

Actions to Combat Antimicrobial Resistance in Mexico: A Perspective from COFEPRIS

Acciones para combatir la resistencia antimicrobiana en México: una perspectiva desde la COFEPRIS

Alejandro E. Svarch

Head of the Federal Commission for Protection against Sanitary Risks (COFEPRIS)
asvarch@cofepris.gob.mx

Miriam Jackeline Loera Rosales

Commissioner for Evidence and Risk Management (CEMAR) at COFEPRIS
mjloera@cofepris.gob.mx

Arlet Veloz Contreras

Health Inspector-Assessor at CEMAR-COFEPRIS
aveloz@cofepris.gob.mx

Holjes Salgado Lugo

Researcher for Mexico at CONAHCYT
holjes.salgado@conahcyt.mx

Liliana Esmeralda Reyes Vázquez

Health Inspector-Assessor at CEMAR-COFEPRIS
lereyes@cofepris.gob.mx

Rosa Camacho Sandoval

Researcher for Mexico at CONAHCYT
rosa.camacho@conahcyt.mx



Abstract

In this article the most important data on antimicrobial resistance (AMR) is presented to enable an understanding of the importance of this global problem. The main strategies implemented at the international and national level to respond to, monitor and reduce this so-called “silent pandemic” are also addressed. In addition, the contribution of COFEPRIS, the National Regulatory Agency that provides transversal support to the national strategy to combat AMR in Mexico, is described. The article concludes with one of the most significant achievements in the health sector that has successfully reduced antibiotic consumption.



Resumen

En este artículo se exponen los datos más relevantes sobre la resistencia a los antimicrobianos (RAM), los cuales permiten comprender la importancia de esta problemática mundial. También se abordan las principales estrategias implementadas a nivel internacional y nacional para cuidar, vigilar y reducir esta “pandemia silenciosa.” Además, se describe la contribución de la COFEPRIS, la agencia reguladora nacional que coadyuva de forma transversal en la estrategia nacional para combatir la RAM en México, y se finaliza con uno de los logros más relevantes en el sector salud que consiguió disminuir el consumo de antibióticos.



Keywords

Antimicrobials, resistance, AMR, COFEPRIS, regulation, ENARAM



Palabras clave

Antimicrobianos, resistencia, RAM, COFEPRIS, regulación, ENARAM

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*Alejandro E. Svarch, Miriam Jackeline Loera Rosales,
Arlet Veloz Contreras, Holjes Salgado Lugo,
Liliana Esmeralda Reyes Vázquez
and Rosa Camacho Sandoval¹*

Antimicrobial resistance: a global risk

To understand the problem of antimicrobial resistance (AMR), it is necessary to know what the substances used to treat infectious diseases are, and how they act. *Antimicrobials* are natural or synthetic compounds (antibiotics, antifungals, antivirals, antimalarials, or anthelmintics, among others) that act against microorganisms (bacteria, fungi, viruses and parasites), destroying them or inhibiting their growth; they are used to prevent and treat infections in humans, animals and plants.

AMR occurs when microorganisms find ways to survive and acquire the capacity to adapt to their environment naturally.² This allows the microorganism to survive the effect of the drug that treats the disease it causes,

¹ The authors thank Mariana Berenice Santillan Cruz, Claudia Tzompantzin Hernández, Yoab Yael Hernández Luna, Noemi Lugo Maldonado and Carlos Eduardo Garnica of the Commission of Evidence and Risk Management for their comments and suggestions on the manuscript.

² National Service for Health, Safety and Quality of Agricultural and Food Products (SENASICA), *Plan estratégico contra la resistencia a los antimicrobianos (RAM) 2023-2024*, Mexico, SENASICA-Ministry of Agriculture and Social Development, 2023, at https://www.gob.mx/cms/uploads/attachment/file/847156/Plan_Estrategico_RAM_VF.pdf (date of access: May 22, 2024).

and even to reproduce at concentrations higher than therapeutic doses,³ leading to its inefficacy. The most notable causes of AMR and its accelerated increase include the indiscriminate and inappropriate use of antimicrobials, the widespread use due to a high incidence of diseases caused by microorganisms, and self-medication.

In addition to the above, AMR has a considerable cost for countries' economies and health systems. Globalization has encouraged the easy spread of resistant microorganisms and, consequently, a global economic impact is expected with economic losses of around USD 100 billion,⁴ as the cost of health care increases due to ineffective medications, longer hospital stays, and hospital-acquired infections.⁵ Similarly, the World Health Organization (WHO) has estimated that 15% to 20% of hospital budgets are spent on treating complications related to AMR.⁶

The WHO estimates that more than 85% of global mortality is due to acute respiratory infections, diarrheal diseases, measles, AIDS, malaria and tuberculosis.⁷ These require the use of antimicrobials for their treatment. Currently, the agents causing these diseases present resistance of up to almost 100%, which significantly affects their treatment.

