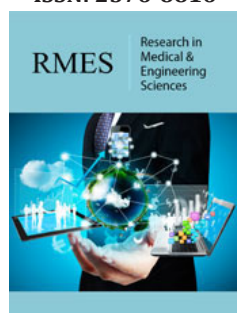


Human and Structural Factors Influencing the Control of Antimicrobial Resistance

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Abstract

Despite global efforts, antimicrobial resistance (AMR) has not been controlled. In 2024, the World Health Organization (WHO) updated its list of priority pathogens to include 15 families of resistant bacteria (critical, high, and medium). Today, the development, transmission, and spread of AMR remain uncharacterized, so the human and structural factors specific to each region that influence its control must be intensified and identified. Annually, 5 million people die from AMR, a number that will increase by 2030, with annual costs to health care and its management potentially reaching 412 billion USD. Unfortunately, it is common to prescribe antibiotics without microbiological studies, ignoring the adverse effects on the patient. A group of experts participated in the identification of 40 human health research priorities (WHO), which include global perspectives in low- and middle-income countries (LMICs). It is estimated that 40% of hospitalized patients receive antibiotics at some point, many of them unnecessarily, generating selective pressure for AMR. In Mexico, previous studies by our group reported an increase in multidrug resistance (MDR), extended-drug resistance (XDR), and pan-drug resistance (PDR), with 69% of gram-positive isolates having shown MDR, XDR or PDR. In fact, two cases of *Pseudomonas aeruginosa* from neonatal intensive care units showed PDR.

An incomplete infrastructure, economy, and education system, as well as inappropriate training, cultural barriers, and uneven policies, contribute to AMR spread. The WHO points out that in developed countries, patients have a 50% adherence to treatment for chronic diseases, this being lower in developing countries. Thus, improving adherence to and proper use of antibiotics is a challenge for the global health system. Countries must implement national action plans (NAPs) and improve global coordination among governments, industries, and public and private organizations, providing resources for expert training and research

Keywords: Antimicrobial resistance; Priority bacterial pathogens; Healthcare-associated infections; Multi-drug resistance; Extended drug resistance; Pan-drug resistance; MDR; PDR; XDR

Abbreviations: AI: Artificial Intelligence; AMR: Antimicrobial Resistance; DHT: Digital Health Technology; FAO: Food and Agriculture Organization; GARDP: Global Antibiotic Research & Development Partnership; HAI: Healthcare-Associated Infections; IAHC: Infections Associated with Health Care; LMIC: Low- and Middle-Income Country; LPS: Lipopolysaccharides; MDR: Multi-Drug Resistance; mNGS: Metagenomic Next-Generation Sequencing; NAPs: National Actions Plans; PDR: Pan-Drug Resistance; PCR: Polymerase Chain Reaction; SDGs: Sustainable Development Goals; UHC: Universal Health Coverage; UK: United Kingdom; UN: United Nations; WHO: World Health Organization; WOA: World Organisation for Animal Health; XDR: Extensively Drug Resistant

Introduction

Despite global efforts to study and contain antimicrobial resistance (AMR) among bacteria, fungi, viruses, and parasites, as well as collaborative initiatives among the World Health Organization (WHO), Food and Agriculture Organization (FAO), and the World Organisation

for Animal Health (WOAH), with guidance documents on action plans to combat AMR in different countries, its incidence has increased significantly [1,2]. The One Health initiative, integrated by WHO, includes, among others, global, regional, and national efforts to combat AMR, with the aim of intensifying the global effort to build a healthier world based on equity, leaving no one behind [3,4]. In May 2024, WHO presented a list of 24 priority pathogens that includes 15 families of antibiotic-resistant bacteria classified into three categories (critical, high, and medium) [5]. In recent years, numerous publications have reported and warned about the increase in AMR, with world experts in agreement that it represents a threat to human health worldwide [6].

Today, due to the number of factors involved and their individual complexities, the development, transmission, and spread of AMR has not been specifically characterized. In response, international efforts and calls are being made to redouble actions to contain its development using different strategies [7,8]. The number of deaths caused by AMR infection, as reported before the COVID-19 pandemic, was 1.27 million people, a number higher than that caused by other endemic infections around the world, and deaths were particularly prominent in low- and middle-income countries (LMICs) [8].

In each country, it is necessary to intensify the identification of the human and structural factors specific to each region that influence the control of AMR, a task involved in the creation of an action model to be implemented in each, in accordance with recommendations of international instances. This will enable regions to overcome more effectively the actions that have been carried out until now in response to the challenges imposed by AMR and its consistent and dangerous threat to the health of the world population.

