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ANTIMICROBIAL RESISTANCE**
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Mr. Chairman, Ladies and Gentlemen:

Let me thank you for the invitation to participate in this Conference on Antimicrobial Resistance and have the opportunity to address some global concerns. It is good to note that this conference seeks not only to advocate about the nature of the problem, but also is an educational opportunity for the attendees. I feel particularly pleased to deal with an issue directly related to infectious diseases and I never cease to remind audiences that my Organization is sustained by the Pan American Sanitary Code which was signed in 1924. The signatory member governments of the Americas found it necessary to establish a formal treaty -one of whose purposes was

The standardization of the measures employed at places of entry for the prevention of the introduction and spread of the communicable diseases of man, so that greater protection against them shall be achieved and unnecessary hindrance to international commerce and communication eliminated.

The original concern of our founders, and one which I am sure was universal, was related to the transmission or spread of infections. One can almost imagine the resignation to the occurrence of infectious communicable disease and the fatalism about the clinical course of the more serious ones.

I recall as a clinical student the euphoria that attended the administration of antibiotics and the sensation that Paul Ehrlich's magic bullet or magic bullets had really arrived to become a part of the medical armamentarium. The possibility of resistance was a very remote one to us. Obviously, I do not have to relate here how that arrogance has almost been supplanted by fear or at least humility. Whereas in the past there was the sensation that new antibiotics would always be there to treat infections. I sometimes sense a feeling of near panic in speaking to some of my infectious disease colleagues as they watched resistance develop to one after another

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antimicrobial. They saw vancomycin as almost the last line of defense against enterococci and there has been something like a sign of relief with the recent approval by the Food and Drug Administration of linezolid as the first of the oxazolinadones, but we know that resistance to this must be developing already.

My own sense of humility at the possibility of conquering microbes globally has been reinforced on the occasions I have heard Joshua Lederberg speak of the evolutionary paradigm of infectious diseases. He describes how our marvelous technology comes up against the ecological conditions that favor the spread of microbes. We cannot rely on biologic selection to protect us. The number of organisms is so huge and their possibility of change so great, that as he puts it, "In the race against microbial genes, our best weapon is our wits, not a natural selection on our genes." We have indeed reached the stage with regards to antimicrobial resistance, where we will indeed have to use our wits, and this call on wits goes beyond national boundaries.

We know that the genetic basis for antibiotic resistance may be innate or may be acquired basically through either mutational resistance or by horizontal genetic transfer. The presence of antibiotics in the environment of the bacteria encourages the spread of resistance through the well accepted phenomenon of selection pressure. While the effect or consequence of this resistance is the inability to treat or cure an individual patient infected with a particular organism, the impact goes far beyond individual personal care medicine to become a problem of public health significance.

The factors that make emergence of resistance, such as indiscriminate or inappropriate prescription of antibiotics are well known. What is perhaps less well documented, is the widespread use of antibiotics without prescription that occurs in many countries. It is easy to go into many pharmacies, at least in Latin America, and simply purchase antibiotics without a prescription. In one study here on the treatment of acute respiratory infections in children, amoxicillin was purchased in almost half the cases simply on the request of the parent or on the suggestion of the pharmacist, and without a prescription. Cephalosporins were similarly obtained in 10% of the cases. Here I should note the bold step of the Government of Chile to make antibiotics available only through prescription. I would hope to see all countries in Latin America with a similar regulation. It is easy to lay blame on health workers, but we must not forget the role of poverty in the spread of antimicrobial resistance. Poor countries often cannot afford the appropriate drugs, and poor patients cannot pay for the necessary therapy.

There are several factors that make antimicrobial resistance a problem which extends beyond nations. First, there is the obvious movement of people who can transmit infections. International travel is one industry that continues to increase every year, and the transmission of resistant strains of organisms to other localities is a real one. The experience of the transmission of resistant gonococcus is one of the more classic examples of international spread of an organism. In some parts of the world, up to 98% of the strains of gonococci are multidrug resistant.

This is one phenomenon that is genuinely global and is encountered in the poorest of our countries. In our Region, for example, studies in Bolivia show that apparently healthy children from the urban areas carried *E. coli*, of which 97% were insensitive to ampicillin and 94% to

trimethoprim-sulfamethoxazole, which were two of the commonly prescribed antimicrobials. In addition, antimicrobials were inappropriately dispensed for 92% of adults with diarrhea.

Second, these organisms may be spread by food. The growing concern for food safety relates both to the quality of the foods themselves, as well as their capacity to transmit infections with organisms that are resistant. The recent debates over the use of virginiamycin in animal feed and its relation to resistance to synercid are examples of the impact of local practice on the appearance of antibiotic resistance at a distance. I am sure everyone here is aware of the action of the European governments to ban the growth promoters: bacitracin, tylosin, spiramycin, and virginiamycin.

The global concern about antimicrobial resistance relates primarily to the health aspects - the prospects of widespread inability to treat communicable diseases and the fact that the problem cannot be circumscribed within any geographical or social grouping. Indeed, this is a classic example of the phenomenon of globalization in the sense that there are profound local effects of things taking place at a distance. But there are also major concerns about the economics of the phenomenon. The treatment of tuberculosis with conventional therapy costs about \$10-\$30 per person, while the cost of treating a patient with multi-drug resistant tuberculosis is several orders of magnitude higher. We also have to consider the cost of lost productivity from premature death or from protracted illness that might have been avoided.

