

Antimicrobial resistance in the age of noncommunicable diseases¹

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Dr. Roses, honorable ministers, distinguished delegates, and colleagues:

The opportunity to address the 51st PAHO Directing Council is a great privilege and one that I approach with considerable humility and hesitancy. Like many of you, last week I was in New York City at the historic United Nations General Assembly Special Session on Non-Communicable Diseases or NCDs. We heard that NCDs were a socioeconomic challenge of “epidemic proportions” that kills about 36 million people a year, mostly in low- and middle-income countries. The Secretary-General characterized the situation as “grim” and “one of the major challenges for development in the twenty-first century.”

Against the historic trumpet call to global action on NCDs, it might seem that my task today is a bit off key; perhaps I am even singing the wrong song. Has the timeliness of a PAHO Directing Council session on antimicrobial resistance been overcome by events? How do we blend the notes that were sung so loudly in New York last week with our task today to address antimicrobial resistance?

First, it is useful to recognize that the consequences of NCDs often include infections. Indeed, it will be a very long time before we no longer need to worry about diabetic skin infections, pneumonias complicating chronic lung disease, and opportunistic infections that arise as a consequence of cancer chemotherapy. Community- and hospital-acquired infectious diseases are a part of the progression of many common NCDs. As the burden of diabetes, cancers, and chronic lung diseases rises, the burden of associated community- and hospital-acquired infections will also likely mount. Resistance will make some of them costly, difficult, and sometimes impossible to treat successfully.

Further concern stems from the increasingly untenable assumption that industry is a ceaseless source of new antibiotics. This faith underlies the courage of many surgeons to undertake operations that put patients at risk of surgical infections. Similarly, oncologists use powerful forms of cancer chemotherapy that undermine the patient’s immune system, believing that antibiotics will rescue those who can’t fend off infections.

Second, many NCDs are considered lifestyle diseases. We can choose what we eat, we can choose to exercise, and we can choose whether or not to smoke. The medical establishment or the state generally has only a limited capacity to demand preventive behaviors. So education becomes the tool of persuasion. Similarly, with respect to mitigating antimicrobial resistance, legislators and the public also need to

be educated and incentivized to achieve better results. However, when public interests are most threatened, governments need to step in. This has been the case in places that have chosen to curb tobacco use in public because second-hand smoke threatens the common good. Likewise, antimicrobial misuse promotes resistance and degrades public health. However, since microbes travel more effectively than cigarette smoke, that damage can have impact not only across the restaurant but also across the globe.

Self-medication with freely available over-the-counter antibiotics is common in some parts of this region. Unfettered use of antibiotics, poorly matched to prevailing resistance patterns, is a recipe for poor individual, national, and global health. Just as students and adults need to be educated about the hazards of tobacco, alcohol, salt, and saturated fats, they also need to become literate in the proper, rational use of antibiotics. Because effective antibiotics are an element of our common treasury, like smoke-free air, and perhaps harder to restore once lost, the state has an interest and a unique responsibility to protect antibiotics from improper use.

The forces of globalization have made the risks and solutions for antimicrobial resistance increasingly dependent on transnational cooperation and mutual commitment. The emergence of resistant organisms in one country threatens its immediate neighbors as well as nations on the opposite side of the world. Once resistance has emerged, the voluntary actions of individuals promote its dissemination in a way that goes far beyond the commercial international relationships that drive many NCDs.

Although patients and providers have the most proximate role in the rational use of antimicrobials, security within our microbe-filled environment requires collective problem solving and action. The traditional solution of developing replacement drugs has lost momentum. The pipeline of new antimicrobial products is now a sobering trickle while plagues like methicillin-resistant *Staphylococcus aureus* (MRSA) continue. And frightening new and virtually untreatable forms of infection, such as extremely drug-resistant tuberculosis (XDR-TB), have become established in certain parts of the world.

Between 1983 and 1987, the US Food and Drug Administration (FDA) approved 16 new systemic antibacterial agents. The 5-year period a decade later yielded only 10 new agents. And a decade later, 2003 to 2007, the number of new FDA-approved systemic antibacterial agents plunged further to just five. The current five-year window is projected to produce only one new molecular entity (1).