In 2019, an estimated 4.95 million deaths worldwide were related to multidrug-resistant bacteria (resistant to multiple antibiotics), of which 1.27 million were directly attributable to AMR.⁸ It is estimated that by 2050 there will

³ WHO, *WHO's Global Strategy for Containment of Antimicrobial Resistance*, Geneva, WHO, 2001, p. 15, at https://iris.who.int/bitstream/handle/10665/66860/WHO_CDS_CSR_DRS_2001.2.pdf (date of access: May 22, 2024).

⁴ Pan American Health Organization, "Operational Research to Tackle Antimicrobial Resistance," in *Revista Panamericana de Salud Pública*, April 19, 2023, at <https://journal.paho.org/en/special-issues/operational-research-tackle-antimicrobial-resistance> (date of access: May 22, 2024).

⁵ WHO, *op. cit.*, p. 11.

⁶ WHO, *Safety of Medicines, A Guide to Detecting and Reporting Adverse Drug Reactions. Why Health Professionals Need to Take Action*, Geneva, WHO, 2002, p. 7, at https://iris.who.int/bitstream/handle/10665/67378/WHO_EDM_QSM_2002.2.pdf (date of access: May 22, 2024).

⁷ WHO, *WHO's Global Strategy...*, p. 1.

⁸ Yameli Celis, German Esparza, Rony Zachariah and Freddy Pérez, "Operational Research to Strengthen Evidence-Based Interventions to Tackle Antimicrobial Resistance in the Region of the Americas," in *Revista Panamericana de Salud Pública*, vol. 47, special issue, April 2023, e78, p. 1, at <https://doi.org/10.26633/RPSP.2023.78> (date of access: May 22, 2024).

be more deaths related to AMR than to cancer. This could get worse if nothing is done to combat it.⁹

In the same year, approximately 84 300 deaths were estimated as attributable to AMR in Latin America and the Caribbean.¹⁰ In Mexico, various issues related to the inappropriate use of antimicrobials have been identified, such as incorrect prescription and the growing trend towards the use of broad-spectrum antibiotics. In addition, an increase in AMR to microorganisms causing common infections and the manifestation of hospital outbreaks caused by multi-resistant bacteria have been reported.¹¹

There is no question that AMR constitutes a serious problem and challenge to public health, one that requires the attention and collaboration of different sectors and stakeholders in society. In this regard, work has been done on developing various strategies to mitigate its impact. On the one hand, in response to the resolutions of the World Health Assembly WHA37.33 (1984),¹² WHA51.17 (1998)¹³ and WHA54.14 (2001),¹⁴ in 2001, WHO's Global Strategy for Containment of Antimicrobial Resistance was established, focusing on surveillance, strengthening and standardizing detection methods.¹⁵ Subsequently, a panoply of projects

⁹ Luis Arturo Camacho Silvas, "Resistencia bacteriana, una crisis actual," in *Revista Española de Salud Pública*, vol. 97, March 20, 2023, e202302013, p. 7, at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10541255/pdf/1135-5727-resp-97-e202302013.pdf> (date of access: May 22, 2024).

¹⁰ Y. Celis, G. Esparza, R. Zachariah and F. Perez, *op. cit.*, p. 1.

¹¹ Patricia Rodríguez-Zulueta, *et. al.*, "First Outbreak of KPC-3-Producing *Klebsiella pneumoniae* (ST258) Clinical Isolates in a Mexican Medical Center," in *Antimicrobial Agents and Chemotherapy*, vol. 57, no. 8, Aug. 2013, pp. 4086-4088, at <https://doi.org/10.1192/bjpo.bp.115.001321> (date of access: May 22, 2024).

¹² 37th World Health Assembly, "Rational Use of Drugs," WHA37.33, 17 May 1984, at https://iris.who.int/bitstream/handle/10665/200087/WHA37_R33_eng.pdf (date of access: May 23, 2024).

¹³ 51st World Health Assembly, "Emerging and Other Communicable Diseases: Antimicrobial Resistance," WHA51.17, May 16, 1998, at <https://iris.who.int/bitstream/handle/10665/79863/ear17.pdf> (date of access: May 23, 2024).

¹⁴ 54th World Health Assembly, "Global Health Security: Epidemic Alert and Response," WHA54.14, 21 May 2001, at https://apps.who.int/gb/ebwha/pdf_files/WHA54/ea54r14.pdf (date of access: May 23, 2024).

