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ROUNDTABLE ON ANTIMICROBIAL RESISTANCE

Containing Antimicrobial Resistance

Introduction

The problem: antimicrobial resistance hinders the control of infectious diseases

1. The Region of the Americas is currently facing a crisis created by the growing resistance of microorganisms to antimicrobial drugs. At one time, it was thought that antimicrobials would keep communicable diseases under control, eliminating them as a public health concern. However, their effectiveness has been steadily waning in recent years, as strains of bacteria emerge that are resistant to multiple drugs and, in some cases, have become nearly “pan-resistant.” Antimicrobial resistance can jeopardize the achievement of MDGs 4¹, 5², and 6³. Nosocomial infections caused by resistant strains were once confined to hospitals, but new community-acquired infections pose an ominous threat. The pressure posed by the antimicrobials that selects bacterial mutations is complex, but the responsibility can be shared by healthcare workers, hospitals, long-term care facilities, the agriculture industry, and even healthcare consumers themselves.

2. Antimicrobial resistance is also imposing an immense burden on health costs, doubling the length of stay, and more than doubling the costs per hospital admission. The economic, social, and emotional costs for the patients are large but unmeasured. Hospitals are incurring expensive risk-reduction efforts to limit the spread of the resistant pathogens.

¹ MDG 4: Reducing under-five mortality by two-thirds.

² MDG 5: Improve maternal health.

³ MDG 6: Combat HIV/AIDS, malaria and other diseases.

Antimicrobial resistance and the consequences for public health in the Americas: higher mortality; higher morbidity, and higher health expenditure⁴

3. In Guatemala, for example, the excess cost of treating a single case of ventilator-associated pneumonia in adults was US\$ 1,500, and for neonatal pneumonia, \$1,200. During the study year, the hospital where the study was conducted had 60 cases of ventilator-associated pneumonia among adult patients, which raised the cost of patient care due to a single nosocomial infection by \$90,000 in a single year⁵. The following topics have been expanded in the background paper attached (see Annex).

- (a) Extent and trends in antimicrobial resistance in the Americas. Data from the “Latin American Antimicrobial Resistance Network” for 2000-2009 showed an increase in the resistance of both community and nosocomial pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophilus influenzae*, *Acinetobacter*, *Shigella*, and *Pseudomonas aeruginosa*.
 - (b) Factors related to the development of antimicrobial resistance:
 - Quality of drugs.
 - Improper use of antibiotics by prescribers, dispensers, and consumers/community.
 - Misuse of antibiotics in agriculture and other areas of the food industry (livestock production, aquaculture).
 - (c) Association with poverty. In low-resource settings, factors such as inadequate access to effective drugs, the unregulated dispensing and manufacture of antimicrobials, and truncated antimicrobial therapy due to cost considerations are contributing to the surge in multidrug resistant organisms. In the Americas, poverty-driven practices such as self-medication (e.g. medication-sharing, the use of “leftover” antibiotics), and the purchase of drugs of questionable quality are likely contributing to antimicrobial resistance.
4. PAHO, in support to countries to address the problem of antimicrobial resistance has included a multifaceted approach: (a) surveillance of resistance; (b) hospital infection surveillance and control; (c) strengthening of country capacity to contain antimicrobial resistance in the health care setting and control healthcare-associated infections; and (d) promotion of the rational use of medicines, including antimicrobials.

⁴ Pan American Health Organization. Costo de la infección nosocomial en nueve países de América Latina (Cost of nosocomial infections in nine countries in Latin America). Salvatierra-González, MR, editor [Internet]. Washington (DC), US: PAHO; 2003 (Document OPS/DPC/CD/271/03) (In Spanish) [cited 2011 April 1]. Available from:

<http://www.paho.org/Spanish/AD/DPC/CD/ee-amr-costo-infec-hospital.pdf>

⁵ Idem.

5. This Roundtable is a response to the need to facilitate and promote a broad, in-depth discussion with the health authorities of Member States on the socioeconomic impact, lessons learned, and successful strategies for meeting the goal of containing antimicrobial resistance, which will allow for more cost-effective control of communicable diseases and decrease the infectious risks associated with health care.