Why is productivity plummeting? Commercial forces drive much drug development, and such development is an extremely expensive proposition. The burgeoning market for drugs to lower blood pressure, to control blood sugar, and to treat depression—products for which individual patients over decades would consume thousands of doses—are a more profitable

R&D investment than antibiotics taken for a week or two.

About 40% of the drugs consumed in the United States of America are manufactured overseas, and about 80% of the active pharmaceutical ingredients used in the formulation of drugs consumed by Americans come from other countries (2). The health of virtually every resident of the Americas is intimately tied to an antimicrobial supply pipeline that extends to other hemispheres. While many quality products are available from this global supply chain, we know that substandard, falsified, and counterfeit antimicrobials can penetrate the borders of even the most vigilant countries. The global flows are now just too great for traditional border screens of imported drugs to be adequate; quality needs to be built in and tracked from the source. A substandard antibiotic that falls short in potency promotes the emergence of resistant organisms wherever the global supply chain takes it. Beyond patients experiencing more difficult clinical courses and even death, they and health systems also experience mounting economic losses as money is wasted on substandard antimicrobials that foster resistance.

Unfortunately, global governance efforts to tackle the public health problem of weak pharmaceutical regulation have highlighted a tension between interests concerned with addressing trademark and patent threats and those that see the effects through a public health lens focused on the hazards of poor drug quality. Oxfam reports that most problems with substandard and falsified medicine are of a public health nature and unrelated to trademark infringement (3). However, the intellectual property issues have often dominated in international discussions. Their conflation with public health concerns has led to a global deadlock in negotiations to craft public health solutions to improve access to safe and effective drugs.

The economic burden of antimicrobial resistance alone should be enough to drive ministries of health to take aggressive action. In Europe, multidrug-resistant bacteria cause at least 400 000 infections and more than 25 000 deaths annually. They result in at least 2.5 million extra hospital days per year, the economic burden of which is at least 1.5 billion Euros annually (4, p. 21). Undoubtedly, these costly problems can be generalized to the Americas. As elderly populations grow in high-, middle-, and low-income countries and spend more time in hospitals receiving care for NCDs, the economic burden of drug-resistant hospital-acquired infections will likely rise. Growing use of neonatal intensive care units, organ transplants, and cancer chemotherapy will further contribute to the cost of treating resistant organisms.

Despite limited resources, antibiotics are a very high priority in the health budgets of developing countries. It was reported in 2000 that developing countries typically spent 35% of their health budgets on antibiotics, compared with 11% in developed countries (5). An increasing need to use more expensive

next-generation antibiotics or more toxic regimens to counter antimicrobial resistance competes for scarce resources to respond to the emerging NCD epidemic.

Contributing to the antimicrobial resistance problem is the use of antibiotics as growth promoters in food animals such as cattle, pigs, and chickens. Widespread use of antibiotics in agricultural settings has been linked to drug-resistant infections in humans. In the United States, more than 70% of the antibiotics used are administered to livestock (4, p. 26). Resistant bacteria are commonly found in foods in US and European supermarkets. In some places, the rise and fall of human infections resistant to a specific antimicrobial has been correlated to its introduction or withdrawal from use in animals. Agricultural use has been associated with food-borne illnesses and may affect human health through expanding reservoirs of resistance in the environment (4, p. 25).

So, what is one to do to shore up the crumbling foundation of our ability to control increasingly resistant infections such as MRSA and XDR-TB? The root causes are multisectoral. A health systems approach is essential to a sustainable, effective response. As with NCDs, providers and patients are central players in achieving the rational use of antibiotics—that is, administering an antibiotic matched to the prevailing resistance pattern, in the correct dose, and for the correct length of time. Patients and providers must be educated to understand that antibiotics are commodities that can be overused, misused, and underused.

The public health community has a leading role in surveilling antimicrobial resistance and in advancing a wide range of interventions to reduce the frequency of infections. This includes active, well-resourced hospital infection control programs based on solid surveillance, epidemiologic analysis, clinical policy, hygiene, and education. There is much room for improvement in hospital infection control in the Americas. Several years ago, the Pan American Group for Evaluation of Hospital Infections reported sobering results. Between 2006 and 2007, this group surveyed infection control activities in 67 hospitals in 7 Latin American countries. Only 43% of the hospitals were conducting active surveillance for hospital-acquired infections, only 30% were tracking monthly rates, and only 24% were judged as able to identify an outbreak of hospital-acquired infections. Even though 57% of the hospitals had a microbiologist, only 22% of the institutions analyzed resistance patterns. Methods for sterilization and high-level disinfection were appropriate, respectively, in only 70% and 52% of the institutions studied. In areas designated for patient care, hand-washing facilities were present in only 19% of hospitals (6).