¹⁵ WHO, *WHO's Global strategy...*

and collaborative actions were created to respond to, monitor and reduce this “silent pandemic.”¹⁶

On the other hand, there is the principle of “One Health”,¹⁷ which has a multifactorial approach that brings together different sectors and stakeholders involved in the health of humans, animals, plants, food production and the environment. This is intended to foster collaboration and the creation of programs, policies, legislation and research with better results.

In Mexico, guidelines have been established to respond to this problem and, consequently, the National Strategy for Action against Antimicrobial Resistance (ENARAM) was published in 2018, and modified in 2022.¹⁸ The strategy is mandatory and establishes five broad objectives, as well as various lines of action aimed at controlling, reducing or eliminating the risks posed by AMR (see Figure 1).

It is important to note that this strategy is not limited to monitoring and protecting human health, but also animal health, food production and the environment, due to the complexity involved in the propagation and dissemination of microorganisms. Antimicrobial-resistant microorganisms can be present in people, food, plants, as well as in water, soil and air and can move from one environment to another relatively easily. The main way of spreading to humans is through food.

¹⁶ WHO, *Global Action Plan on Antimicrobial Resistance*, Geneva, WHO, 2016, at <https://iris.who.int/handle/10665/193736> (date of access: May 22, 2024); and WHO, Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (WOAH), *Antimicrobial Resistance and the United Nations Sustainable Development Cooperation Framework. Guidance for United Nations Country Teams*, Geneva/Rome/Paris, WHO/FAO/WHOSA, 2021, p. 1, at <https://www.woah.org/app/uploads/2021/10/unsdcf-amr-guidance-en-final-approved.pdf> (date of access: May 22, 2024).

¹⁷ WHO, “WHO Urges Investing in ‘One Health’ Actions for Better Health of the People and the Planet,” press release, November 3, 2023, at <https://www.who.int/news/item/03-11-2023-who-urges-investing-in-one-health-actions-for-better-health-of-the-people-and-the-planet> (date of access: May 22, 2024).

¹⁸ Consejo de Salubridad General, “Acuerdo por el que se declara la obligatoriedad de la Estrategia Nacional de Acción contra la Resistencia a los Antimicrobianos,” *Diario Oficial de la Federación*, June 5, 2018, first section, pp. 70-91; and Consejo de Salubridad General, “Acuerdo que modifica el Anexo Único del diverso por el que se declara la obligatoriedad de la Estrategia Nacional de Acción contra la Resistencia a los Antimicrobianos, publicado el 5 de junio de 2018,” *Diario Oficial de la Federación*, November 9, 2022, pp. 15-31.

Figure 1. Background and objectives of ENARAM and actions implemented by COFEPRIS



In addition to this, there are practices in different fields that, unintentionally, also contribute to the presence and transmission of AMR. A couple of examples: the veterinary application of antibiotics, as a preventive measure to avoid losses of animals for consumption, and the application of fungicides and/or bactericides to crops, as a way of protecting them from pests. These measures have a negative impact because the regular application of these compounds generates resistance in the microorganisms that may be present, and they reach people via the subsequent consumption of these foods.

Another way of spreading these microorganisms to people, animals and food is exposure through contaminated water. Water is widely used in agriculture and is a vital resource, which makes it one of the main risk factors for contamination and spread. Monitoring it is one of the most important actions in controlling AMR.

This gives rise to the importance of a unified multi-sectoral approach to AMR. In Mexico, efforts are being made by the different departments and entities of the federal public administration to ensure that prevention, reinforcement and research into AMR are carried out in accordance with their responsibilities.

The Federal Commission for Protection against Sanitary Risks (COFEPRIS) is responsible for the regulation, control, promotion and surveillance of sanitary risks to protect the health of the population and is one of the primary institutions that deals with human, animal and environmental health in a cross-cutting manner. One of the main tasks of COFEPRIS is the prevention of diseases caused by pathogens, thereby helping to reduce the risk of developing AMR. Key prevention actions we can highlight include:

- Monitoring the quality of the water for human use and consumption distributed through supply systems. The Commission is responsible for ensuring that the water that reaches homes meets the bacteriological and physicochemical quality requirements to avoid damage to health and, where appropriate, to identify or prevent related health risks. The risks include the transmission of diseases caused by infectious agents.
- Monitoring the sanitary conditions of food. Inspection visits are carried out at food service establishments to ensure that they comply with the minimum requirements of good hygiene practices and to

prevent contamination throughout their processes and the spread and transmission of diseases caused by the presence of toxic or pathogenic agents in food.

