ANTIBIOTIC RESISTANCE: AND NOW WHAT?

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Abstract

Antimicrobial resistance (AMR) represents a global threat that affects all populations and ecosystems equally, partly driven by the massive and improper use of antibiotics since their discovery in the 20th century. While microorganisms' ability to develop resistance is a natural adaptation mechanism, human practices have dramatically accelerated this process, compromising the therapeutic efficacy of these drugs and generating health, economic, and political consequences on a global scale. In this context, the "responsible use of antimicrobials" emphasizes the commitment, shared responsibility, and conscious action of all actors involved in the life cycle of these medications, as part of an urgent and sustained systemic response to this crisis.

This narrative review explores the impact of AMR in Latin America and Argentina, the use of antimicrobials in animal health, and its impact on the environment, proposing various strategies for change.

This document serves as a compelling call to action, recognizing the ubiquitous involvement of all stakeholders – the community (including the environment) and the healthcare sector– as both contributors to and potential mitigators of AMR. Ensuring a future where antimicrobials remain effective tools for human, animal, and environmental health is a collective mission for all.

Key words: antimicrobial resistance, antibiotics, education, antimicrobial stewardship programs, infection control programs, Diagnostic stewardship programs

Resumen

Resistencia a los antibióticos: ¿Y ahora qué?

La resistencia a los antimicrobianos (RAM) constituye una amenaza global que afecta a todas las poblaciones y ecosistemas por igual, impulsada en parte por el uso masivo e inadecuado de antibióticos desde su descubrimiento en el siglo XX. Aunque la capacidad de los microorganismos para desarrollar resistencia es un mecanismo natural de adaptación, las prácticas humanas han acelerado dramáticamente este proceso, comprometiendo la eficacia terapéutica de estos fármacos y generando consecuencias sanitarias, económicas y políticas a escala planetaria. En este contexto, el "uso responsable de antimicrobianos" enfatiza el compromiso, la corresponsabilidad y la acción consciente de todos los actores involucrados en la cadena de vida de estos medicamentos, como parte de una respuesta cultural urgente y sostenida frente a esta crisis.

En esta revisión narrativa se explora el impacto de la RAM en Argentina, el uso de antimicrobianos en salud animal y su impacto en el ambiente proponiendo diferentes estrategias para el cambio.

Este documento es una convocatoria a la acción de todos como parte de un problema, la RAM, y parte de la solución, en la comunidad, en el ámbito de la salud o en el medioambiente. Asegurar un futuro donde los antimicrobianos sigan siendo herramientas eficaces para la salud humana, animal y ambiental es una misión de todos para todos.

Palabras clave: resistencia antimicrobiana, antibióticos, educación, programas de optimización de antimicrobianos, programas de control de infecciones, programas de optimización de diagnóstico

KEY POINTS
Current knowledge

- Antimicrobial resistance is an expanding global health threat.
- Argentina reports high rates of multidrug-resistant organisms.
- Carbapenemase-producing Enterobacterales and carbapenem-resistant *A. baumannii* cause substantial morbidity and mortality.
- Integrated surveillance is essential to understand their impact.

Contribution of this article to current knowledge

- Summarizes the epidemiology of antimicrobial resistance in Argentina and the region.
- Integrates evidence across human, animal, and environmental health sectors.
- Describes clinical impact, resistance mechanisms, and local circulation patterns.
- Provides a data-driven framework to guide shared responsibilities and coordinated action.

"If you did not learn it to demonstrate it through deeds, for what purpose did you learn it?"
Epictetus (Stoic philosopher)

"I still have in my mind to change something... Still, and thankfully, still..."
Juan Carlos Baglietto (popular Argentinian singer-songwriter)

The discovery and subsequent development of antimicrobials in the 20th century represented a substantial advance in medicine, contributing significantly, alongside vaccines and access to clean water, to the improvement of global population health and life expectancy. However, their excessive and inappropriate use has notably accelerated the phenomenon of antimicrobial resistance (AMR), particularly over the last three decades. This situation has reached a point of seriously compromising global health, causing concern not only for health-related organizations but also for the economic and political sectors[1-7].

Mechanisms of antibiotic resistance are innate strategies microorganisms developed to survive in hostile environments, whether in living organisms such as humans and other animals, or in media like soil, water, and even air. This phenomenon poses a dramatic problem that indiscriminately affects the entire planet, transcending cultures, social status, age groups, and levels of healthcare access. Its impact extends to an intrinsically interconnected ecosystem encompassing the animal world and the environment[8-14].

The administration of antibiotics exerts undeniable selective pressure that inevitably drives the development of bacterial resistance. Although the intrinsic propensity of each species to generate or acquire resistance-conferring mutations plays a role, the evolutionary trajectory of this phenomenon is strongly influenced by antimicrobial usage practices. Inadequate and widespread antibiotic use accelerates the selection and dissemination of resistant strains, perpetuating the current AMR crisis for global health.

Conversely, responsible use could mitigate the speed of this bacterial adaptation and preserve the medicine's sustained therapeutic efficacy over time.

"Rational" versus "responsible": a necessary paradigm shift

The phrase "rational use of antibiotics" is frequently employed to denote appropriate, timely management based on clinical evidence and the pharmacological properties of these drugs. "Rational" is understood as pertaining to reason, logic, reasonableness, equity, and fairness, thus appealing to good judgment[15]. However, it can evoke negative interpretations, as the one expressing it (and how it is expressed) may present themselves as possessing the necessary "reason and good judgment" in the use of tools like antimicrobials. This can potentially establish a division between "those who know" and those who seemingly lack that knowledge, whose understanding is considered insufficient, or who simply hold a different opinion.