Overview and global perspective

Five million deaths are associated with AMR annually, and these numbers are projected to increase [8] and by 2030, such that additional yearly costs of medical care and treatment required for AMR bacterial infections could reach up to 412 billion USD [4].

In the United Kingdom (UK) and countries such as Ireland, the “Start smart then focus” tool is available for hospital care, which includes optimal antibiotic prescribing based on the following points: making the right diagnosis, using the right drug at the right dose for the correct duration, and applying therapy aimed at reducing or broadening the spectrum, stopping or transitioning to oral antimicrobials, and finally eliminating or at least controlling the infection’s source [9].

Another important global problem nowadays is the burden of disease generated by the SARS-CoV-2 coronavirus pandemic, which has disrupted life in different areas, mainly in terms of coexistence, the economy, and health. Due to disease characteristics, superinfections, similarities in clinical manifestations, the indiscriminate use of antibiotics, and the lack of knowledge of this new pathogen, negative consequences in treatment have been

identified. In addition to AMR, which has forced all health systems on high alert, strains have emerged that present multi-drug resistance (MDR) and pan-drug resistance (PDR) among common bacteria and, undoubtedly, in viruses, parasites, and fungi. Patients with COVID-19 presented concomitant nosocomial infections, especially individuals with such comorbidities as diabetes, as is the case of *Acinetobacter baumannii* infection-based MDR and other community-acquired bacteria, in addition to such MDR fungi as *Candida aureus*, which requires an antimicrobial combination and synergy, highlighting the importance of communication among physicians, laboratory technicians, epidemiologists, and infectious disease specialists to address increasing AMR efficiently. Lower respiratory tract infections accounted for more than 1.5 million resistance-associated deaths in 2019, and AMR is now a leading cause of death worldwide, with the highest burdens in low-resource settings [7,10].

Human factors

Social exclusion in diagnosis: Social exclusion in health is a global problem that limits equitable access to essential health services. At the global level, efforts to address social exclusion include integrating health into the United Nations (UN) Sustainable Development Goals (SDGs) and promoting universal health coverage (UHC). However, studies suggest that progress is slow due to a lack of adequate investment, fragmented policies, and systematic discrimination [11]. Social exclusion in diagnosis refers to practice limiting access to timely infections diagnosis across the population, especially in low-resource countries. This includes the use of new technological laboratory tests, such as nucleic acid analysis, among which the most notable are multiplex polymerase chain reaction (PCR) assays or next-generation metagenomic sequencing (mNGS), whose sensitivity, specificity, and positive and negative predictive values are significantly higher than those of traditional microbiological cultures [12].

Culture, beliefs, values, and attitudes: Antibiotic prescribing may be influenced by physicians’ cultural beliefs and attitudes. In the face of diagnostic uncertainty, the prevailing notion is that antibiotic administration is necessary to protect the patient from deterioration or immediate harmful consequences, as in surgical prophylaxis, and to protect physicians from possible ethical, legal, and reputational consequences, particularly for indicating an inadequate treatment. A common practice is to prescribe antibiotics even before knowing the results of the microbiological culture and the antibiogram, regardless of the consideration of possible adverse effects on patients. The definition of authority and the responsibilities among the medical staff of a hospital can also influence the prescription of antibiotics, as it has been documented that it is common for younger physicians to avoid questioning the decisions of their superiors [9,13].

Experts in antimicrobial resistance: A group of experts from different research domains, AMR areas, geographic representations, income settings, and populations participated in the identification of 40 WHO research priorities for AMR in human health from both

global and low- and middle-income countries' (LMIC) perspectives that are recommend to be undertaken between now and 2030. Among these, 33 priorities include: drug-resistant bacterial and fungal infections, specifically research on prevention, diagnosis, treatment, and care and such general topics as awareness, education, policies, and regulations [14]. What is worrying is that in several countries among all geographic regions, no AMR experts were found, at least with the criteria established by the WHO to form the group. It is therefore necessary that this information be considered, as the lack of experts, especially in LMICs, is a human factor that undoubtedly and significantly affects the establishment and monitoring of AMR control strategies.

