INNOVATIVE CONTRACTING MECHANISMS TO INCREASE THE ADOPTION OF NOVEL ANTIMICROBIALS IN ARGENTINA AND COSTA RICA

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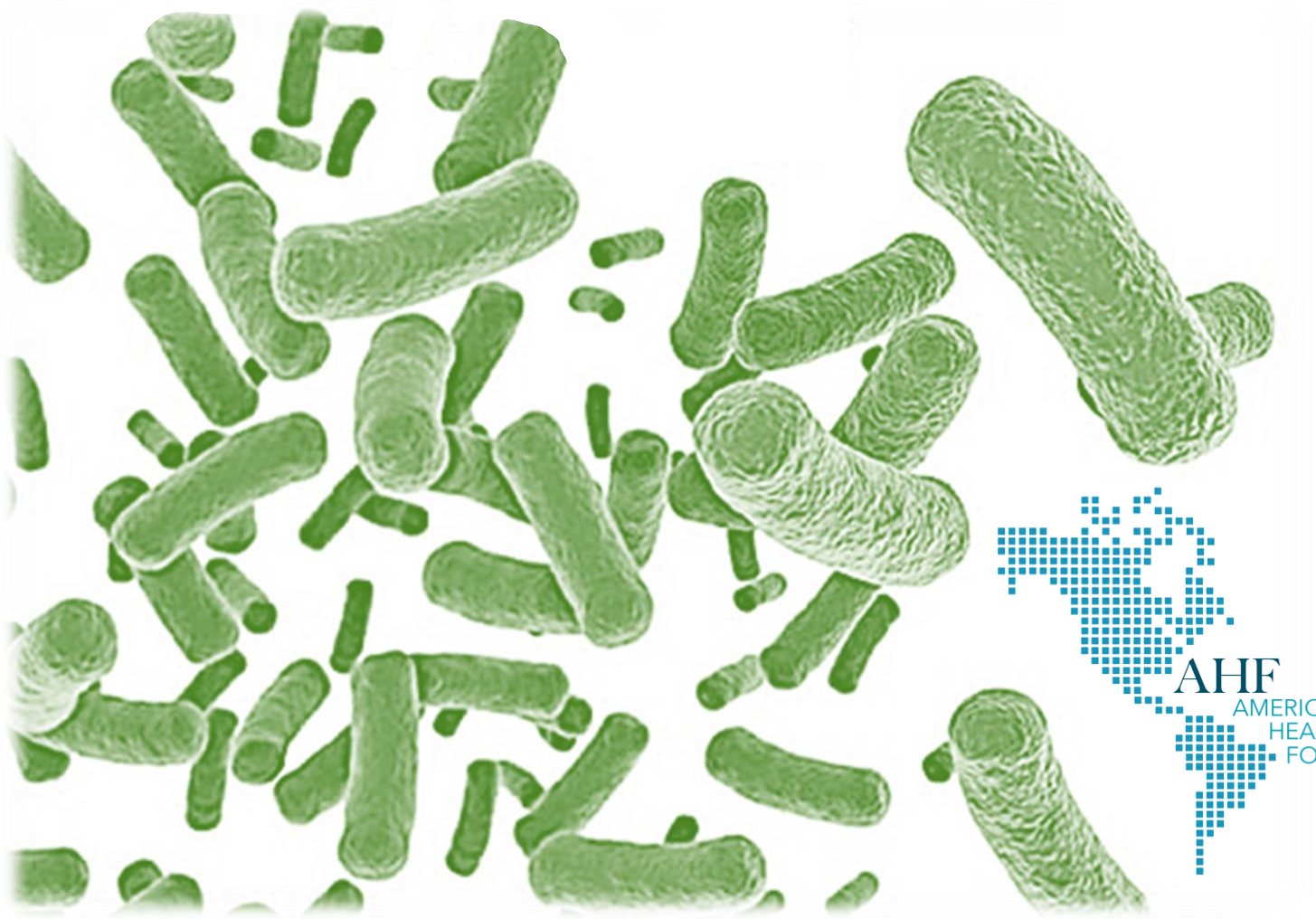

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ANTIMICROBIALS RESISTANCE, NOVEL ANTIMICROBIALS, AND INNOVATIVE CONTRACTING MECHANISMS:

