South Health and Policy. 2026; 5:367
doi: 10.56294/shp2026367

REVIEW

Antimicrobial resistance and a versatile pathogen in the spotlight

Resistencia antimicrobiana y un patógeno versátil en el punto de mira

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Cite as: López Berrio S, García Milera Y, Calaña Domínguez Y, Colome González T, Herrero Díaz A. Antimicrobial resistance and a versatile pathogen in the spotlight. South Health and Policy. 2025; 5:367. https://doi.org/10.56294/shp2026367

Submittted: 10-02-2025 **Revised:** 10-06-2025 **Accepted:** 25-12-2025 **Published:** 01-01-2026

Editor: Dr. Telmo Raúl Aveiro-Róbalo

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ABSTRACT

Introduction: antimicrobial resistance is an emerging global phenomenon and is one of the most serious health problems today. The irrational use of antimicrobials has led to the early emergence of resistance mechanisms. Staphylococcus aureus is one of the pathogens classified as high priority for research and development plans for new antimicrobials due to its incidence causing infections with a high impact on health.
Objective: to carry out an updated review of the problem of antimicrobial resistance of Staphylococcus aureus, at a global and national level since the discovery of antibiotics, related factors and mechanisms.
Method: a literature search was carried out in different databases such as Pubmed, SciELO, Science Direct, Google Scholar, MEDLINE and on the PAHO/WHO websites on the topics of microbial resistance and use of antimicrobials. Original and review articles published between 1998 and 2024 were consulted.
Results: the information collected on the topics was analyzed and argued
review objects carried out under an integrative approach. What is happening in Cuba was also explained.
Conclusions: the reproduction power of bacteria is faster than the speed of research and development. Faced with the difficult battle against bacteria such as Staphylococcus aureus, given the development of new resistance mechanisms to eliminate the clinical effectiveness of antibiotics, the necessary measures must be adopted to stop the development of bacterial resistance.

Keywords: Antimicrobial Resistance; Resistance Mechanisms; *Staphylococcus Aureus*.

RESUMEN

Introducción: la resistencia a los antimicrobianos es un fenómeno mundial emergente constituye uno de los problemas en salud más graves en la actualidad. El uso irracional de antimicrobianos ha propiciado una pronta aparición de mecanismos de resistencia. *Staphylococcus aureus* es uno de los patógenos clasificados como de prioridad alta para los planes de investigación y desarrollo de nuevos antimicrobianos por su incidencia provocando infecciones de alta repercusión a la salud.
Objetivo: describir la resistencia antimicrobiana desarrollada por Staphylococcus aureus.
Método: se realizó una búsqueda de literatura en diferentes bases de datos como Pubmed, SciELO, Science Direct, Google Académico, MEDLINE y en los sitios web de la OPS/OMS sobre los temas de resistencia microbiana y uso de antimicrobianos. Se consultaron artículos originales y de revisión publicados entre 1998 y 2024.
Resultados: se analizó y argumentó la información colectada sobre los temas objetos de revisión llevado a cabo bajo un enfoque integrador. Se expuso, además lo que acontece en Cuba.

Conclusiones: el poder de reproducción de las bacterias es más rápido que la velocidad de investigación y desarrollo. Frente a la difícil batalla contra las bacterias como *Staphylococcus aureus,* ante el desarrollo de nuevos mecanismos de resistencia para eliminar la efectividad clínica de los antibióticos, se deben adoptar las medidas necesarias para frenar el desarrollo de la resistencia bacteriana.

Palabras clave: Resistencia Antimicrobiana; Mecanismos de Resistencia; *Staphylococcus Aureus*.

INTRODUCTION

Antimicrobial resistance (AMR) is not a recent phenomenon, as reported by Torres Caycedo et al., cited by Camacho Silvas. Almost in unison with the emergence of the antibiotic era, bacteria began to develop mechanisms capable of evading the mechanisms of action of this group of drugs.