In this context, we strongly advocate for the adoption of the concept of "responsible use" of antimicrobials. This is not merely a semantic issue but rather a reflection of a proactive attitude in preserving these essential drugs for current medical practice. "Responsible" is defined as exercising care and attention in one's actions or decisions and being accountable for something or someone. This approach, while also appealing to good judgment and equanimity, inherently empowers all stakeholders involved in the lifecycle of these pharmaceuticals: from researchers and the pharmaceutical industry, through regulatory agencies, prescribers (physicians, dentists, veterinarians), dispensers (pharmacists), those who administer them (nurses, caregivers, family members), and finally, the community that demands or receives them.

This chain of "responsibilities" signifies a crucial cultural shift in response to a scenario of considerable gravity, demanding immediate action. Such actions are not limited to large-scale initiatives inherent to health authorities at various levels but also encompass every day, smaller-scale interventions that each actor in this "vital chain" can implement. It is critical that these actions are sustained over time, across every link involved in the use of these medicines.

A compelling reality: Argentina under the spotlight

In recent years, Argentina has witnessed a significant surge in AMR, with high percentages of carbapenemase-producing Enterobacteriaceae (CPE), particularly those producing metallo-β-lactamases (MBLs). Additionally, the country is experiencing a growing incidence of carbapenem-resistant *Acinetobacter baumannii*[16-18].

The global epidemiological situation and its impact on patient morbidity and mortality are critical and particularly pressing in Latin America and Argentina. Recent global studies have verified the high mortality attributable to antimicrobial resistance. A study published in *The Lancet* estimated that in 2021, 1.14 million people died due to this health threat. For Latin America and the Caribbean, AMR-associated mortality is projected to reach 650 000 people by 2050, with 148 000 attributable deaths[19].

These studies have been conducted based on projections derived from mathematical models informed by the current situation. However, in Argentina, the impact on patient mortality has been demonstrated through real-world studies. The EMBARC-AR Project observed a 52.4% mortality rate associated with carbapenem-resistant Gram negative bacillus (CRGNB) bacteremia[27]. Nonetheless, 30-day mortality in patients treated with new drugs available in Argentina was substantially lower in those with an INCREMENT score greater than eight. This suggests that more critically ill patients could benefit from the use of these new antimicrobial agents due to their impact on this outcome[20].

Furthermore, a recent study on prevalence across 164 adult critical care units in Argentina, involving 1799 patients, revealed that 933 patients (51.9%) had a reported infection[21]. Among confirmed infections with an identified microorganism, 45.5% (273/599) were due to multidrug-resistant organisms (MDROs). The most frequent infection was ventilator-associated pneumonia (100/344; 29.1%), and the most common MDROs were carbapenem-resistant *Acinetobacter baumannii* and CPE (98/344, 28.5% each). In-hospital mortality in the critical care unit was 27.1% (487/1799), being significantly higher in the presence of an MDRO infection (35%). This accurately reflects the current reality in Argentina.

According to data from the Antimicrobial Resistance Surveillance Network (WHONET-Argentina), which includes 93 hospitals, a total of 18,900 Enterobacterales isolates were reported in 2024[16]. Among these, 3,067 (16.2%) were confirmed as carbapenemase-producing Enterobacterales (CPE). The highest CPE prevalence was observed in respiratory (23.6%) and bloodstream (20.0%) infections. Adults aged ≥65 years were more frequently affected than pediatric patients (17.4% vs. 9.8%), and CPEs were more common in male patients compared to females (19.9%

vs. 12.7%) ($p< 0.05$). *Klebsiella pneumoniae* was the leading contributor to carbapenem resistance, with a CPE rate of 40.2% among isolates. Metallo-β-lactamases were the most prevalent carbapenemase (61.9%) ($p< 0.05$), followed by KPC (24.7%) and OXA-48-like enzymes (5.5%). Dual carbapenemase producers, predominantly KPC+NDM combinations, accounted for 7.9%. Regarding carbapenem-resistant *Acinetobacter baumannii* in blood samples, the percentage reached 80%[16-18].

Concerning Gram positive bacteria, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in blood samples is 33.6%, and in skin and soft tissue infections, it rises to 42.6%[16]. Notably, for MRSA, resistance levels appear to have decreased in recent years. The NRL data indicate that the prevalence of MRSA in skin and soft tissue infections decreased from 65.5% in 2010-2011 to 43.4% in 2023, and in bacteremia, it dropped from 46% to 33.4% during the same period. However, the situation is different for Gram negative bacilli. For example, carbapenem resistance in *Klebsiella pneumoniae* has significantly increased, from 10% in 2013 to approximately 40.2% in 2024.

Threatened animals: the unforeseen consequences of antibiotic use

Antibiotics are tools, and like all tools, they are morally neutral. Their use can be appropriate or inappropriate, leading to either beneficial or detrimental outcomes, with the user bearing full responsibility. This analogy holds true not only for human health but also for animal and environmental health, particularly concerning AMR[22].