Antimicrobial resistance (AMR) occurs when microorganisms adapt the ability to grow in the presence of medications that once prevented their growth. In recent years, inappropriate and excessive use of antimicrobial drugs has exponentially accelerated this process. The main causes of AMR are unrestricted and unjustified use of antimicrobials in agricultural and industrial settings and common ambulatory infections, excessive use of broad-spectrum antimicrobials in hospital settings, antimicrobial self-administration, non-adherence with dosing requirements, and non-application of prescription sale restrictions. Further, infection control measures are often insufficiently applied in developing countries (e.g., Latin America due to a lack of effective and reliable surveillance systems and poor dissemination of research information.)[1]

The WHO declared AMR to be one of the top 10 public health threats. Global AMR trends are not slowing down, and the threat is greater in developing countries.[2,3,4,5] In 2014, the United Kingdom Review on Antimicrobial Resistance estimated that deaths from AMR could rise from approximately 700,000 to nearly 10 million deaths per year by 2050.[6,7] By 2030, AMR could push 24 million people into extreme poverty.[5] However, reliable estimates of the true burden are scarce.[8] Globally, there are considerable variations in AMR patterns, and individual countries face different primary threats regarding strains of AMR pathogens and public health impacts.

Multidrug-resistant microorganisms (MDRMs) cause increased morbidity and mortality in patients admitted to hospitals. MDRMs reduce therapeutic options to the point that only a single treatment remains, or possibly none. Without new antimicrobials, it will become increasingly difficult to effectively treat infections, and procedures such as organ transplantation, cancer chemotherapy, and common surgical operations will carry a higher risk of untreatable infection. The

consequences of AMR in terms of mortality, disability, and economic costs are significant for healthcare systems, especially in low- and middle-income countries, where AMR incidence is higher and accessing last-line antimicrobials is far more difficult. Data from the Latin American Network for Antimicrobial Resistance Surveillance (ReLAVRA) show an increasing trend in resistance of hospital pathogens in Latin America since 2014.[3]

Unmet Needs in Access to Novel Antimicrobials

Treatment of multidrug-resistant infections is difficult given the lack of available anti-infective options that cover MDRM and access to new antimicrobials. Therefore, physicians are forced to recycle older antimicrobials, which would otherwise remain unused or avoided whenever possible due to their severe adverse events. Their toxicity, frequent use as broad-spectrum antimicrobials, and the lack of scientific evidence demonstrating their true efficacy make them deleterious options.[6]

Antimicrobial stewardship (AMS) programs aim to address issues of antimicrobial prescribing, particularly overprescribing, to improve individual patient care, reduce the burden of AMR, lower hospital costs, and slow the spread of AMR. These programs are crucial because they help ensure the efficacy of available antimicrobials, but creating these programs throughout hospitals in resource-limited settings is challenging. Hospitals in such countries or regions should tailor their choice of strategies to their specific needs and available resources.[3]

International Centre for Medical Research and Training

(CIDEIM) created the Colombian Nosocomial Resistance Study Group, which has been tracking data from 31 public and private hospitals in 12 cities. Improvements in antibiotic administration, reduced or stabilization resistance levels, and cost savings were tied to assessments of generic antibiotic outcomes,[9] which are associated with greater mortality.[10] Further, in Colombia these antibiotic generics are not necessarily bioequivalent to the branded product.[11] Colombia provides an example of stewardship and multidisciplinary approach that other Latin American countries could emulate.

Current development of new active antimicrobials against resistant pathogens is insufficient to face the increasing emergence and spread of resistance at a global level. The evolution of resistance occurs faster than the production of innovative drugs effective in treating resistant infections. In 2017, WHO published a list of antimicrobial-resistant "priority pathogens," which includes 12 families of bacteria that pose the greatest threat to human health.[12] The list serves as a guide for R&D of novel antimicrobials and has been divided into medium, high, and critical priorities, based on the urgency, and need for new drugs.