Structural factors

Hospital committees for nosocomial infections: In hospitals, antimicrobials are among the most frequently prescribed medications, and it is estimated that up to 40% of patients receive antibiotics in the hospital at any time. Further, it is recognized that some of these prescriptions are unnecessary and generate significant selective pressure for the emergence of resistance [15], hence the need for Multidisciplinary Nosocomial Infection Committees in hospitals that include the participation of the medical director, those responsible for Investigation and Development (I+D) and for infection control programs, epidemiologists, laboratory personnel (microbiology area), pharmacists, and those responsible for quality control. These committees apply international standards, procedures, criteria, and recommendations through clear and effective communication among all professionals involved, which allows, based on local evidence, the categorization of microorganisms as susceptible or resistant to antibiotics and treatment regimens, considering international experiences [16], and the identification the antibiotics that the hospital pharmacy should keep and the specific needs of each patient. Consequently, these committees decide with greater certainty the most suitable antibiotics to be used in each case; establish treatment regimens, maximum doses, and maximum treatment times for first-line antibiotics before using new-generation or latest-frontier antibiotics, thus avoiding PDR promotion-as it must be considered that new antimicrobial molecules are not designed and developed as quickly as required and, of course, reducing the risk of healthcare-associated infections (HAIs).

Access to drugs and health products: There are difficulties in accessing appropriate antibiotics in some public hospitals, especially if they are not included in the so-called basic institutional list, whether due to policies or budget, consequently leading to incomplete treatments. Currently, difficulties and delays in the implementation of new or updated regulations that have been evaluated, such as the example of the new European regulations on medical devices and *in vitro* diagnostics, represent an additional challenge in accessing medicines and medical devices in LMICs, necessitating effective regulatory solutions more urgently than before [15].

Information and notification networks: The lack of accurate

information and evidence-based data on the prevalence and burden of disease prevents reliable estimates of AMR, especially in settings with inadequate laboratory capacity and data notification systems, such as in several LMICs [14]; hence, there is a need to implement effective and complete information recording systems, as well as adequate supervision, to ensure information is not omitted in a timely manner, such as in increasingly accessible systems that use artificial intelligence (AI).

Challenges in low- and middle-income countries: In Mexico, AMR is evolving. In a retrospective study conducted by our group during 2016 to 2019 in a tertiary hospital in Mexico, an increase in MDR, extended-drug resistance (XDR), and PDR was found, with 69% of gram-positive isolates showing MDR, XDR, or PDR and *Staphylococcus epidermidis* being the most frequently isolated Gram-positive bacteria with MDR. *Escherichia coli* and *Klebsiella sp.* were also found among the most frequent MDR Gram-negative bacteria. In two cases, clinical isolates of *P. aeruginosa* isolated from the neonatal intensive care unit showed PDR [17]. In another study, 56% and 44% of isolates were found to be Gram-negative and Gram-positive, respectively. Significant risk factors were: 1) Length of hospital stay; 2) Previous use of antibiotics; 3) Nosocomial infection; 4) Use of antibiotics for more than 10 days; 5) Use of two or more antibiotics; and 6) Co-infection, with each of the last four being an independent risk factor for bacterial infection and MDR [18].

In 2010, the National Health Council of Mexico issued an agreement suspending the free sale of antibiotics without a prescription in all pharmacies in the country, a measure that was not well received by the pharmaceutical industry [19]. However, the free sale and consumption of antibiotics is still ongoing, to a lesser extent, from consulting rooms in pharmacies, and worse, without control over time and form. As in many countries, inappropriate therapeutic adherence has also been observed [19].

In these times of a troubled global economy, LMICs should be given greater access to quality review and availability of *in vitro* diagnostic devices by expanding the WHO prequalification program to provide access to safe, high-quality, and effective medical products. To this end, public policies should be implemented that promote direction toward regulation and number of medical products in use by the Working Group on Global Harmonization. In some countries, regulations, requirements, and costs generate "social exclusion in diagnosis" by not giving the entire population access to diagnostic tests using new technology, as occurred during the H1N1 and COVID-19 pandemics [20,21].

Discussion

In recent years, the global adoption of digital health technology (DHT) has increased. In 2022 particularly, the global digital health market was valued at US\$ 211 billion, with an annual growth rate of 18.6%. However, global imbalances in access to DHT are also reported, and poor data quality persists between regions, with untimely management and control and a decrease in scientific

evidence, especially in LMICs. Incomplete infrastructure, little financial support, inappropriate education and training, and uneven cultural and political barriers are highlighted. Even further, given the dissimilar conditions around the world, it is estimated that there will be an increase in global inequalities in the access to and quality of data [22-24].