The arrival of the SARS-CoV-2 virus represented a powerful catalyst for the rise of AMR. The irresponsible behavior of the population, motivated partly by ignorance and misinformation in society, was the enabling factor.[1]

From today's perspective, antimicrobial resistance (AMR) is one of the biggest crises threatening global public health in developed and developing countries.[2]

The World Health Organisation (WHO) places AMR in the *top ten* of the most serious global public health problems, causing around 700000 deaths yearly. By 2050, some 10 million deaths per year are expected to be directly or indirectly related to this phenomenon, displacing neoplasms as the leading cause of death.[3]

Negligent and inappropriate behavior related to the use of antimicrobials by the population, the use of these drugs to maximize yields in the livestock industry, the absence of measures to control and prevent infections associated with sanitary environments, the delay in microbiological diagnosis, poor hygienic-sanitary scenarios and the absence of new antimicrobials, are all factors that favor bacterial resistance.[4,5,6]

The World Health Organization (WHO) published its new list of priority bacterial pathogens for 2024. To facilitate prioritization, it lists 15 families of antibiotic-resistant bacteria in three categories (critical, high, and medium). This list provides guidance for new treatments needed to stop the spread of antimicrobial resistance.

High priority:

- Fluoroquinolone-resistant *Salmonella* Typhi.
- Fluoroquinolone-resistant *Shigella* spp.
- Vancomycin-resistant *Enterococcus faecium*
- Carbapenem-resistant *Pseudomonas aeruginosa*
- Fluoroquinolone-resistant non-typhoidal salmonellae
- *Neisseria gonorrhoeae* resistant to third-generation cephalosporins and/or fluoroquinolones
- Methicillin-resistant *Staphylococcus aureus*.[7]

Staphylococcus aureus (S. aureus) microorganism classified as a high priority, specifically the methicillin-resistant variant, is a microorganism that presents a high frequency of isolation in our laboratories, causing various conditions mainly in the skin and soft parts, has particular characteristics of virulence and resistance to antibiotics. It is an aetiological agent of multiple human infections, ranging from mild to severe. It can be found in community settings as well as in healthcare settings. Over the last decades, there has been a trend towards the spread of strains with high resistance to commonly used antimicrobials.[8,9]

Staphylococcus aureus exhibits indigenous forms of drug resistance, such as reduced membrane permeability and a limited drug absorption and flow system, through which drug efflux and overproduction of **β**-lactamase are favoured.[10]

S. aureus shows the worldwide distribution of strains resistant to methicillin and other drugs, and this is notoriously observed in regions such as Africa, the Western Pacific, America, the Eastern Mediterranean, Southeast Asia, and Europe.[11] Our country and territory do not escape this problem.

In our country, there has been an unusual increase in the number of cases caused by this bacterium in children and adults, some of them very serious and related precisely to soft tissue sepsis. Attending physicians and microbiologists from different hospitals, whose profiles include clinical-surgical, gynaeco-obstetrics, and pediatrics, report these cases. This has motivated the interest in its study by many nationwide researchers.

As Staphylococcus aureus is a microorganism of marked pathogenicity and resistance to current antimicrobial therapies, we aim to describe the antimicrobial resistance developed by Staphylococcus aureus.

METHOD

A search for information was carried out in different databases, such as Pubmed, SciELO, Science Direct,

Google Scholar, MEDLINE, and the websites of PAHO/WHO, FAO, and OIE on the topics of microbial resistance and Staphylococcus aureus (initiation of antibiotic therapy, emergence and evolution of AMR, mechanisms, One Health approach to its containment and use of antimicrobials.

Original and review articles published between 1998 and 2024 were consulted. Keywords in Spanish and English related to the subject were used. Once the articles to be included in the review had been selected, a critical reading and analysis of the information necessary for the drafting of the manuscript was carried out, which updates and argues about the current problems of antimicrobial resistance and *Staphylococcus aureus*.

DEVELOPMENT

Antibiotics were developed to control infections caused by bacteria. Their discovery and use are one of the main reasons, together with the implementation of health policies and vaccines, for the remarkable decrease in morbidity and mortality from infectious diseases during the 20th century.

Molds and plant extracts have been used for millennia to treat infections. Some of the oldest civilizations used molds and plant extracts to treat infections: the ancient Egyptians, for example, applied moldy bread to infected wounds.

Historically, essential dates stand out when discussing antibiotics: in 1670, the Dutch merchant Anton van Leeuwenhoek discovered microscopic life. In 1859, Louis Pasteur linked the germ to disease, and in 1928, Alexander Fleming discovered penicillin, thus initiating the modern era of antimicrobials.

In the early 20th century, the German physician Paul Ehrlich synthesized a chemical compound called *arsphenamine*, which was effective for the treatment of syphilis, a venereal disease of bacterial origin. In 1910, it began to be marketed under the name *salvarsan: it* was the first antibiotic designed as such. Ehrlich called these substances *"magic bullets "* because they attack invading microorganisms, causing little harm to the body.