Background

6. The 41st Directing Council adopted Resolution CD41R14 (1999) on *Emerging and Reemerging Infectious Diseases and Antimicrobial Resistance*, which resolves in paragraph 1(c): “To urge the Member States to review the policies and legal mechanisms governing the rational use of antimicrobials, with a view to introducing changes aimed at controlling the growth of resistance to these drugs”.

7. The World Health Assembly, in Resolution WHA58.27 (2005), requested the Director-General to expand and strengthen the provision of technical support to Member States in order to accelerate the implementation of Resolutions WHA51.17 (1998) and WHA54.14 (2001) concerning the containment of antimicrobial resistance. It also noted that the strategy for the containment of antimicrobial resistance had not been widely implemented and reemphasized the need for a comprehensive, integrated national approach to promoting the containment of that resistance.

8. World Health Day (2011) was devoted to antimicrobial resistance to offer a valuable conduit for ensuring that measures that can reduce and prevent the spread of often lethal drug-resistant forms of disease are established and enforced.

Objectives

- To analyze and assess the socioeconomic impact of antimicrobial resistance and healthcare-associated infections on health and identify strategies and sources of financing to reduce risks in hospitals and communities.
- To share lessons learned in the surveillance and containment of antimicrobial resistance in the Member States.
- To strengthen coordination and cooperation among the health sector, technical, and financial partners, nongovernmental organizations, professional societies, civil society, and other sectors to tackle antimicrobial resistance.

Roundtable Structure

Containing antimicrobial resistance	
<i>Keynote address: Antimicrobial resistance: implications for Global Health.</i> Dr. Patrick Kelley, Institute of Medicine (20 minutes)	
Discussion panels: (90 minutes)	
Discussion panel 1	
Subject:	<i>The Health, Social, and Economic Impact of Antimicrobial Resistance.</i>
Moderator:	President, Directing Council
Presentation of the Discussion Item	Susan Foster, Alliance for the Prudent Use of Antibiotics
Discussion Guide:	<ul style="list-style-type: none"> • Linking antimicrobial consumption and resistance. • Burden of health –care associated infections. • Cost-effectiveness analysis. • Indirect consequences of AMR in health care (treatment of oncology patients, use of second-line antibiotics).
Discussion panel 2	
Subject:	<i>The extent of antimicrobial resistance in the Region and its trends. Data for action.</i>
Moderator:	Vice President, Directing Council
Presentation of the Discussion Item	Mario Raviglione, WHO
Discussion Guide:	<ul style="list-style-type: none"> • Challenges for antimicrobial resistance surveillance. • Reliability of the data: quality of microbiology laboratories. • Data sharing: from local to global scenarios. • Use of data for policy- and decision-making. • Surveillance of healthcare-associated infections.
Discussion panel 3	
Subject:	<i>Towards a multifaceted approach to contain antimicrobial resistance.</i>
Moderator:	Vice President, Directing Council
Presentation of the Discussion Item	José G. Orozco, Re Act Latinoamerica
Discussion Guide:	<ul style="list-style-type: none"> • Analysis of the different stakeholders: a richer discussion environment. • Integrating surveillance and defining common actions with other sectors. • Role of consumers and civil society in antimicrobial use. • Availability and quality of drugs: the first step in addressing antimicrobial resistance containment. • National strategies for the rational use of medicines. • Improving prescribing practices. • Public incentives for new antimicrobials' development.