As other researchers emphatically predicted over 15 years ago, the release of antibiotics likely represents one of the most significant anthropogenic impacts on the biosphere, and we are now experiencing its devastating effects. It's estimated that annual antibiotic production could cover the entire land surface with a layer of inhibitory concentrations approaching 1 μg/ml[23]. This level is capable of altering the genetic structure of microbes, an effect that is very likely irreversible.

Contrary to popular belief, most antibiotics produced globally are intended for animal health, particularly for livestock (bovine, porcine, poultry, and also in the fishing industry). Furthermore, their use is primarily for preventive purposes (prophylaxis and meta phylaxis) and as growth promoters, rather than solely for therapeutic treatment[24].

A 2017 report indicated that China accounted for almost 50% of the total antimicrobial consumption in animals. The next nine countries with the highest consumption for this purpose were Brazil (7.9%), the EE. UU. (7%), Thailand (4.2%), India (2.2%), Iran (1.9%), Spain (1.9%), Mexico (1.7%), and Argentina (1.5%)[25]. Notably, Argentina has prohibited the commercialization and use of veterinary products containing antimicrobial active ingredients (alone or in combination) for growth promotion as of 2024 (SENASA Resolution 445/2024)[26].

In addition to livestock, companion animals (primarily dogs and cats) receive various forms of antimicrobials in their food. This scenario, coupled with the inappropriate use of antibiotics, fosters the development and carriage of resistant microorganisms and their subsequent dissemination to humans and the environment[27-29].

Furthermore, insects in production units act as vehicles, transporting resistant microorganisms over several tens of kilometers. They also function as "bio-augmenters," facilitating the replication of microorganisms within their digestive systems. Similarly, migratory birds carry resistant germs on their feet, beaks, and feathers over thousands of kilometers[30-32].

Dangerous liaisons: the interplay between climate change, antimicrobial resistance and environmental pollution

Global warming and climate change have increased vector-borne infections such as dengue, malaria, and yellow fever, among others.

These observations are logical: the conditions necessary for the development of these infections have afflicted humanity since time immemorial, strongly motivating the search for solutions to both control them and facilitate commercial progress in affected geographical areas (which are becoming increasingly widespread) that produce essential goods consumed by millions of people[33]. However, this phenomenon is also observed to promote AMR due to a simple fact: the rise in temperatures (above 35°C) creates the optimal growth environment for bacteria, similar to how they are routinely cultivated in laboratories for both research and clinical microbiology diagnostics in healthcare institutions[34].

Furthermore, there is growing evidence of the impact of environmental pollution by multidrug-resistant microorganisms. Effluents from healthcare facilities, non-sanitary industries, and even domestic sources, contain waste with antimicrobial activity that is not adequately removed by current water treatment systems, thereby perpetuating the contamination cycle. A problem to be resolved in many countries, including Argentina, is the management of expired antibiotic disposal. With the exception of healthcare institutions, which dispose of them as hazardous waste, this process is not appropriately regulated or organized[35].

Just as various organizations linked to the climate phenomenon warn that we should no longer speak of "climate change" but rather of "climate disaster and its consequences," it is also necessary to stop referring to "antimicrobial resistance" as a simple phenomenon. Instead, we must begin to name it for what it truly is: the "disaster" of antimicrobial resistance and its concrete, current, and multidimensional impacts on human, animal, and environmental health.

Who said that all is lost? Strategies for change

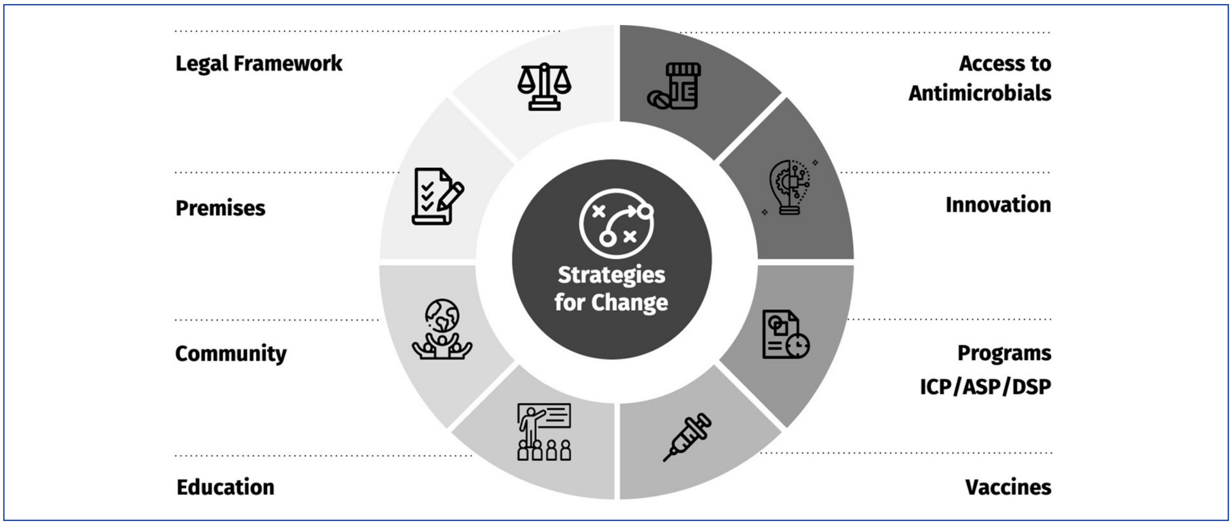
Implementing effective strategies demands coordinated action from all involved individuals and organizations. While various institutions, governmental, and non-governmental bodies have promoted the development of new molecules to combat infections with alarming fatality rates, we believe it's crucial to highlight other equally relevant perspectives. These directly involve decision-makers and regulatory bodies but can also inspire and motivate the remaining stakeholders in this powerful "chain of responsibilities" (Fig. 1).