According to a recent WHO report, only 11 new antimicrobials were approved in the past five years, of which 80% belong to existing drug classes.[12] The current clinical antibacterial pipeline contains 43 antimicrobials, of which 26 are active against the WHO priority pathogens. Most of them are in classes already in use, meaning that if they have similar mechanisms of action, resistance probably occurs rapidly because well-defined bacterial resistance mechanisms already exist to inactivate them. Seven antimicrobials in the report have novel mechanisms of action, but only two of them target critical gram-negative bacteria. Moreover, it takes several years for each new drug to advance through the development pipeline, it is estimated that in the next five years, only eight new antimicrobials now in development will be approved. [12,13, 14]

Incentivizing the Pharmaceutical Industry to Create Novel Antimicrobials will require Innovative Contracting Mechanisms (ICMs)

Historically, "push" incentives have been used to encourage pharmaceutical companies to develop antibiotics. Push incentives are largely based upon public-private partnerships, industry-academic interactions, grants, and tax credits. They aim to lower the costs of R&D.[13,15,16,17] Although somewhat easier to organize and implement than pull incentives, push incentives usually support both successful and unsuccessful R&D efforts and have proven effective for accelerating the initial steps of research. However, this approach has not worked with antimicrobial R&D because the investment remains far greater than the incentives (e.g., patient extensions, tax breaks, research grants, contracts, direct payments, public-private partnerships for R&D outlays). In other words, push incentives offer direct support (including payments) for the effort of developers. They also depend upon the continued link between the volume of antibiotics sold and the price paid, that is, between R&D funding and total sales.[18] Health economic experts believe removing this link ("delinkage") is key to ICMs.[19] These incentives are easier to apply in countries where substantial R&D takes place. Therefore, the impact in many Latin American countries may be limited.

"Pull" incentives are based upon the provision of higher reimbursements, patent extensions, tradable exclusivity vouchers, options market, market-entry rewards (MERs), or ICMs only to successful developments and thus, may prove instrumental in fostering the availability of new molecules. Pull incentives typically offer longer-term, widespread advantages to companies willing to develop novel antimicrobial agents. Rather than focusing on R&D funding, pull incentives reward successful development by increasing or ensuring future revenue.[20] They can be offered as separate, joint, or complementary approaches with delinking. They encourage private sector engagement by creating real market demand and with it, reward for success. Examples of pull incentives include ICMs, advanced market commitments, tax credits for defined milestones, diagnosis-related group carve-outs, and regulatory incentives (e.g., market exclusivity, priority review vouchers, tradable patent vouchers).[21] Nevertheless, some pull modalities may not be suitable for antimicrobials, because all volume-based strategies promote overuse, and higher reimbursement or patent extensions directly defy patient (and provider) accessibility to the new technologies.[22]

With traditional linkage and push incentives receding in influence, there is more room and the need for approaches that encourage antimicrobial R&D within the pharmaceutical industry and move away from

economic assessments based only on sales volume. Antibiotic delinkage is key to solving these problems regarding inadequate market incentives for 1) R&D investment, including attention to well-placed timing, 2) protecting resources from overuse or premature resistance, and 3) ensuring global access.[23] Furthermore, there is a need within hospital-based systems for a reimbursement reform for antibiotics that improves patient health outcomes and encourages pharmaceutical companies to develop pathogen-sparing drugs.[24] There are some promising examples to modify current price and reimbursement practices for novel antibiotics in the USA and Europe.[25,26,27,28,29]

Thanks in part to CIDEIM, Colombia has enacted two pay-for-performance agreements that aim to prop up the R&D side of this conversation in the region.[30] This has prompted pilot-like programs in Argentina, Brazil, Colombia, and Mexico to determine how ICMs can adequately incentive antimicrobial R&D while also ensuring higher levels of reimbursement.[12] Thus, some Latin American governments may be prepared to deepen their commitment to collaborating with pharmaceutical companies on innovative market structures that provide more dependable and sustainable market models. However, it is important to recognize that healthcare markets operate differently from country to country, and different sets of incentives may be needed accordingly.[1]

INNOVATIVE CONTRACTING MECHANISMS IN ARGENTINA & COSTA RICA

In recent years, governments and international organizations have implemented plans to combat AMR. WHO developed the global action plan using the "One Health" approach, which was adopted by the 68th World Health Assembly in 2015 to reduce the widespread rise of AMR.[31] Argentina is implementing the AMR National Action Plan published in 2015 based on the articulated work of various actors, organizations, and institutions that constitute the National Commission for the Control

of Antimicrobial Resistance.[32] Argentina has participated in ReLAVRA since 2000 and enrolled in Global Antimicrobial Resistance and Use Surveillance System in 2019. With the same objective, the Ministry of Health (MoH) of Costa Rica presented the National Action Plan to combat AMR during 2018–2025.[33] Important to remember that the effects of the COVID-19 on AMR are extensive.[2]

This consensus paper focuses on how Argentina and Costa Rica are prepared to address the barriers to combating AMR focusing on ICMs (pull incentives). We identified key barriers for implementation and offered recommendations for overcoming them, including necessary regulatory and policy changes. We chose these countries in part because they represent two health system archetypes: one centralized and one fragmented.