Reports	
Rapporteur reports: The three rapporteurs from the three <i>discussion groups</i> meet and prepare a joint report.	
Presentation of the report in the plenary session (10 minutes)	Dr. Marcos Antonio Espinal, Manager, Health Surveillance, Disease Prevention and Control Area, presents the report to the plenary session of the Directing Council.
Participants and guests	
Official Member State delegates to the Directing Council	
<ul style="list-style-type: none"> • Organization of American States (OAS) • Inter-American Development Bank (IDB) • Pan American Development Foundation (PADF) • Inter-American Institute for Cooperation on Agriculture (IICA) • Economic Commission for Latin America and the Caribbean (ECLAC) • World Bank • Centers for Disease Control and Prevention • Institute of Medicine • Cooperation agencies: Canadian International Development Agency (CIDA), U.K. Department for International Development (DFID), Swedish International Development Cooperation Agency (SIDA), Spanish International Development Cooperation Agency (AECID), European Commission Humanitarian Aid Office (ECHO), among others. • Partners and allies: Alliance for the Prudent Use of Antibiotics (APUA), Center for Global Development, Instituto Carlos G. Malbrán (Argentina), Management Sciences for Health, ReAct Ecuador, <i>Asociación Panamericana de Infectología</i>, and <i>Sociedad Latinoamericana de Infectología Pediátrica</i>. • Members of the Technical Advisory Group on Antimicrobial Resistance and Infection Prevention and Control will be co-facilitating the discussions. 	

Presentation

9. Member States are invited to discuss successful initiatives and experiences on antimicrobial resistance containment.

10. Graphics, printed matter, and audiovisual material will be exhibited in the areas contiguous to the Directing Council session rooms.

Action by the Directing Council

11. The Directing Council is invited to participate in the roundtable and take note of the report and its recommendations, and, moreover, to disseminate its results in other forums.

Annex

ROUND TABLE ON ANTIMICROBIAL RESISTANCE (Background paper for the debate)

Antimicrobial Resistance

1. Antimicrobial resistance is a serious threat to infectious disease control worldwide. In the past decade, the emergence and spread of resistant pathogens have jeopardized the successes achieved in this area.

2. In the mid-1990s(1), countries began monitoring the resistance of microorganisms as a key tool for understanding the extent of the problem, examining trends and assessing the impact of interventions. In this context, the *Latin American AMR Monitoring/Surveillance Network (RELAVRA)* has steadily increased its ability to detect and monitor antimicrobial resistance, with a growing number of participating countries (21 countries in 2010) and a greater number of isolates: in 2000, 72,000 of the latter were analyzed, and in 2008, 257,409.

3. Since 2000, surveillance has covered hospital and community pathogens, including enteropathogens, providing relevant data for decision-making in public health. There has been a steady increase in the resistance of pathogens such as methicillin-resistant *Staphylococcus aureus*, which represented 30% of the strains isolated in hospitals in 2000, reaching 50% by 2007. There is significant variability from country to country, with figures ranging from 12% in Honduras to as high as 60% in Chile, Guatemala, and Peru (2). *Enterococcus faecium* and *Pseudomonas aeruginosa* have also exhibited increasing resistance to broad-spectrum antimicrobial drugs. In the case of *E. faecium*, growing resistance to vancomycin continues to be observed, up from 5% in 2002 to 30% in 2008. These data have led the countries to strengthen surveillance of healthcare-associated infections, supported by a regional surveillance strategy spearheaded by PAHO (3). Recently, the spread of an emerging resistance mechanism known as “carbapenemase” among the Enterobacteriaceae has begun to challenge health services. This mechanism has been documented in Argentina, Brazil, Colombia, Uruguay, Venezuela, and more recently, Panama, where outbreaks of *Klebsiella pneumoniae* with the presence of *K. pneumoniae* carbapenemase (KPC) have produced mortality and difficulties preventing the spread of the pathogen.

4. At the community level, *Shigella flexneri* is the most common cause of endemic shigellosis. Classically, *Shigella flexneri* has been sensitive to a wide range of antibiotics. Some 60 to 80% of the strains isolated in the Region are ampicillin- and trimethoprim-sulfamethoxazole-resistant. The emergence of a virtually untreatable new strain of *Neisseria gonorrhoeae* is cause for concern (4). Sulfonamides, penicillin, tetracyclines,

fluoroquinolones, and macrolides were used as first-line treatments for gonococcal infections until *N. gonorrhoeae* became so resistant to all these classes of antimicrobials that their use was no longer recommended. Thus, only the third-generation cephalosporins remain as effective treatment for this multidrug-resistant pathogen. Of major concern is the fact that the altered susceptibility to these "last-line," third-generation cephalosporins recorded over the past five years is beginning to manifest itself as clinical treatment failure, particularly with the oral preparation, cefixime. Reports of clinical treatment failure have been received from countries as diverse as Australia, Japan, Norway, the United Kingdom, and the United States (5).