Legal framework

Governmental agencies play a key role in implementing and monitoring rational antibiotic-use policies. National law provides a unified legal framework that establishes clear responsibilities for all stakeholders, including healthcare professionals, farmers, regulatory authorities, and the pharmaceutical industry. Without such legislation, actions can become fragmented, lacking coherent and coordinated direction.

Argentina's National Antimicrobial Resistance Law (Law 27.680), enacted in 2020, marks a crucial step in the fight against AMR[36]. This legislation establishes a regulatory framework for the prevention, surveillance, and control of AMR within the country, addressing a problem

Figure 1 |Chain of responsibilities



IPC: Infection and Prevention Control Programs; ASP: Antimicrobial Stewardship Programs; DSP: Diagnostic Stewardship Programs that impacts global public health and seriously compromises the effectiveness of antimicrobial treatments.

This law (Table 1) was enacted through a parliamentary process that resulted in near-unanimous approval in both chambers of Congress. This consensus stemmed from several years of collaborative work among legislators; key state agencies such as the National Agri-Food Health and Quality Service (SENASA), the National Administration of Laboratories and Health Institutes "Dr. Carlos G. Malbrán" (Anlis-Malbrán), and the National Institute of Epidemiology (INE); as well as renowned scientific associations like the Argentinian Society of Infectious Diseases (SADI), the Association for Infection Control (ADECI), and the Argentinian Society of Intensive Care (SATI).

While a crucial initial step has been taken, it remains insufficient. Possessing a law that is being observed with great interest across the continent necessitates establishing the level of compliance with its respective regulations. This will provide an organized advancement in common and articulated actions from the perspective of animal, environmental, and human health. What can be done from "the ground up"? From civil society, a sincere and urgent dialogue is undoubtedly imperative, especially in a scenario where the healthcare system exhibits deficiencies and demands short-, medium-, and long-term solutions. It requires testing creativity and imagination to address shortcomings and overcome daily obstacles. It is necessary to think from specific circumstances towards the macro, finding shared perspectives and aligned viewpoints. This is not about abandoning the "comfort zone," but rather expanding it[37].

Enforcing this law across all jurisdictions and in every institution connected to human and animal health demands a collective effort. This initiative starts with health authorities at various decision-making levels, scientific societies, and active community organizations. Incorporating environmental aspects, which are currently absent from this legislation, is an essential step to complete the cycle of care for our vital surroundings.

Reproducing and improving upon this legislation in countries with similar realities to Argentina presents an urgent opportunity and can serve as a valuable reference for similar initiatives. In this regard, given its environmental impact, it is crucial to emphasize the need to promote sustainable laboratories (green labs). Healthcare practices leave a clear footprint: hospitals operate 24 hours a day, generating large quantities of waste (infectious, hazardous, and solid), using potentially toxic materials (some

Table 1 | Aspects regulated by Argentina's national antimicrobial resistance (Law N° 27.680)

Regulated aspect	Description
Sale of systemic antimicrobials	Requires an archived prescription
Advertising of antimicrobials	Prohibited for medicines containing them
Pharmaceutical presentations	Must be adapted to usual doses and treatment durations
Use in livestock	Eliminates the use of antimicrobials as growth promoters
AMR surveillance	Strengthened at the national level
Infection control programs	Promotes their implementation in all healthcare institutions, with surveillance of healthcare-associated infections (HAIs)
Awareness and education	Promotes awareness of the impact of HAIs and AMR on human, animal, and environmental health.
Research and development	Fosters new antimicrobials and rapid, efficient microbiological diagnostic methods
Declaration of public interest	The prevention and control of antimicrobial resistance are declared of national public interest, establishing a framework for mandatory national compliance

HAIs: healthcare-associated infections; AMR: antimicrobial resistance with microbicidal activity), and consuming significant volumes of water and energy[38-40]. It is fundamental to prioritize these issues to limit the impact of AMR on human and animal health. AMR often originates within the very healthcare institutions (or those linked to them) that, paradoxically, dedicate immense efforts to combating infections caused by resistant microorganisms. This vicious cycle must be broken.

Bridging the gap: access to scarce antimicrobials

Ensuring that appropriate antibiotics reach those who genuinely need them is a complex undertaking, particularly in low- and middle-income countries. This challenge is compounded by the inherent economic disincentive for developing new antimicrobials, given their relatively rapid obsolescence and their typical use for short-term, acute conditions. Furthermore, responsible stewardship of newer, more expensive antibiotics often dictates reserving them for the most severe or critical cases. The core challenge, therefore, lies in reconciling the economic interests of developers who undertake the risks of novel drug creation with a model that demands broad availability yet restricted or controlled use[11,41-44].

A revealing analysis conducted in the United Kingdom demonstrated that the incremental health benefits derived from investments in new drugs recommended by NICE (National Institute for Health and Care Excellence) in England between 2000 and 2020 were particularly significant for antibiotics when compared to drugs in other therapeutic categories, such as oncological and immunological agents. Additionally, antimicrobials yielded the greatest benefits in terms of total costs incurred (in millions of British Pounds), total quality-adjusted life years (QALYs) gained (in thousands) relative to those lost (also in thousands), and positive net health effects (thousands of British Pounds)[41]. Responsible management of new drugs is the responsibility of all prescribers and must be implemented from the moment they are introduced. This cannot be effectively achieved without Antimicrobial Stewardship Programs (ASPs) and Diagnostic Stewardship Programs (DSPs).