The PAHO Antimicrobial Resistance Technical Advisory Group has met a number of times over the past decade to explore the regional problem of antimicrobial resistance. It has reviewed microbiology laboratory performance evaluations. As with infection control, the results have been uneven and

have highlighted the importance of investing in improved diagnostics, improved data systems, improved systems of quality assurance, and improved laboratory and epidemiologic training. Even some national laboratories have fallen significantly short of norms in terms of their proficiency to identify bacterial species and conduct antimicrobial susceptibility testing. The competency of national laboratory networks must be constantly and actively monitored. If clinicians do not trust microbiology laboratories enough to base treatments on their results or if the reports come too late, the work of those laboratories is a waste of resources. Laboratories must be incentivized to have their quality documented through appropriate periodic external accreditation. Without good labs, much money is wasted on the suboptimal use of antibiotics due to weak surveillance and trial-and-error clinical diagnoses.

The Technical Advisory Group has urged raising the issue of hospital infection control with this PAHO Directing Council since poor hospital infection control is costing the health ministries of this region millions of dollars and patients pay sometimes with their lives for preventable infections acquired during a hospital stay. Highlighting shortcomings of this type in one's health system takes courage, but ethically it is the right thing to do for patients and for taxpayers. Weaknesses will not be corrected if there is no accountability, but assessing accountability is not always a negative activity. Recognizing and rewarding exemplary institutions can be a valuable and positive way to incentivize all institutions to improve staff capabilities and eliminate unacceptable patient care.

The Technical Advisory Group has been pleased to support PAHO's fourth edition of clinical guidelines for the treatment of infectious diseases (7). This is critical to improve the knowledge of practitioners as surveys in regional training hospitals have identified that critical gaps in knowledge are not rare (8). Preferring autonomy, many clinicians refuse to use evidence-based guidelines even when that practice clearly threatens individual and public health and incurs costs. Institutionalized quality-of-care peer review may address this issue. Consumers also fall short in their responsibilities. Household and individual surveys in two PAHO countries showed that inappropriate antibiotic use occurred more than half the time.

As I noted at the beginning, it is a privilege for me to share with you my personal observations since you have the power to take action. My comments have been informed by the efforts of the Antibiotic Resistance Technical Advisory Group. Fortunately, the excellent work of PAHO—and for many years the passionate, capable, and visionary leadership of Dr. Gabriel Schmunis—has defined well the issues across the spectrum of the health system. This problem identification is the first step to accountability. Though much work remains to be done, I believe that health ministers are now well positioned to develop and implement national strategic plans for quality-assured surveillance and control of antimicrobial resistance.

Transnational relationships have been cultivated so that more advanced national laboratory systems can assist their neighbors to improve. Perhaps even a regional convention to support a common framework or agenda to contain antimicrobial resistance is feasible.

The next steps will take some courage and mutual encouragement. States will need to consider some potentially unpopular interventions to better control access to precious antibiotics. Popular education on antibiotic use needs to be paired with education to prevent communicable and noncommunicable diseases.

There are economic interests at play in controlling access to antibiotics but the commitment to ethical, quality care demands putting science-based policy first. Restrictions on access to antimicrobials need to be approached in light of the parallel need to maintain access to effective and life-saving care. Clinicians need to be incentivized to move from expert-based practices to evidence-based practices that reflect rational clinical guidelines for antimicrobial use. To be accredited,

institutions should support microbial surveillance to guide clinicians and ensure that all staff follow sound infection-control procedures.

I commend this critical task to the leadership of each PAHO country as one of the most important investments for not only achieving quality individual patient care but also for preserving for as long as possible the miracle of antibiotics that have been foundational to personal and global health for the last 70 years. Transnational cooperation is an essential part of this. To paraphrase a 1944 speech by Wilbur Sawyer, then president of the American Society of Tropical Medicine and Hygiene, "No country can live to itself in disease prevention [and that includes the avoidance of antimicrobial resistance]. A failure of one is a failure of all."

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