5. Drug-resistant tuberculosis is a growing public health problem in the Americas, regularly reported by most of the countries in the Region as multidrug resistance (Isoniazid and rifampicin-resistant MDR-TB) but also appearing as extensive drug resistance (second-line drug-resistant XDR-TB –MDR-TB). The latter has a higher mortality rate due to less effective treatment (6). Countries are monitoring the prevalence of resistance through surveys. The way to address this problem is for countries to strengthen basic prevention and control measures like DOTS and expand the recommended clinical and programmatic management of MDR-TB, including infection control.

6. For decades, chloroquine was the treatment of choice for malaria, and most countries still use it to treat *Plasmodium vivax* malaria. However, the *P. falciparum* parasite has developed generalized resistance to chloroquine. As a result, today, the recommended treatment in areas of the Region where chloroquine resistance has been confirmed, particularly countries in the Amazon basin, involves a combination of artemisinin-based drugs, making it substantially more expensive (7).

7. Universal access to antiretrovirals for treating people with HIV continues to expand in the countries of the Region; however, it is jeopardized by the growing resistance of the virus to these drugs. Some 15% of the people in treatment in the Region are already taking second- or third-line drugs for resistant infections (8). These drugs can cost up to 100 times as much as first-line drugs. Thus, growing HIV resistance poses a challenge to the sustainability of programs for universal access in lower-income countries. It is essential that countries continue to strengthen the health services that provide antiretroviral therapy and improve the quality of care for people living with HIV to minimize the emergence and transmission of resistance.

8. Well-functioning epidemiological surveillance makes it possible to document resistance and its economic impact and provides information for improving policies and practices in the countries. This is especially important for promoting the dissemination of knowledge, the application of appropriate prevention practices, and finally, the implementation of measures that facilitate rational use of antibiotics.

Integrated monitoring of antimicrobial resistance

9. Integrated surveillance systems for antimicrobial resistance have adopted a tripartite approach to include information on three important aspects of the work on antimicrobial resistance: enteric pathogens and commensal organisms in the food and agriculture sector (on the farm, in slaughterhouses; at retail points of sale), enteric pathogens isolated from humans, and the use of antimicrobial drugs in humans and animals. This extensive monitoring is part of a comprehensive reporting system that exists in only a very few countries. In many cases, its data are not always comparable, since the countries study different reservoirs (chickens, cattle, pigs) and use different species of indicator bacteria, antimicrobial agents, and cut-off points, as well as laboratory techniques.

10. In order to monitor the evolution of antimicrobial resistance, several countries in the Region of the Americas have set up harmonized surveillance systems for antimicrobial resistance, among them the National Antimicrobial Resistance Monitoring System (NARMS) in the United States. (<http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm>); the Canadian Integrated Surveillance Program for Antimicrobial Resistance (CIPARS), (<http://www.phac-aspc.gc.ca/cipars-picra/index-eng.php>); and the recent Colombian program for integrated surveillance of antimicrobial resistance (http://www.corpoica.org.co/sitioweb/Personaje/personaje.asp?id_personaje=212). The objectives of these programs include the provision of descriptive data and trends in antimicrobial susceptibility/resistance patterns in foodborne zoonotic and commensal bacteria.

11. It is important to monitor information on the use of antimicrobial drugs. Countries in the Region limit themselves to keeping records of the total amount consumed. The registries are by animal species and class and are not separate from antimicrobial drugs. Continuous monitoring of the presence and distribution of foodborne pathogens by source and their antimicrobial resistance is also critical. The WHO-GFN Network (www.who.int/gfn) works to obtain monitoring data so that it can take early action when resistance appears, determining the size and scope of the problem. Standardization and quality control of the protocols used in the diagnosis and characterization of these microorganisms has also been a priority for the network, which has improved regional surveillance.