Optimizing access to essential antimicrobials is fundamental and requires a multifaceted approach. This includes, among other possible initiatives, promoting local drug production, establishing strategic drug banks, and actively participating in international efforts such as the Global Antibiotic Research and Development Partnership (GARDP)[45]. Exploring new models of agreements and contracts between producers and buyers is also crucial. GARDP, established by the World Health Organization (WHO) and the Drugs for Neglected Diseases initiative (DNDi), plays a key role in developing and providing innovative and effective antibiotic treatments for multidrug-resistant infections, facilitating their availability in regions or countries where these antimicrobials were previously not marketed[46].

Additional strategies to enhance access include creating a national antimicrobial fund dedicated to the centralized acquisition of essential drugs, which could generate economies of scale and more favorable pricing. Furthermore, regional collaboration through joint procurement or pricing agreements with other countries, seeking technology transfer agreements to foster lower-cost local production, and continuously strengthening cooperation with the Pan American Health Organization (PAHO) for access to technical support and drug acquisition programs, all represent vital avenues to ensure equitable and timely access to these critical therapeutic resources.

To innovate or not to innovate: is that the question?

Can new technologies assist in the search for solutions to combat antimicrobial resistance? The answer is a definitive yes. The process of identifying new targets and candidate molecules, as well as the entire preclinical and clinical development of a novel antibiotic, is notoriously slow, complex, and expensive.

New technologies, particularly artificial intelligence (AI), are already playing an increasingly predominant role in this endeavor. They not only dramatically accelerate timelines but also significantly reduce development costs. While the application of cheminformatics in drug design is not new, having begun several decades ago, the predictive accuracy of these models was insufficient until the more recent incorporation of molecular representation algorithms based on neural networks. The innovation currently available in these networks allows for the automatic learning of diverse chemical compound representations by mapping molecules into continuous vectors. These vectors are subsequently used to predict their properties. This approach decreases the cost of identifying candidate molecules by making the screening process more efficient. Concurrently, it increases the hit rate for structurally novel compounds that retain desired biological activity and reduces the time and effort required for selecting these compounds from several months or years to just a few weeks. The more focused process enables the evaluation of at least two orders of magnitude more compounds than traditional empirical screening[47-50].

Similarly, advancements in experimental structural biology are optimizing the vaccine design process, a topic we will address in detail later. This optimization is achieved by identifying specific patterns of immune response to various antigens, which helps predict relevant aspects of their immunogenicity. In this context, artificial intelligence (AI) can be integrated to accelerate vaccine development by identifying novel antigen candidates, predicting the most suitable epitopes to induce an effective immune response (known as "reverse vaccinology"), predicting peptides with affinity for HLA system antigens and Major Histocompatibility Complex Class II epitopes, designing universal prototypes, and performing predictive analysis of systemic immune responses[51-54].

Parallel to this, innovation in the development of novel therapies must be driven forward. In this regard, phage therapy is regaining significant interest, especially considering the slowdown in novel drug discovery over the past two decades. This growing interest in alternative approaches to mitigate the effects of AMR also extends to other new alternatives. Although known for over 100 years, the development of phages was overshadowed by the widespread use of antibiotics[55,56]. Phages are considered the most abundant biological entities on the planet and are used in the food industry to eliminate major enteropathogenic bacteria. Phages exhibit bactericidal effects with low influence on the intestinal microbiota, do not present cross-resistance with antibiotics, and lack tropism for mammalian cells. Furthermore, their effects could extend to other microorganisms, such as adenoviruses and *Aspergillus* spp. Their activity against biofilms suggests their potential use in treating difficult-to-resolve infections. Other potential uses include the cleaning of hospital surfaces and the sanitation of contaminated effluents. Their application in animal health opens up interesting prospects given the low environmental impact of phages. Ultimately, their applications could be broad and extensive, limited only by ingenuity and creativity. However, certain questions still persist regarding their administration, PK/PD characteristics, and safety, among others, which require further clarification[57-59] (Fig. 2).

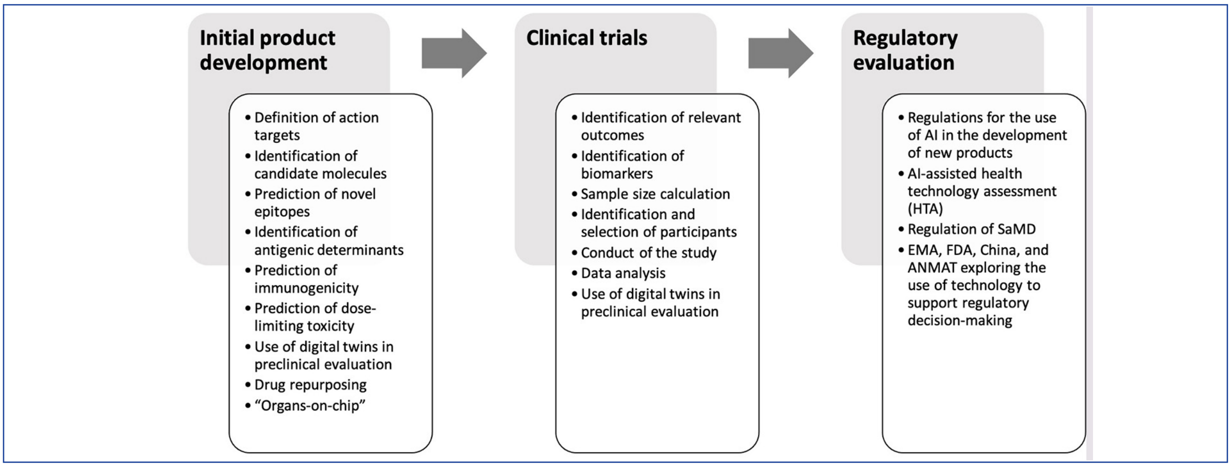
I do the programming, you do the programming, we all do the programming!