Thus, it is necessary to question how many pediatric cases are not studied appropriately due to the different factors mentioned related to education, training and resources, and the masking of clinical manifestations associated with a variable severity spectrum of signs and symptoms due to infection in children, which leads to inadequate use of antibiotics and underreporting due to a lack of data management. Such is the case with Pediatric Multisystem Inflammatory Syndrome, which occurred during the last pandemic and generated, in addition to deaths, short, medium, and long-term sequelae; a lack of timely diagnosis; decreased quality of life; and increased years of life with disability [25].

Several rigorous studies and analyses, especially those published by WHO, have revealed that in developed countries, treatment adherence by patients with chronic diseases is only 50%, and available data indicate that compliance is even lower in developing countries. Improving adherence and proper use of medicines is one of the major challenges facing the global health system. According to WHO data, lack of therapeutic adherence causes thousands of premature deaths annually in each country and produces prohibitive costs for the family economy and for each National Health System. Non-compliance with antimicrobial treatment is one of the main causes of or reasons for not obtaining all the benefits of antibiotics, promoting the generation of AMR both in hospitals and in community bacterial resistance [26].

Furthermore, in many countries, antibiotics can be purchased without a prescription, facilitating their misuse in both humans and animals. This includes overdosing, underdosing, and inappropriate use in livestock and agriculture. In addition, it should be considered that both health professionals and the general population often lack knowledge about the impact of inappropriate use of antimicrobials and the need to adhere to best practices in administration and teaching, through educational programs at universities in all related areas of knowledge.

The global burden of AMR must be comprehensively addressed by allocating appropriate resources and making informed, region-specific policy decisions in all countries. Infection prevention and control programs, access to essential antibiotics, and investigation and development (I+D) of new vaccines and antibiotics [7] should be strengthened, as well as education and outreach programs on the main pathogen-drug combinations; and to further explore recent findings on the relationship between plasma levels of lipopolysaccharides (LPS) and AMR in Gram-negative bacterial infections [27,28].

G20 countries have agreed since 2017 to strengthen the implementation of National Actions Plans (NAP) in line with the One Health approach, which integrates human, animal, and

environmental health. They highlighted the importance of reducing the misuse and sale of antimicrobials without a prescription, particularly in veterinary medicine and agriculture, and they promoted investment in new antibiotics, rapid diagnostics, and therapeutic alternatives, stressing the need for global collaboration to share information and develop capacities in countries with fewer resources [24]. Initiatives such as SECURE, led by the WHO and the Global Antibiotic Research and Development Partnership (GARDP), are being implemented to expand access to critical medicines. In addition, the Industry Alliance against AMR has documented advances in I+D, diagnostic support, and antimicrobial stewardship programs.

Conclusion

Although AMR is on the WHO international agenda, not all countries have effectively implemented their NAPs. As such, there are disparities in resources and capacities between countries, especially in LMICs. Global coordination, although improved, remains fragmented among key actors, including governments, industries, and multilateral organizations. It must thus be stressed that combating AMR requires significant investments in research, surveillance, and health systems, and the economic model for developing new antibiotics appears insufficient.

In many countries, the capacity to monitor AMR and antimicrobial consumption is insufficient, making it difficult to collect the data needed to guide effective policies. Environmental contamination by antimicrobial residues, originating from the pharmaceutical and agricultural industries, thus contributes to the development and spread of resistant bacteria. In effect, regulations to control these wastes are limited or non-existent in some countries.

Overcoming these barriers, which are identified as poor or insufficient human and structural factors, requires collaborative and sustained efforts, as well as innovations in public policies, financial incentives for industry, and global awareness campaigns. However, social exclusion in diagnosis can limit the access of certain groups to timely and accurate diagnoses, a practice that can arise from economic barriers, discrimination in health systems, and differences in the availability of advanced technologies.

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No information to report.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. World Health Organization (2015) Global action plan on antimicrobial resistance.
2. World Health Organization (2024) Antimicrobial-resistance. A manual for developing national action plans, Geneva, Switzerland.
3. WHO bacterial priority pathogens list (2024) Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance.