- Strengthening regulation of the quality and safety of medicines and vaccines. Regulatory frameworks for the regulation of these products are produced or updated. For example, COFEPRIS carried out the harmonization and implementation of international guidelines such as those of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).
- Participation in the regulation and sanitary control of the supply and production chain of medicines for human use and establishing surveillance, training and awareness-raising strategies with pharmacists.
- Participation in the working groups of the Interinstitutional Command for the Health Sector (COISS), made up of different public institutions in the health sector that work to generate strategies to prevent risks in establishments related to medicines, such as pharmacies, hospitals, clinics, and laboratories.

It is important to mention that, even before the publication of the ENARAM, the Ministry of Health had already begun work aimed at containing AMR. One example of a strategy implemented to improve the use of antibiotics was the regulatory policy of only selling antibiotics with a medical prescription, starting in 2010. It is important to note that the success of strategies is related not only to the way they are executed, but also to whether they are based on a relevant and up-to-date scientific basis. Likewise, it is imperative to use scientific processes and methodologies that allow us to assess, as accurately as possible, the magnitude of health risks in order to choose the most appropriate prevention, precaution and/or mitigation measures.

Risk assessment for regulatory decision making

As mentioned, AMR is a multifactorial problem that requires a coordinated response in order to address its root causes and mitigate its impacts on public health. Over the past decade, important work has been developed

and made available internationally regarding the use of risk assessment and analysis to address this issue.¹⁹

Risk analysis is a tool that allows us to identify the cause of adverse or harmful effects and to select the measures to control them, in order to protect health. This analysis consists of three distinct but closely linked components: risk assessment (the determination of the likelihood of harm occurring and the magnitude of that harm), risk management (the process of evaluating, selecting and implementing alternatives to mitigate risks, in light of the risk assessment), and risk communication (the exchange of information and opinions related to hazards and risks among interested parties).²⁰

Risk assessment is the central scientific element of a risk analysis, since the rest of the components are built upon it. Generally, it consists of four elements: hazard identification, hazard description, exposure assessment, and risk description.

In Mexico, COFEPRIS has the power to evaluate, manage and communicate health risks. Within this institution, the Commission of Evidence and Risk Management (CEMAR) identifies and evaluates health risks in its competent areas, proposes options for their management, and issues prevention and control measures of a regulatory and non-regulatory nature in order to ultimately establish, together with the other commissions and departments, surveillance and monitoring actions.

¹⁹ See WHO, FAO and WOAH, *Taking a Multisectoral, One Health Approach—A Tripartite Guide to Addressing Zoonotic Diseases in Countries*, Geneva/Rome/Paris, WHO/FAO/WOAH, 2019, at <https://www.woah.org/app/uploads/2021/03/en-tripartitezoosesguide-webversion.pdf> (date of access: May 23, 2024); Terrestrial Animal Health Code, Chapter 6.10. Risk analysis for antimicrobial resistance arising from the use of antimicrobial agents in animals, at https://www.woah.org/fileadmin/Home/eng/Health_standards/tahc/current/chapitre_antibio_risk_ass.pdf (date of access: May 23, 2024); and Codex Alimentarius, “Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance,” CXG 77-2011, 2021, at https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252Fstandards%252FCXG%2B77-2011%252FCXG_077e.pdf (date of access: May 23, 2024).

²⁰ FAO and WHO, *Codex Alimentarius Commission. Procedural manual*, Rome/Geneva, FAO/WHO, 2022, at <https://openknowledge.fao.org/items/dfc93e42-67f3-4de9-9dad-b33fb1600b32> (date of access: May 23, 2024); and WHO, *WHO Human Health Risk Assessment Toolkit. Chemical Hazards*, 2.a ed., Geneva, WHO (Harmonization Project Document No. 8), 2022, at <https://www.who.int/publications/i/item/9789240035720> (date of access: May 23, 2024).

In the context of AMR, work has mainly focused on identifying hazards associated with AMR. For this reason, applicable regulations have been strengthened, particularly those concerning antibiotics, as well as the monitoring of sources of exposure to resistant microorganisms, such as water for human use and consumption. However, it is important to remember that this is a multidisciplinary issue, which is why COFEPRIS works together with other competent authorities in order to mitigate the risks to the population.

Finally, it is important to base decision-making on risk assessment because it allows for the establishment of appropriate strategies to prevent, control or mitigate the risks that arise and, consequently, ensure effective, efficient, timely, integrated, and equitable decisions that are aligned with national and international goals, objectives and initiatives.