Improper use of antibiotics by prescribers, dispensers, and consumers/community

12. The rational use of antibiotics is closely tied to perceptions and customs in the countries. The sale of antibiotics by prescription only is key to rationalizing their use. The majority of the countries of the Region have legislation in place to ensure the safe prescription of antibiotics. However, sale and distribution practices are still inadequate.

An analysis of national consumption patterns should be used when formulating guidelines on proper antibiotic use.

13. Countries must increase efforts to inform the community about safe and appropriate use of antibiotics. Antimicrobial drug resistance is related to the irrational use of antibiotics. In partnership with scientists and academic societies, the countries should educate the community about the proper use of antibiotics.

Misuse of antibiotics in agriculture and other areas of the food industry (animal husbandry, aquaculture)

14. The antimicrobial agents used for livestock are often the same as those used for people. Resistant bacteria that have developed and are present in livestock can be transmitted to people (mainly through food, the environment, and direct contact with the animals). The most common examples include *Escherichia coli*, *Salmonella* SPPS, *Enterococcus*, *Clostridium difficile*, and *Staphylococcus aureus*. It is critically important to minimize the risk of resistant bacteria emerging in animals with the potential to transmit them to people. This is especially true for "critically important" antimicrobial drugs (http://www.who.int/foodborne_disease/resistance/cia/en/) for human medicine. Examples of particular concern are *E. coli* and *Salmonella* resistant to third- and fourth-generation cephalosporins and to fluoroquinolones; *Staphylococcus aureus* resistant to all β -lactam cephalosporins (MRSA); and enterococci resistant to vancomycin; and, *C. difficile*.

15. Resistance develops when antibiotics are used in promoting growth in livestock. In order to limit the emergence of resistance, the authorities in each country should ensure that antimicrobials are prescribed only in specific cases for treatment and prophylaxis. Guidelines should be drafted and distributed to assist veterinarians in selecting the right agents in the right dosage for the right duration in each case. Several countries have published guidelines on the proper use of antibiotics (among them, the Netherlands [1986], Denmark [1998], the United States [1999/2000], and Germany [2000]). Codex completed its work on the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance, (http://www.who.int/foodborne_disease/resistance/cia/en/). The Guidelines lay the scientific foundation for risk analysis methods and processes and their application to antimicrobial resistance stemming from the nonhuman use of antimicrobial agents. The purpose of these guidelines is to evaluate the human health hazards associated with the presence of resistant microorganisms in food and fodder and their transmission through these media, determining their resistance to the antimicrobial drugs. The Guidelines include the risks associated with the different areas in which antimicrobial agents are used, such as veterinary applications, plant protection, aquaculture, and food preparation.

Antimicrobial resistance and poverty

16. Poverty and lack of education have long been recognized in the international community as a driving force behind antimicrobial resistance (9). Multiple poverty-driven factors contributing to the development of multidrug-resistant organisms have been identified, such as inadequate access to effective drugs, the unregulated dispensing and manufacture of antimicrobials, and truncated antimicrobial therapy due to cost considerations. In the Americas, poverty-driven practices such as self-medication (e.g. medication-sharing, the use of “leftover” antibiotics), are likely fueling antimicrobial resistance. The problem of multidrug resistant organisms in developing countries can also directly affect and threaten more developed countries, because international travel allows these strains to spread more easily.

Healthcare-associated infections

17. Health-care associated infections (HAIs) are a global public health problem. The burden of disease in developing countries is high. The overall prevalence of healthcare-associated infections is 15.5 per 100 patients; in particular, the rate of catheter-related sepsis is 11.3 per 1,000 catheter days and 22.9 ventilator-associated pneumonias per 1,000 ventilator days. In neonatology, the situation is worse, with the overall HAI at 30.0/1,000 patient days. The pneumonia rate is 28.0/1,000 ventilator days. The rate of catheter-related sepsis is 18.7/1,000 per 1,000 catheter days (10). The availability of data varies dramatically in the Region. Some countries have very good surveillance of healthcare-associated infections in health facilities but lack national data; others have data from health facilities and national data; and still others have neither structured surveillance in health facilities nor national data (11, 12, 13). Efforts should be made to strengthen the capacity of health facilities to identify outbreaks and better understand the burden of disease caused by healthcare-associated infections. PAHO is providing support to the Member States to improve their surveillance systems.