In Costa Rica, the Caja Costarricense del Seguro Social (CCSS) covers almost 100% of the national territory. A private healthcare system also exists, and some may choose to pay a premium for coverage that offers them preferential care. This private sector does not have the authority to negotiate medical pricing or access. CCSS requires hospitals to follow its regulations, often without giving the hospitals sufficient resources to make these regulations work efficiently, particularly regarding accessing novel pharmacologic options.

Conversely, the healthcare system in Argentina is fragmented. Its federal form of government has 24 provincial health systems, 24 provincial social insurances, nearly 300 national social security funds, and approximately 300 private insurance entities (i.e., prepaid

[1] *See Appendix A (Click Here) for details on AMR, barriers to AMR solutions, and R&D for novel antimicrobials, and Appendix B (Click Here) for details on push & pull incentives and improving patient access to and affordability of novel antimicrobials.*

2 See Appendix C (Click Here) for details on the magnitude of COVID-19's impact.

medical companies, health mutual funds, and cooperatives).[34] In August 2020, the country had 29,352 healthcare centers registered in the Federal Register of Healthcare Centers, 11,171 belonged to the public and 18,181 to the private sector.[35] These subsystems are insufficiently coordinated with each other; therefore, developing a centralized clinical information system is a key goal.[3]

RECOMMENDATIONS TO OVERCOMING BARRIERS TO IMPLEMENT INNOVATIVE CONTRACTING MECHANISMS IN COSTA RICA AND ARGENTINA

ICMs represent a field of major potential to contribute to the objective of optimizing the adoption of new antimicrobials. However, neither Costa Rica nor Argentina has implemented any in the public sector besides centralized purchasing. Thus, there is a clear need to address the potential obstacles for the adoption of new antibiotics as a substantial component of the response to the AMR threat. The barriers and recommendations listed below are based on a thorough review and discussion of the available economic and scientific data analyzing ICMs regarding novel antimicrobial treatments in both countries.

Legal framework: Although the law does not contain formal restrictions for creating and implementing ICMs, the lack of experience with navigating the legal and healthcare systems to streamline new agreements poses a challenge. Working under the existing legislation could accelerate the speed of application reviews that are tied to specific medical needs.

Experience with ICM: The adequately trained personnel needed to monitor financial-based agreements and the infrastructure necessary to implement and monitor performance-based agreements are extensive. The costs of these activities can be borne by the pharmaceutical companies as a value-added services agreement or shared between the companies and the local government.

Degree of healthcare system fragmentation: As opposed to Costa Rica's centralized system, Argentina's fragmented system limits its capacity to implement ICMs in a centralized manner, as each subsystem will have its own final decision. However, national health authorities can contribute to the promotion of these types of agreements through federal policy coordination bodies and the oversight bodies of the main healthcare payers outside the public system, such as social security superintendence and private insurance associations.

Data collection: Argentina lacks centralized clinical data, although significant strengths exist in data collection mechanisms on an institutional level (though enormous variations among institutions exist), which is more developed than in Costa Rica. It is necessary to develop and strengthen centralized electronic medical records and other health information tools to monitor health outcome data. This may include the potential integration among the various current databases within a country.

Performance and outcomes indicators: Defining the right indicators is critical, particularly for antimicrobials, to identify the most appropriate time frame for any outcome assessment and establish the optimal markers or measures to fully assess performance. Other potential challenges include suboptimal adherence, inadequate diagnoses, off-label use, and the frequent need for simultaneous treatments with other antimicrobials. In supporting ICMs, data may reflect actual effectiveness and safety in routine clinical care, which often differs from clinical trials. Poor quality of information and medical care may lead to the need to restrict the initial application of the agreements to centers of excellence.