The global attention to antimicrobial resistance is a manifestation of the increasing concern for the international transfer of health risks. These health risks come from global environmental problems, the promotion of unhealthy lifestyles by international propaganda – smoking is a classic example, and of more relevance here, the clinical practices that result in antibiotic resistant strains of organisms.

Global health risks require global attention and the World Health Organization (WHO) has been developing and promoting the kinds of approaches that are appropriate for global threats. Two years ago, the 51st World Assembly considered the issue of antimicrobial resistance in the context of emerging and other communicable diseases. The Resolution that was adopted urged the Member States to develop the systems to detect antimicrobial resistance, to improve the education on the proper use of antimicrobials, and to improve the practice in the field of communicable diseases.

WHO itself was charged with supporting countries in strengthening their laboratory capacities and in developing their national policies. There should be collaboration among all the numerous actors that are involved in the production, distribution, and use of antimicrobials. The sharing of information among countries and the stimulation of research for development of new agents was clearly a necessity.

More recently, WHO has formulated a global strategy for containment of antimicrobial resistance. There are six main elements to the strategy as it addresses the five major players in the chain of antibiotic protection and use, and the sixth area relates to the nonhuman use of antimicrobials.

The strategy emphasizes that education of the patients and the public is essential, not only for discouraging self-medication with antimicrobials, but also for creating a critical awareness of when microbials should be prescribed in the first place and the need for adherence to the prescribed regimen. The prescribers and dispensers have the responsibility to observe best practices. Everyone is aware of the over prescription of antibiotics and there are several studies documenting the practice in even the most sophisticated societies. Hospitals should have oversight committees that must be concerned not only with the cost of antibiotics, but with their proper use. The growing use of clinical treatment guidelines supplanting much individual anecdotally-based practice is a step in the right direction.

Governments have a role in that they can establish schemes to ensure that only appropriate outlets dispense antimicrobials. Their role also extends to insisting on the bioequivalence of the many generic antimicrobials available and paying attention to good local manufacturing practices.

The pharmaceutical industry is called upon to work with governments and academia in carrying out the necessary research. The production of new agents by the pharmaceutical companies very much depends on the willingness of the individual company to risk its research effort and also on the potential market. Of equal importance is the requirement for providing prescribers with accurate information.

WHO has been firm in calling for the prohibition of the use of growth promoting agents in animal foods, as they may lead to the development of resistance in humans to other antimicrobials. This is an issue of intense commercial and political debate.

Essential drugs' policies that are being vigorously promoted by WHO represent a powerful tool in the efforts to reduce antimicrobial resistance globally. The centerpiece of these policies is the essential drug list. Proper use of these lists has been shown to have an impact on the availability and rational use of most of the commonly used antimicrobials.

WHO has been involved in a very active partnership with the International Union Against Tuberculosis and Lung Disease that has established a Global Project on Anti-Tuberculosis Drug Resistance Surveillance. This has produced invaluable information on the global situation. One of the good features of this project, which has extended to some 72 geographical settings in various parts of the world, has been the standardization of criteria for diagnosis and the use of good epidemiological practice.

There have been serious attempts to stimulate regional action in the Americas in this field. One of the key requirements, in our view, has been the strengthening of the capacity of the national laboratories to diagnose the infections and detect antimicrobial resistance. PAHO has been collaborating actively with the Canadian Laboratory Center for Disease Control in this effort. Laboratories from 18 countries are currently participating in a network that originally concentrated on establishing the pattern of antibiotic sensitivity for salmonella, shigella, and v. cholera. These organisms were selected because they are potent causes of diarrhea and are often treated with antibiotics. Of course, salmonella may also be transmitted by foods to far distant places.

PAHO has also paid special attention to the prevalence and antibiotic sensitivity of streptococcus pneumoniae because of its impact on child health, and has involved 70 hospitals in 30 cities of six countries in a surveillance system to determine the prevalent serotypes and antibiotic sensitivity. Our efforts have been concentrated recently on the laboratory aspect, which we believe is fundamental for the production of any good data on the prevalence and seriousness of antimicrobial resistance. Our colleagues in the Eastern Mediterranean Region of WHO, have produced an excellent set of Guidelines for Antimicrobial Resistance Surveillance. These guidelines give indicator organisms the antimicrobials to be tested, the method of testing, and advocate a quality control program that should validate the results. I am sure that there are similar efforts underway in other regions.

The global nature of the threat and the need for a global effort are clear, and I was pleased to note that the Select Committee on Science and Technology recognized this in its Seventh Report. This area is one that is ripe for technical cooperation among countries. Our experience shows that this is indeed feasible and I hope that this Conference will stimulate thinking and action along these lines. I insist that what is needed is technical cooperation among countries and not cooperation among developing countries. The problem has its genesis in all countries, and it is in the interest of all that the approach to a solution be genuinely international and free from any connotation of a donor/recipient relationship. It is clear for us that this is the only way we can fulfill our pristine purpose of "achieving greater protection against the communicable diseases of man." A major complication now, of course, is that in some ways we are approaching the situation that existed in 1924 when the means of effective treatment of these diseases were few. But I take heart in the fact that our wits are as sharp now as they were before antimicrobials appeared.