pioneering work in microbial genetics of Joshua Lederberg (Nobel Prize in Physiology or Medicine 1958) and his wife, Esther Lederberg, shed light on this resistance. It revealed two mechanisms: mutation and horizontal gene transfer (HGT) where bacteria readily swap resistance

genes like trading cards. Notably, exposure to even low antibiotic doses could accelerate mutagenesis and this ominous genetic exchange.



Mutation in DNA causes antimicrobial resistance. (Wikimedia Commons)

Animal husbandry: an unexpected culprit, science alerts, industry denials

As new, broad-spectrum antibiotics like tetracyclines were used not just in humans but also in animal farming, a new front in the resistance war opened. Ephraim S. Anderson, Naomi Datta, and H. William Smith in the United Kingdom in the 1960s documented an alarming scenario. Industrial animal farming, fueled by routine antibiotic use, was selecting for *multi-resistant* bacteria like *Salmonella* and *Escherichia coli*. As long as clinicians had multiple antibiotics at their disposal, infections by bacteria resistant to a single antibiotic could be treated effectively. The existence of bacteria resistant to multiple antibiotics significantly reduced treatment options. These zoonotic bacteria, capable of infecting humans, carried plasmids - portable resistance gene packages - that they readily shared, fostering "infectious drug resistance." In Japan, Tsutomu Watanabe and Susumu Mitsuhashi described increasing resistance in *Shigella* and *E. coli* isolated from diarrhea and their ability to be transferable by plasmids.

The Swann Report in the United Kingdom and Congressional hearings in the US in the 1970s and 1980s brought the issue to light. Scientists like Richard Novick warned of regressing to the “pre-antibiotic era”, while Stuart B. Levy starkly declared: "Resistant bacteria thwart our ability to treat even common diseases." Yet, the animal husbandry and pharmaceutical industries often minimized the risks, citing potential economic losses from stricter regulations.

A looming crisis ignored despite mounting evidence

For nearly 80 years, warnings about the grave public health global threat posed by antimicrobial resistance (AMR) echoed largely unheeded. Despite visionary pioneers like Drs. Dubos, Finland, and Weinstein urging caution, the widespread use and often misuse of antibiotics fueled the very nightmare they predicted.

The work of many molecular microbiology laboratories in the 1960s and 1970s, especially in the United States, identified the molecular substrate of Gram-negative bacterial plasmids and of the DNA units containing the resistance genes, the interbacterial transmission genes and of structures containing resistance genes able to jump among all these structures (transposons). These researchers, including Stanley Falkow, Royston Clowes, Stanley N. Cohen, Robert Rownd, and Donald Helinski, called attention to and confirmed the ability of these plasmids to recombine to generate multiple antibiotic resistance plasmids which could then spread among bacterial populations in vivo in humans and animals and where they were able to exert their negative influence over antimicrobial therapy.

The rise of new synthetic drugs such as quinolones offered fleeting hope, only to be dashed by the remarkable adaptability of bacteria. New molecular methods exposed the chilling reality: resistant bacteria, birthed in animal farms due to routine antibiotic use, readily infected humans. Resistant *Salmonella*, *E. coli*, *Campylobacter*, and *Enterococcus* became familiar names, not just in livestock barns but also in hospital wards.

The ability of resistant bacteria and resistance genes to jump continents via travelers, water, and food underscored the global nature of the crisis. The finding that resistance genes could be captured from environmental bacteria added complexity to the problem. Yet responses were slow and disjointed. Patient groups fought for recognition, scientists sounded alarms, and the Alliance for Prudent Use of Antimicrobials (APUA) pushed for education. Similarly, in 1981 a group of 147 scientists from 27 countries led by Stuart B. Levy published a statement indicating that antimicrobial resistance was a "worldwide public health problem", and that increased "awareness of the dangerous consequences of antibiotic misuse at all levels of usage: consumers, prescribers, dispensers, manufacturers, as growth promoters in farm animals and government regulatory agencies" was needed.

This highlights the perpetual dance between our ingenuity in developing antimicrobials and the relentless evolutionary prowess of bacteria. It paints a picture of continuous evolution of resistance towards "superbugs" in humans, animals, and plants fueled by antibiotic overuse and misuse. It underlines the urgency for responsible antibiotic use, research, and awareness to ensure these lifesaving tools remain effective for generations to come.

An inheritance of inaction, a turning point, but still a long road

Gradually, the tide began to turn. Research revealed new genetic elements mediating resistance such as transposons, integrative and conjugative elements (ICE), and integrons. Studies in Europe confirmed that restricting antimicrobial use in animals could curb resistance in animals and humans. However, implementing such measures is often met with resistance from economic interests. Only in the 2000s did we begin to confront AMR as a global emergency.

A more serious and global approach to the problem was suggested by Joshua Lederberg in 1988. He stated that it was necessary to introduce "measures to ensure the availability and

usefulness of antimicrobials and to prevent the emergence of resistance. … These measures should include the education of health care personnel, veterinarians, and users in the agricultural sector regarding the importance of rational use of antimicrobials (to preclude their unwarranted use)." Ten more years would pass before some countries in Europe banned the use of antimicrobials as growth promoters in animal husbandry, ten more for the European Union to do so, and yet another ten for the Food and Drug Administration to take this action in the United States. It would take the World Health Organization and many government and non-governmental public health institutions until the early years of this century to wrestle with antimicrobial resistance as a global, increasing, and urgent problem of public health.

This brief history reveals an unfortunate tale of ignored warnings, conflicting interests, and delayed action. However, it also offers a roadmap for the future. Education, responsible antibiotic use, and continued research to develop new antimicrobials remain our best weapons against this evolving threat. In the spirit of Dr. Dubos, we must "think globally, act locally" to reclaim the magic of antibiotics and secure a healthier life for future generations. Today, under the One Health umbrella, we recognize the interconnectedness of human, animal, and environmental health in tackling AMR. Yet, concerted global action remains elusive. This inaction in the face of knowledge had Dame Sally Davies, Chief Medical Officer of Great Britain, to state in 2013. "This is a threat arguably as important as climate change for the world."

In summary,

- AMR warnings predate widespread antibiotic use.
- Misuse in humans and animals fueled resistance emergence.
- Genetic and molecular methods proved the global reach of resistance genes.
- Despite the scientific evidence, action was slow and fragmented.
- The One Health approach recognizes interconnectedness in tackling AMR.
- Education, responsible use, and research are essential to combat resistance.