Widely recognized, Infection and Prevention Control Programs (IPC), ASP, and DSP are essential institutional strategies. Their importance lies not only in mitigating AMR and reducing associated mortality but also in lowering costs, which allows for the reallocation of resources[60,61].

A central paradox of antimicrobial resistance is that its greatest burden is felt in resource-limited countries, yet these are the very settings where proven mitigation strategies—including IPC, ASP, and DSP—are least implemented [62,66].

To initiate or optimize evidence-based strategies for reducing AMR, such as IPCs and ASPs, it's crucial to explore implementation projects that bridge the gap between recommendations and their practical application, especially in resource-limited countries. Models like GAIHN-AR or INVERA's "Brotherhood Hospitals Project" (Research in Antimicrobial Resistance) offer a path forward[62,63]. The latter is an initiative designed to reduce AMR through a multimodal strategy adapted to the specific needs of each healthcare institution, taking into account their capabilities and available resources. This strategy is based on combining ASP measures, which include implementing local treatment guidelines (based on institutional and service-specific epidemiology where the project is initiated), optimizing antibiotic dosing and duration, and monitoring anti-

Figure 2 | Applications of artificial intelligence in the different stages of biomedical product development



AI: artificial intelligence; HTA: health technology assessment; SaMD: software as a medical device; EMA: European Medicines Agency; FDA: Food and Drug Administration; ANMAT: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

microbial consumption. Additionally, it incorporates the optimization of AMR diagnosis in the pre-analytical, analytical, and post-analytical phases (DSP) and, finally, an IPC that strengthens practices to prevent the dissemination of resistant microorganisms, such as hand hygiene, and the surveillance of healthcare-associated infections (HAIs) and AMR. The synergy among ASP, IPC, and DSP strategies allows for a comprehensive approach to AMR, yielding short- and medium-term results[64].

One of the key characteristics of this project is its adaptation to local needs: with the support of institutional management and (whenever possible) local health authorities, voluntary members of the institutional team join, choose the problem to address, and the hospital sector where fieldwork will begin. A tailor-made strategy is then designed to fit the needs and resources of each participating institution[63-65]. This initiative has reported achievements such as the establishment of HAI and antibiotic consumption rates where none existed previously, the initiation of multidrug-resistant organism surveillance, a reduction in HAI rates and colonization/infection by resistant germs, the development of new treatment guidelines based on local epidemiology with strengthened AMR diagnostics, and optimized antimicrobial use with consequent cost reductions. Infection Control Committees and ASP teams have been created or strengthened, personnel have been incorporated, and the strategy has been extended to other hospital sectors. The project emphasizes close and continuous training, problem-solving throughout the project with permanent availability of INVERA's external advisory group, empowering healthcare teams, making them protagonists of their own achievements, and learning in the field how to collectively overcome the difficulties and challenges that arise during project implementation.

GAIHN-AR , for its part, is an initiative led by the EE.UU Centers for Disease Control and Prevention (CDC) that specifically focuses on detecting, preventing, and responding to AMR threats in hospitals and other healthcare facilities[62]. This global network connects healthcare institutions, laboratories, and ICP experts with defined common objectives. Its main goals are to prevent the spread of AMR in healthcare settings by optimizing IPC practices, to detect AMR threats early by strengthening laboratory capacity and surveillance, and to respond quickly and effectively to the identified threats to contain their spread. Its core strategies include improving hand hygiene, contact precautions, and environmental hygiene. Furthermore, it focuses on detecting multidrug resistant organisms in laboratories and improving communication between these and IPC teams for a timely response. In Argentina, GAIHN-AR is active, collaborating with two pilot hospitals, laboratories, the PAHO, the ANLIS-Malbrán National Reference Laboratory, and the National Institute of INE [66].

Vaccines as a complementary tool in the fight against antimicrobial resistance

The WHO, along with various other organizations and research studies, has emphasized the role of vaccination not only in preventing diseases that directly necessitate antibiotic use (e.g., pneumococcal disease, pertussis, typhoid fever) but also in reducing antibiotic use by mitigating potential complications (influenza, COVID-19, RSV) or simply decreasing unnecessary usage in scenarios where they are often employed (rotavirus disease, dengue). Over the last decade, the "effect beyond efficacy" of certain vaccines has become evident, including the prevention of cardiovascular and cerebrovascular events[6,67-72]

Furthermore, a decline in antibiotic prescriptions has been observed, particularly in pediatric, at-risk, and elderly populations, following the implementation of robust vaccination programs. The vaccines with the greatest impact in this regard are, as might be easily anticipated, those targeting the prevention of respiratory infections (influenza, pneumococcus, respiratory syncytial virus, SARS-CoV-2, *B. pertussis*). Regarding the recent licensure of the RSV vaccine in Argentina and other countries in the region, a mathematical model study estimated that (even considering an efficacy lower than that observed in clinical studies in adults) it could prevent 2 954 465 disease cases, 321 019 chest X-rays with community-acquired pneumonia (CAP), 16 660 deaths, and 1 343 915 prescribed antibiotic courses over three years. Other vaccines, such as those for varicella, rotavirus, typhoid fever, and even dengue, could also play a significant role in reducing unnecessary antibiotic use[73-82].