Information asymmetry: Manufacturers normally know more about the new technology than health authorities, while health authorities know more about the results during the agreement. Addressing this asymmetry requires a strong commitment from both parties to share all new and relevant information. Maintaining confidentiality of the clinical data used for outcome assessments is required, thus, a third-party auditor may be an option. Such a process could contribute to a culture of trust between the parties.

Confidential discounts and rebates: There are concerns that the adoption of this practice by many countries may allow the manufacturer to maintain a high reference price, which has resulted in increasing calls for

3 See Appendix D (Click Here) and E (Click Here) for details on Costa Rica's and Argentina's health system.

Click Here for appendix A-E references

transparency. However, this must be balanced against appropriate incentives for pharmaceutical companies to develop new technologies, including antibiotics, to address areas of unmet need. 36, 37, 38, 39 Moreover, the traditional methods of HTA used to support decisions may not be enough by themselves in this context. As a result, more robust and innovative models including multicriteria decision analyses may be required to aid decision-making.40,41

Prescription guidelines: Financial-based agreements do not guarantee that a novel antimicrobial will be administered to the most suitable patients, especially when the agreed-upon budgets have been exceeded. Thus, prescription guidelines should be developed with the participation of MoH representatives and scientific societies to reduce potential inequities and HCPs should adhere to them.

CONCLUSIONS

The need for new antimicrobials is well established. One of the greatest challenges to ICMs in Costa Rica and Argentina is suboptimal knowledge and experience about creating and implementing them. In general, substantial legal changes are not required for these agreements. Minor regulatory changes may be necessary for successful implementation. Given the geography, size, and socioeconomic situations of Costa Rica and Argentina, it is noteworthy that the progress and technology around novel antimicrobials and AMR in large hospitals are often different than in small hospitals, where consolidated clinical data are less available.

A concerted will from all stakeholders and detailed proposals are required. A compelling case must be made to address AMR within the framework of any innovative contracting proposal, which must then be presented to regulatory authorities, MoH, key public officials, and pharmaceutical companies. The input of active national medical associations would be extremely helpful. Once a majority, if not all, stakeholders support a particular proposal, initial ICMs can begin to address some of the most urgent unmet medical needs. Some proposals can be fast-tracked because there is existing widespread agreement among the entities involved in the proceedings. One example of such a proposal is replacing

currently used antimicrobials that have high toxicity with innovative antimicrobials that are targeting new mechanisms of action.

Overall, the culture surrounding antimicrobials needs to change, and every entity and stakeholder must play a part in reducing AMR as an empowered multidisciplinary AMR working group. It is critical to continue increasing awareness and educating general physicians, specialists, pharmacists (especially those operating in rural areas as they often take the role of primary physicians), and the public about the harms of self- or over-medicating with antimicrobials. Healthcare Professionals (HCP) should comply with current local guidelines on antimicrobial use, provided they are available. A thorough selection of antibiotics based upon actual microbiological isolates and derived from a thoroughly considered formulary is vital, not only to provide adequate treatment now and increased options for subsequent treatments, but also to reduce the burden of AMR. Moreover, specialists must become immersed in the challenges of AMR and engage in AMS programs.

Focus groups may help to establish outcomes and greater transparency. With the aid of sufficient resources, HTA processes, AMS programs, and data collection systems, the added value of novel antimicrobials can be assessed based on clinical outcome information. Ultimately, maximizing patient outcomes (vs. prioritizing the cost of patient care) is needed. However, questions need to be answered: Are outcomes-based contracts suitable for novel antimicrobials? If not, are there changes that can be enacted to make them suitable if it is deemed the preferable incentive mechanism for drug manufacturing and distribution?

Thus, the issue of trust is critical for the successful implementation of these recommendations. The commitment of different government and healthcare institutions, public entities, physicians, pharmacists, and private companies is instrumental. All interested parties should be at the table from the outset of addressing goals related to ICMs as they relate to AMR.

Finally, it is important to mention that the ideas expressed in this paper are intended to further improve the quality of healthcare in countries like Costa Rica and Argentina. The paper´s main objective is to describe the perceived barriers of introducing novel antimicrobials into each country's respective national healthcare system so that policy recommendations for optimizing the adoption of new antibiotics can be recognized and, when possible, implemented. This paper is intended to be part of an ongoing conversation about the unmet needs regarding access to antimicrobials in these countries and, in doing so, to address the challenges presented by AMR, particularly in Latin America.

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