Actions to prevent AMR: dispensing of antibiotics

In Mexico, in 2010, due to the high consumption of antibiotics as a result of the AH1N1 influenza epidemic, the Ministry of Health issued an emergency measure to combat the increase in complications of infectious diseases,²¹ controlling the supply of these drugs to ensure they were only made available with a medical prescription. This avoided self-prescription, inappropriate use and the development of resistance. COFEPRIS, within its sphere of competence, was responsible for ensuring the implementation of this measure.

This was a significant step in the health sector in regulating the sale of antibiotics, contributing to a reduction in the level of consumption of these drugs. The use of antibiotics involves the participation of doctors who prescribe them, the people in charge of the establishments that dispense them, the patients who consume them, and the regulatory environment that regulates them.

²¹ Ministry of Health, “Acuerdo por el que se determinan los lineamientos a los que estará sujeta la venta y dispensación de antibióticos,” *Diario Oficial de la Federación*, vol. DCLXXX, no. 1827, May 2010, second section, pp. 6-7.

In order to strengthen this regulatory framework, an analysis of the scientific evidence was carried out within COFEPRIS to identify the risks of the inappropriate use of antibiotics (see Figure 2) and, together with the committee of experts, the decision was made to include the chapter “Control of Antibiotics” in the sixth edition of the *Supplement for Establishments Dedicated to the Sale and Supply of Medicines and Other Health Consumables* of the Pharmacopoeia of the United Mexican States (FEUM).²²

This chapter addresses the health requirements that must be met for the sale and dispensing of antibiotics. It specifies that pharmacies must operate a Standard Operating Procedure (SOP) on the control of antibiotics, which includes the acquisition, sale, supply and dispensing, and entry and exit records of antibiotics. They must also consecutively register and safeguard medical prescriptions and make them available to COFEPRIS. Regarding hospital pharmacies, it is emphasized that antibiotics must be prescribed by a physician and there must be a SOP that specifies the distribution process of these medications at the hospital level.

This was a step forward in improving the dispensing of antibiotics to the community. However, in a hospital setting the use of these drugs is intensive and, since highly vulnerable patients are present, there is a potential risk of resistant pathogenic microorganisms appearing. This means it is necessary to promote programs for the proper management and use of antimicrobials in the hospital sector.

In this regard, COFEPRIS continues to work, through CEMAR, on the appropriate use of antimicrobials so that, in coordination with other commissions, departments or institutions, strategies continue to be generated to combat AMR. In relation to their use in hospitals, the aim is to generate strategies that make it possible to optimize the use of antimicrobials, reducing the incidence and spread of healthcare-associated infections (HAIs) and linking therapeutic decisions with the supply of the medication, as well as carrying out adequate and continuous monitoring.

²² FEUM, “Capítulo 20. Control de antibióticos,” in *Suplemento para establecimientos dedicados a la venta y suministro de medicamentos y demás insumos para la salud*, 6th ed., Mexico, Ministry of Health-FEUM, 2018, pp. 219-224.

Figure 2. Example of the process of actions taken to control the sale and dispensing of antibiotics.



Final considerations

Effective antimicrobials are essential to combat life-threatening diseases and to ensure that procedures such as surgery and chemotherapy are carried out with low risk. However, the misuse and abuse of these drugs have put everyone at risk due to the emergence of AMR.

We must bear in mind that when we talk about AMR we are not only referring to direct consequences for human health, but also the threat to the health of animals and plants used in food manufacturing, which impacts

food safety and the environment. There are many social and environmental factors that contribute to the accelerated generation of resistant microorganisms and their spread; these include a lack of awareness and education regarding the risks of AMR and the appropriate use of antimicrobials.

While it is true that antibiotic resistance has been given greater emphasis recently, it should be noted that AMR is a broader term that involves not only antibiotics, but also drugs used to treat viral, parasitic and fungal diseases. To bring AMR to a halt, it is essential to develop and follow clear and solid strategies at global, regional and local levels that have an impact on society and obtain results in the short and medium term.

Furthermore, the fact that decisions are based on a risk assessment allows AMR strategies to be directed, taking into account all the information available in this regard to ensure that results are aligned with the stated goals and objectives. This favors the adoption and implementation of good regulatory practices and ensures that decision-making is based on technical and scientific evidence.

While the guidelines set out in the global framework are clear and often robust, countries still face major challenges in adopting the vast majority of the objectives established, despite investments in time, infrastructure and economic sustainability. In Mexico, although these guidelines have been adopted it is necessary to continue actions to combat AMR, aligned with ENARAM, in order to protect the health of the country's population.