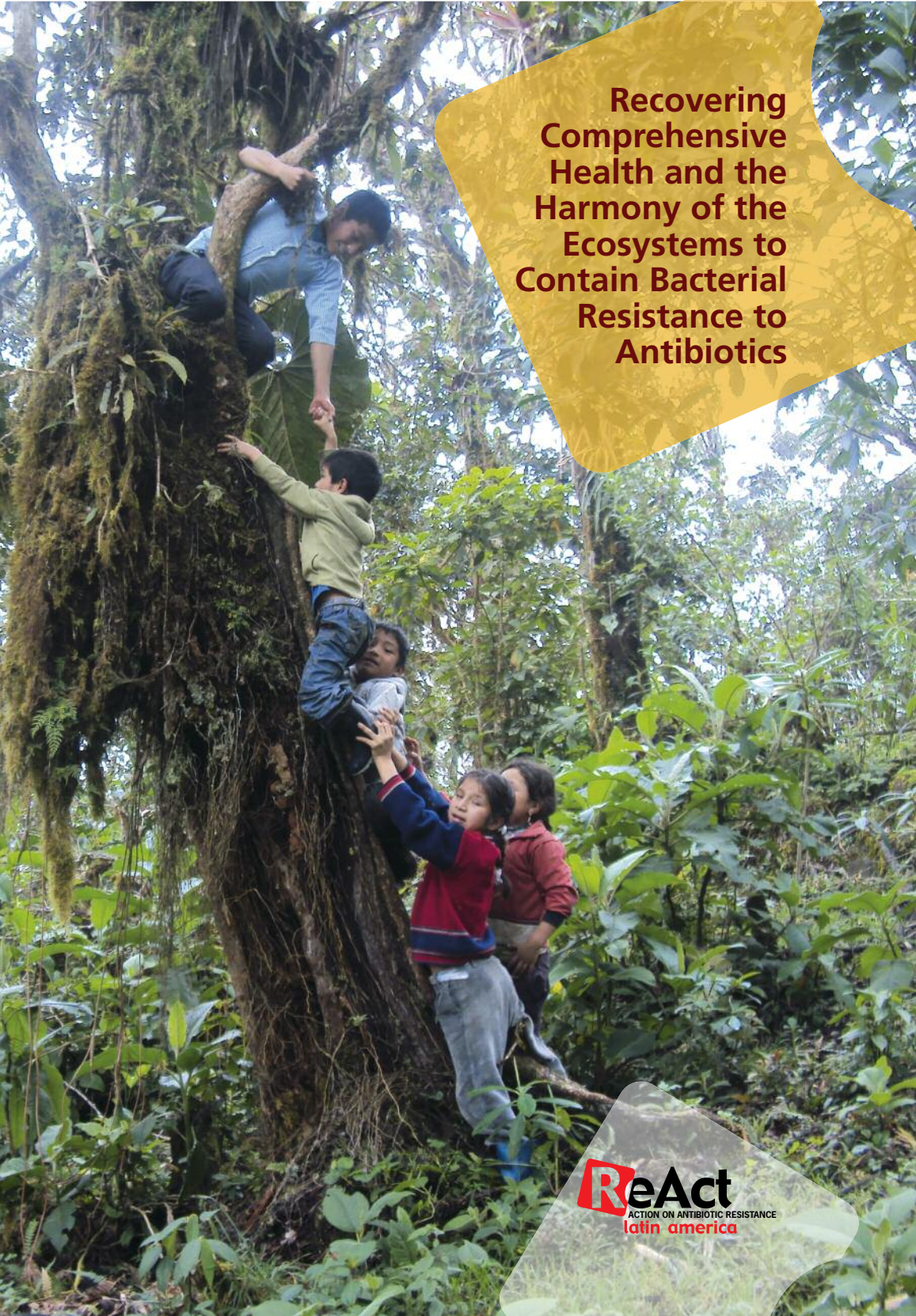

Recovering Comprehensive Health and the Harmony of the Ecosystems to Contain Bacterial Resistance to Antibiotics

ReAct
ACTION ON ANTIBIOTIC RESISTANCE
latin america

Recovering Comprehensive Health and the Harmony of the Ecosystems to Contain Bacterial Resistance to Antibiotics

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Cuenca, Ecuador, 2011.