In 1928, the British physician and scientist Alexander Fleming found that a substance produced by certain fungi, scientifically named *Penicillium notatum*, destroyed microbial cultures. Thus came penicillin, the first antibiotic obtained from a natural source.

The word 'antibiotic' ("anti": contrary and 'bio': of life, of living things) was first used in 1941 by the Ukrainian-American inventor and microbiologist Selman Waksman, who discovered more than 20 antibiotics in his lifetime. The term antibiotic thus refers to a substance that can eliminate or interrupt the growth and proliferation of various pathogenic microorganisms.[12]

Evolution of Antimicrobials

The so-called 'Golden Age' of antibiotics began 1941 with penicillin production in 1941. The large-scale production of penicillin was followed by the development of new antibiotics such as streptomycin (1944), chloramphenicol (1947), and aureomycin (1948).

In the 1950s, erythromycin and vancomycin appeared. In the 1960s gentamicin, ampicillin, cephalothin, and amikacin. Thus, successively, the evolution of the production of new antibiotics continues. The production of new antibiotics continues. After 2000, extended-spectrum quinolones were introduced.[13]

Alexander Fleming, when he received the Nobel Prize for Medicine in 1945, warned about resistance when he said: "The time will come when anyone in business can buy penicillin. There is a danger that an ignorant man can easily apply an insufficient dose of antibiotic and, by exposing the microbes to a non-lethal amount of the drug, make them resistant".[14]

Unfortunately, humans did not become aware of this warning, and the first resistant isolates soon appeared as part of the natural evolution of bacteria adapting to their environment. This phenomenon accelerated over time due to the inappropriate use of antibiotics in different ecosystems, which was facilitated by the lack of regulations and control of antibiotic use. Other factors included poor treatment, over-the-counter or internet sales, marketing of counterfeit or poor-quality antimicrobials, and the lack of control of antimicrobial residues in production plants.[15]

History of a resistant pathogen

The emergence of methicillin-resistant *Staphylococcus* in the 1960s confirmed the severity of antimicrobial resistance. This phenomenon became more dramatic with the rise of ampicillin resistance in the 1970s, the emergence of vancomycin-resistant *Enterococcus* in the 1990s, and the spread of resistance to different families of antimicrobials in line with their speed of use and amount in medical practice, which now involves even the latest generation of antibiotics.[13]

Staphylococcus aureus is a highly virulent pathogen with increasing resistance to antimicrobial drugs and is considered the primary agent responsible for infections at both community and nosocomial levels. Koch and Pasteur had already observed them, but Ogston, in 1880, first named them *Staphylococcus sspp* (from the Greek *staphyle*, cluster, and *kokkos*, grains). Later, it was Rosenbach, in 1884, who coined the binominal name for

this species. In 1903, Loeb discovered coagulase, an enzyme whose determination, to this day, helps classify species within this genus.

It is the most versatile of the pathogenic microorganisms. It can produce disease by toxins or superantigens, invade any organ or tissue, cause suppuration, tissue necrosis, vascular thrombosis, and bacteremia. It is the micro-organism with the most significant capacity to cause metastasis via the hematogenous route. It can grow in the cell cytoplasm, form biofilms, cause persistent bacteremia or chronic infection, or remain quiescent and reactivate months or years later. It colonizes certain areas of the skin and mucous membranes, from where it causes reinfection, contaminates the environment, and spreads to other patients. On the other hand, if the bacterial population density in the infectious focus is high, *S. aureus* can become resistant to most antibiotics used in monotherapy.[16,17,18]