According to the World Health Organization report, existing vaccines could annually prevent[83]

- More than 160 million AMR-related deaths
- 9.1 million disability-adjusted life years (DALYs)
- $861 million in hospital costs
- $5.9 billion in productivity losses associated with AMR
- 142 million Defined Daily Doses (DDDs) of antimicrobials

Finally, the WHO promotes the development of vaccines for other microorganisms, especially Gram-negative multidrug-resistant bacteria (BGNMR) such as *A. baumannii, K. pneumoniae, and P. aeruginosa*, among others, with some currently in Phase II trials[84,85].

It is noteworthy that there is a lack of awareness within the medical community regarding the impact of vaccines on AMR. A recent survey conducted by INVERA among healthcare professionals from non-infectious disease disciplines revealed that 60% were unaware or did not consider that vaccines could be useful in mitigating AMR.

It is urgent to strengthen vaccine coverage globally (particularly in Argentina, whose National Vaccination Calendar, once so comprehensive and robust, has deteriorated following the SARS-CoV-2 pandemic) as a key strategy to reduce selective pressure on antimicrobials. Argentina's AMR Law (N° 27.680) and Vaccination Law (Law 27. 491) represent a strong legal framework that must be effectively implemented and overseen[36,86].

Education: a cornerstone of antimicrobial resistance control

The WHO emphasizes that prescribers and dispensers of antimicrobials must receive training from their formative or undergraduate stages. However, the issue of AMR is often not formally integrated into university curricula. Instead, it typically appears as temporary initiatives, optional courses, or non-mandatory workshops in a limited number of institutions. Furthermore, prescribers across all medical specialties, along with dentists and veterinarians, can prescribe antibiotics throughout their professional lives. Yet, this practice often isn't accompanied by a dynamic uptake of rapidly evolving knowledge regarding the appropriate use of specific drugs, the abandonment of unnecessary prescriptions, correct dosages, restricted durations, and a better understanding of older drugs, as well as the fervent need to safeguard new ones. Crucially, the tools for accurate microbiological diagnosis, essential for guiding these treatments, are also frequently overlooked[87,88].

It is vital that physicians, dentists, veterinarians, and pharmacists fully comprehend the mechanisms of AMR, local resistance patterns, updated treatment guidelines, and the critical importance of ASPs. Continuous education ensures that healthcare professionals are informed about the best prescribing practices, including selecting the correct antibiotic, determining the appropriate dose, and optimizing treatment duration. This ultimately allows them to offer patients the best possible antimicrobial treatment with the fewest adverse effects. Pharmacists play a key role in patient education when dispensing antibiotics, reinforcing medical instructions and cautioning against the risks of incorrect use. Enhanced awareness and understanding of AMR would serve as a crucial driving force for responsible prescribing and dispensing. Finally, education on AMR must extend to the agricultural production sector. It is essential to disseminate information on the appropriate use of antibiotics in animal production, aiming to avoid or significantly reduce their use as growth promoters and restricting them to necessary treatments under the supervision of veterinary professionals. This approach is critical for reducing selective pressure in this sector.

The community: lead or supporting actor?

It is striking that while efforts to mitigate AMR are broadly directed at the ultimate recipients of antibiotics (patients), the active participation of these drug recipients in preventing a potentially devastating effect on themselves is quite limited. From our perspective, this primary actor should not adopt a passive attitude when receiving antibiotics prescribed by a professional; quite the opposite. The “responsible” use of antibiotics also extends to the recipients. Obviously, we set aside critical situations where patients cannot make decisions, and scenarios where, in the prescriber’s judgment, the use of these drugs is reasonably imposed[89].

Educating the community about the AMR problem is essential for fostering awareness and understanding. Teaching what antibiotics are, when and how they should be used, and the consequence of inappropriate use is fundamental to reducing unnecessary demand and self-medication. For instance, many people are unaware that antibiotics are ineffective against viral infections such as the flu or common cold, and this is one of the most frequent reasons for inappropriate antimicrobial use in the community. An informed population is more likely to follow medical instructions, complete prescribed treatments (even if they feel better), avoid sharing antibiotics, and safely dispose of unused medications[90].

Education on AMR should encompass not only responsible antimicrobial use practices but also infection prevention measures. Hand hygiene, proper food handling, vaccinations, and infection control in healthcare settings can reduce the incidence of infections, thereby decreasing the need for antibiotics and, consequently, the selective pressure for AMR.