4. Burki T (2024) New report outlines cost of inaction on AMR ahead of UN high-level meeting. *Lancet Respir Med* 12(6): e36.
5. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, et al. (2018) Quantifying drivers of antibiotic resistance in humans: a systematic review. *Lancet Infect Dis* 18(12): e368-e378.
6. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, et al. (2016) Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 387(10014): 176-187.
7. Antimicrobial Resistance Collaborators (2022) Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet* 399(10325): 629-655.
8. Mendelson M, Laxminarayan R, Limmathurotsakul D, Kariuki S, Gyansa-Lutterodt M, et al. (2024) Antimicrobial resistance and the great divide: inequity in priorities and agendas between the Global North and the Global South threatens global mitigation of antimicrobial resistance. *Lancet Global Health* 12(3): e516-e521.
9. O'Gorman S, Jackson A, Fitzmaurice K (2024) Prescribing for change-safer antimicrobial use in hospitals. *Clin Med (London)* 24(6): 100261.
10. Portillo-Gallo JH, Sánchez-González JM, Velo-Méndez G, Rivera-Cisneros AE, Ishida-Gutiérrez C, et al. (2022) *Acinetobacter baumannii* with extended resistance in a post-COVID-19 patient. *Rev Mex Pathol Clin Lab* 68(3): 137-139.
11. G20 Leaders' Declaration (2017) Shaping an interconnected world. Hamburg, Germany.
12. Jiang X, Guo H, Sun J, Guan Y, Xie Z (2024) Diagnostic value of metagenomic next-generation sequencing for bronchoalveolar lavage diagnostics in patients with lower respiratory tract infections. *Diagn Microbiol Infect Dis* 111(2): 116620.
13. Pandolfo AM, Horne R, Jani Y, Reader TW, Bidad N, et al. (2022) Understanding decisions about antibiotic prescribing in ICU: an application of the Necessity Concerns Framework. *BMJ Qual Saf* 31(3): 199-210.
14. Bertagnolio S, Dobrev Z, Centner CM, Olaru ID, Donà D, et al. (2024) WHO global research priorities for antimicrobial resistance in human health. *Lancet Microbe* 5(11): 100902.
15. European Center for Disease Prevention and Control (2024) Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. ECDC, Stockholm, Sweden.
16. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2024) Expected susceptible phenotypes. Version 1.1. 2022.
17. Camacho-Silvas LA, Portillo-Gallo JH, Rivera-Cisneros AE, Sanchez-Gonzalez JM, Franco-Santillán R, et al. (2021) Multidrug resistance, widespread resistance and pan-resistance to antibacterial agents in northern Mexico. *Cir Ciruj* 89(4): 426-434.
18. Sánchez González JM (2024) 10th Congress of Clinical Pathology and 4th Latin American Congress of Clinical Laboratory Technologists. The challenge of bacterial resistance and the role of the laboratory. Cuba.
19. Official Gazette of the Federation Government of Mexico. Ministry of Health (2010) AGREEMENT determining the guidelines to which the sale and dispensing of antibiotics will be subject.
20. Rodriguez-Manzano J, Subramaniam S, Uchea C, Szostak-Lipowicz KM, Freeman J, et al. (2024) Innovative diagnostic technologies: navigating regulatory frameworks through advances, challenges, and future prospects. *Lancet Digital Health* 6(12): e 934-e943.
21. Cuesta J, López-Noval B, Niño-Zarazúa M (2024) Social exclusion concepts, measurement, and a global estimate. *PLoS One* 19(2): e0298085.
22. WHO (2021) Global Strategy on Digital Health 2020-2025.
23. Kasoju N, Remya NS, Sasi R, Sujesh S, Soman B, et al. (2023) Digital health: Trends, opportunities and challenges in medical devices, pharma and bio-technology. *CSIT* 11: 11-30.
24. Leonard E, de Kock I, Bam W (2020) Barriers and facilitators to implementing evidence-based health innovations in low- and middle-income countries: A systematic literature review. *Eval Program Plan* 82: 101832.
25. Sánchez GJM, Castellanos MJM, Portillo GJH, Castellanos-Gutiérrez A, Lazcano BS (2022) SARS-COV-2 associated with pediatric multisystem inflammatory syndrome: About two cases. *Enf Inf Microbiol* 42(3): 106-114.
26. World Health Organization (2003) Adherence to long-term therapies: Evidence for action. World Health Organization, Geneva, Switzerland.
27. Sharma A, Martins IJ (2023) The role of microbiota in the pathogenesis of Alzheimer's disease. *Acta Scientific Nutritional Health* 7(7).
28. Martins IJ (2017) Antibiotic resistance involves antimicrobial inactivation in global communities. *Scholarena Journal of Pharmacy and Pharmacology* 1(1): 1-3.