S. aureus has a short history of antimicrobial susceptibility. Today, most hospital-derived isolates, and more than 80 % of community isolates, are resistant to penicillin. Between 1955 and 1960, methicillin (the first generation of semi-synthetic penicillins) began to treat infections caused by penicillin-resistant *Staphylococcus aureus*.[17,18,19] Only 2 years after its introduction, the first isolation of methicillin-resistant *S. aureus* (MRSA) was described, and in 1963 the first nosocomial epidemic outbreak (MRSA-HA). This resistance is due to the *mec*A gene, which encodes a penicillin-binding protein (PBP), known as PBP2a or PBP2', which confers low affinity for beta-lactam antibiotics. The *mec*A gene is part of a mobile complex*(mec*) that resides within a genomic island at a specific site within the *Staphylococcus aureus (S. aureus)* chromosome*,* staphylococcal chromosome cassette (SCC).[20,21] In the mid-1980s, an increase in community-acquired methicillin-resistant *Staphylococcus aureus* infections (CA-MRSA) began to be observed in patients with no risk factors and no history of hospitalization. This phenomenon spread throughout the world and reached its peak in 2000. It mainly affects children and young people, as well as people living in overcrowded, unhygienic conditions. The most frequent clinical presentation is skin and soft tissue infection. It spreads rapidly, and 93 % produces Panton-Valentine leukocidin. This exotoxin causes rapid destruction of leukocytes and polymorphonuclear cells, with a high tendency to cause collections of pus that require incision and drainage, in addition to antibiotic treatment; do not exhibit joint resistance to other antibacterials as is characteristic of MRSA-AH, but are resistant to all beta-lactams, and occasionally to macrolides and azalides, but retain sensitivity to different families (such as trimethoprim-sulfamethoxazole, aminoglycosides, fluoroquinolones, clindamycin, and tetracyclines). Knowing these characteristics allows better treatment of staphylococcal infections. The first *Staphylococcus aureus* with intermediate sensitivity to vancomycin (VISA) was reported in 1996, and the first resistant isolates (VRSA) in 2002.[22,23]

According to data from the Centers for Disease Control (CDC), the proportion of antibiotic-resistant infections in the United States has been increasing. The National *Nosocomial Infectious Surveillance System*(*NNIS*), also in the United States, found that the prevalence of MRSA strains in hospitalized patients increased from 4 % in 1980 to 31,9 % in 1996. In 2001, the prevalence was 55 %, and by 2004 it had reached 63 %. In 2005, MRSA caused more than 94,000 life-threatening infections and almost 19000 deaths in the United States, most of which were linked to healthcare institutions.[24,25] This situation did not change on the European continent. In Spain, according to the results published in the 2011 Prevalence Study of Nosocomial Infections in Spain (EPINE), nosocomial infections due to *Staphylococcus aureus* had a prevalence of 8,1 %. Of these isolates, 43,0 % turned out to be methicillin-resistant.[26]

In Latin America, more than a quarter of *S. aureus* isolates are methicillin-resistant. The implications are excess mortality, increased expenditure on antibiotic treatment, and increased hospitalization in all regions of the world.[27]

Cuba is no stranger to this situation, as this microorganism is responsible for high rates of nosocomial and community infection throughout the island and has been best studied in provinces such as Havana City, Camagüey, Matanzas, and Villa Clara. Research has shown MRSA, with values fluctuating between 20 % and 80 %, to be responsible for hospital or nosocomial infections.[28]

In our hospital, this pathogen occupies first place in isolations in the skin and soft tissue secretions from hospitalized patients and from the community who come to our laboratory, which deals with microbiological diagnosis in four municipalities in the central northern region of Villa Clara province; these isolates are led by the methicillin-resistant variant, which brings with it resistance to other groups of antimicrobials.

All of this has demonstrated the urgent need to work hard on the work agendas of each country based on five fundamental objectives:

- Increase studies and efforts to create new antimicrobial therapies and drugs capable of responding to the current needs of microorganisms.
- To monitor compliance with antimicrobial policies and the correct and necessary support in microbiological mapping.
- To massify information, prevention, and education campaigns to reduce negligent attitudes on the part of the population.
- Control the use of antibiotics in the livestock industry with a view to their elimination.

- Prepare both health personnel and health systems for the arrival of future pandemics, which, like the most recent one caused by COVID-19, will hamper the fight against AMR.

CONCLUSIONS

Society is constantly developing and progressing under the promotion of science and technology. In a few decades, antibiotics have gone from being 'miracle drugs of great health impact' to 'a non-renewable and endangered resource.' The reproductive power of bacteria is often faster than the speed of research and development. However, in the face of the uphill battle against bacteria with the development of new resistance mechanisms to eliminate the clinical effectiveness of antibiotics such as *Staphylococcus aureus*, humans must not allow antibiotics to be freely prescribed. The necessary measures must be taken to curb the development of bacterial resistance, and new treatments and methods of infection prevention and control must be explored. The cost of antibiotic resistance is high, with very high mortality rates and health costs. Increase studies and efforts to develop new antimicrobial drugs and therapies capable of responding to the current needs of microorganisms.

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FUNDING

None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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