Several interesting initiatives, promoted by European countries among others (e.g., ReAct, E-bug), offer excellent educational materials and tools for various levels. Integrating AMR education into school and university curricula presents another challenge in this scenario. This strategy offers a valuable opportunity to equip future generations of citizens and healthcare professionals with a solid understanding of the issue and an intrinsic commitment to the responsible use of these drugs[91,92]. In this context, INVERA, in collaboration with provincial experts and local Ministries of Education and Health, launched a far-reaching educational project in early 2024. Through both in-person and virtual modalities, over 16 000 teachers from public and private sectors, covering all educational levels from early childhood to teacher training programs, received training (at the time of this manuscript’s completion). Before and after the training, a survey was conducted to assess teachers’ perceptions of AMR. Initially, “correct” concepts were observed at low or intermediate levels, reflecting the limited prior dissemination of this issue. However, after the training, a significant increase was recorded in the perception of AMR and the “One Health” approach, as well as in the understanding of the problem’s relevance and the active role teachers can play as health promoters. Most participants considered it important to include the topic in school activities and expressed strong motivation to be an active part of the response to AMR[93].

Other key stakeholders are patient communities. In the field of infectious diseases, we are not accustomed to working closely with patients suffering from chronic diseases. However, these organizations are highly proactive and interested in anything that improves their quality of life. Collaborating with them and developing joint initiatives on AMR and its effects, as well as prevention measures, can lead to a multiplying effect of responsibility and awareness[94].

Educating the public could even promote changes in public policies on AMR and optimize their implementation. An informed population could support public policies aimed at combating AMR, such as regulations on antibiotic sales. Finally, education could spark interest in AMR-related research and scientific thinking, incentivizing future researchers to seek new strategies for the prevention, diagnosis, and treatment of resistant infections.

Ten premises for responsible antibiotic use

As previously highlighted, the responsibility for antimicrobial use rests with various stakeholders: veterinarians, pharmacists, scientific societies, the general community, educators, and the media. Antibiotics are a diminishing treasure, and it is crucial to promote education and awareness regarding the problem's magnitude and the actions individuals can take. These interconnected principles lay the groundwork for what we consider responsible antimicrobial use, aligning with similar proposals[95-98]. The initial decision to initiate or withhold treatment is intertwined with the precise selection of the agent, considering its pharmacokinetics, the infection's focus, and the necessary antimicrobial spectrum. This is further complemented by individualizing the dose and administration routes based on the patient's severity and condition, as well as the de-escalation strategy and switching to oral administration (if parenteral administration was initially used) when clinical evolution permits. Treatment duration is optimized, favoring the current trend toward shorter courses in patients with good clinical outcomes[99]. This modification in prescribing patterns is solidly backed by extensive scientific evidence exploring the topic across multiple infectious scenarios. Ultimately, minimizing the adverse effects intrinsic to the use of these drugs constitutes another primary objective of ASPs.

Implementing these precepts aims to mitigate the selective pressure driving the emergence and dissemination of bacterial resistance, thereby safeguarding the utility of available antimicrobials. This involves reviewing and modifying prescribing and dispensing habits, seeking to contain associated costs without compromising care quality. Finally, the comprehensive adoption of these guidelines translates into a substantial improvement in healthcare quality and more favorable patient health outcomes, ensuring the efficacy of antibiotics for future generations[95-98]. Below, we share these 10 premises for responsible antibiotic use:

1. Make the decision to initiate or withhold antimicrobial treatment with responsibility and clinical judgment.
2. Select the drug based on its pharmacokinetic characteristics, the infection's focus, and the microorganism(s) to be covered.
3. Never forget the drainage of infection foci: often, a good surgeon is the first antibiotic.
4. Rationally choose the administration route (oral, parenteral). The parenteral route is not always superior.
5. Timely de-escalation to narrower-spectrum drugs or to the oral route.
6. Optimize antimicrobial treatment duration, adhering to the new "less is more" trends, whenever the patient's evolution allows.
7. Complete treatments according to current recommendations.
8. Involve the patient in their care by sharing potential adverse events associated with antimicrobial use.
9. Ensure that your patients do not share their antibiotics with others.
10. Do not dispose of antimicrobials in regular trash or down the drain.

Conclusion: an "epic of the day- to- day" is also possible

"The only valid hero is the 'group hero,' never the individual hero, the solitary hero."
Hector G. Oesterheld - writer and screenwriter, in the prologue to his comic "The Eternaut"

AMR is not merely a scientific or medical challenge; it is a global crisis that impacts the entire planet, indiscriminately affecting all groups and environments. An entire interconnected ecosystem is at risk, substantially affecting Latin America and Argentina, and demanding a profound shift in the culture of antimicrobial use. Transitioning from a purely "rational" approach to a genuinely "responsible" one requires empowering every societal actor, from producers to consumers, in protecting this invaluable resource. Only through coordinated action, improved access to antimicrobials, education, innovation, and the effective implementation of proven strategies, alongside concrete, audited, and sustained public policies, can we mitigate the advance of this "pandemic." This "pandemic" is no longer silent; it "shouts" dramatically in the most impoverished countries and regions.

This document serves as a call to action for everyone, right here and now. It aims to offer ideas and inspire changes in attitude: we are all part of the problem (in this case, AMR) and also an indispensable part of the solution within the community, healthcare, and the environment. From our seemingly mundane household tasks to our professional activities, whether health-related or not, we can contribute to mitigating this grave and pervasive pandemic. Ensuring a future where antimicrobials remain effective tools for human, animal, and environmental health is a mission for all, by all. Just as our INVERA group was formed in 2014, sometimes it all begins sharing a coffee, seeking models based on cooperation, reciprocity, and connection to build common and compelling visions[100].

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