18. The costs associated with infection control are substantial. The cost outcomes for HAI can be calculated from the perspective of the hospital, the patient, and society (14). From the hospital perspective, the hospital-related cost of HAI in the United States was estimated at some \$35.7- \$45 billion (in 2007 dollars, using the CPI for inpatient hospital services) (15), while in developing countries, the costs represent some 10%-30% of the total operating costs of intensive care units (ICUs)(16). When the nosocomial infection is caused by a resistant organism, treatment costs are higher. The difference in the cost of treatment for resistant microorganism and susceptible microorganisms ranges from \$27,600.00 to \$127,000.00 (U.S. dollars), depending on the baseline cost of care (17).

19. Indirect costs are harder to measure, and the data are insufficient. Lack of effective treatment for bacterial resistance is associated with higher patient costs, including travel and lost work.

20. In 2008, the World Health Organization convened an expert meeting on the control of healthcare-associated infections to identify the core components of national and health facility-based programs for the prevention and control of healthcare-associated infections (18). The group concluded that the core components of a program are: organization, technical guidelines, trained human resources, surveillance of healthcare-associated infections, assessment of compliance with international recommendations, support from microbiology laboratories, the environment, program evaluation, and collaboration with public health or other services.

21. Infection prevention and control programs (IPCs) are cost-effective (19, 20, 21, 22). IPC programs can yield savings by reducing nosocomial infections and making appropriate use of antimicrobials or disinfectants and medical supplies. IPC programs are also important for improving the quality of care.

22. Between 2006 and 2007, PAHO, in partnership with national experts, conducted an assessment of the status of prevention and control programs for healthcare-associated infections at 67 hospitals in seven countries in the Region (23). As a result of that assessment, the countries took steps to improve their programs. PAHO is addressing the issue at the regional level.

23. Epidemiological surveillance and the diagnosis of healthcare-associated infections were among the areas found to be in need of additional attention. An analysis of the surveillance situation obtained through the assessments revealed that over half the participating institutions need to improve their surveillance activities.

24. In summary, HAI is a public health problem associated with high direct and indirect costs. Few countries in the Region have a structured HAI surveillance system with integrated national and subnational data available for decisionmakers inside health facilities.

Next steps

25. In the roundtable discussion, the ministers of health will have an opportunity to discuss the impact of antimicrobial resistance from different perspectives: health, social and economic impact; epidemiological information and its potential use; and containment approaches. The conclusions of this discussion should help guide strategies and activities for the containment of antimicrobial resistance. For the ministries to exercise governance, they will have to consider analyzing the six lines of action proposed by the WHO (24) to provide the framework for specific interventions:

- (a) Commit to a comprehensive, financed national plan with accountability and civil society engagement.
- (b) Strengthen surveillance and laboratory capacity.

- (c) Ensuring uninterrupted access to essential medicines of assured quality.
- (d) Regulate and promote rational use of medicines, including in animal husbandry and ensure proper patient care.
- (e) Enhance infection prevention and control.
- (f) Foster innovations and research and development for new tools.

26. Antimicrobial resistance is a threat to health that requires a multisectoral response. Government stewardship is therefore key to success. In practice, stewardship starts with a legal, policy, and regulatory framework that covers all aspects of drug supply and use. It also means bringing together departments across government, together with the private sector and nongovernmental organizations, in ways that promote concerted action. It falls to the ministries of health to head this multisectoral effort, with technical support and relevant standards and guidelines. In this context, the ministers of health could stipulate the need for a regional strategy or plan on antimicrobial resistance containment, to be implemented by the Bureau, that can serve as the framework for future processes.

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