Note on the cover photograph: Children from Molleturo - Azuay province, Ecuador, playing in a forest.

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Introduction

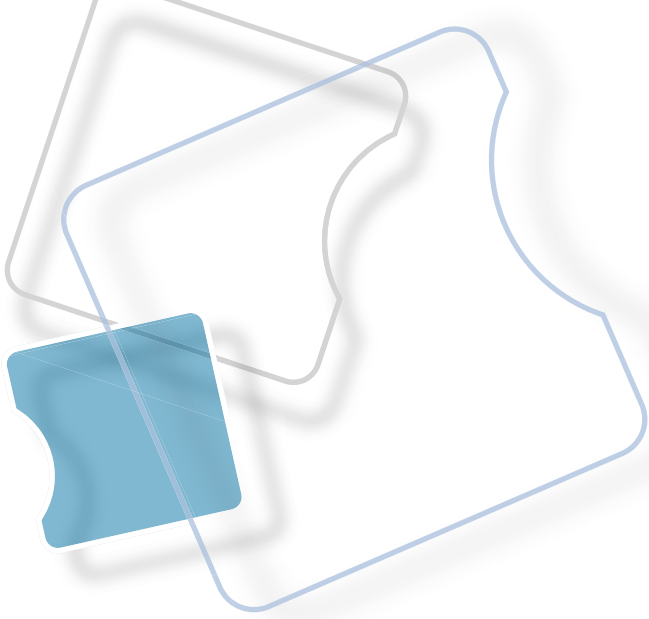
Bacterial resistance to antibiotics or more commonly referred to as Antibiotic Resistance (ABR) is a global health problem. It occurs in low- and middle-income countries as well as in high-income countries, and in both hospital and in community settings with strong impacts in terms of morbidity, mortality and costs.

Infections from microorganisms resistant to antibiotics constitute part of the group of re-emerging diseases, the incidence of which has increased dramatically in humans in recent years, and which poses a therapeutic challenge for the future.

The technical aspects needed to contain antimicrobial resistance were set out in the *Global Strategy for Containment of Antimicrobial Resistance* of WHO,[1] published in 2001. However, until now there are no practical guidelines to establish priorities or initiate social and political processes for the creation of national programs on the subject.

The World Health Assembly resolution of May 2005, *Improving the containment of antimicrobial resistance* (WHA58.27),[2] called on all countries to initiate activities and work toward the structuring of national groups on ABR.

There is little awareness, little monitoring and limited policies to address the problem and to promote the appropriate use of antibiotics at the level of the community, health professionals and the authorities. This is due to the lack of scientific information and the fact that comprehensive training and community based programs do not exist.



The environmental pollution from antibiotics, that triggers selection of resistant bacteria, adds an ecological dimension to the problem.[3] It must be remembered that the problem is connected to a broad spectrum of factors (medical, social, economic, political), and actors, including governments, international organizations, pharmaceutical companies and the general population.

So our main challenge is to create an atmosphere of alertness, awareness and commitment of professionals, authorities, academics and community to contribute to successful regional, national and local action.

This challenge is being met by gradually building up a sustainable and participatory network that generates long term energy, commitment, planning and executive actions that are relevant and effective for peoples' lives.

A key aspect is to create strong ties between academic institutions, organizations and experts in Latin America that work in infectious diseases, resistance to antibiotics, microbiology, pharmacology, and social and community organizations.

The actions we undertake should incorporate the problem of ABR into practical activities to confront the causes of resistance.

By uniting with regional groups with research, training and technical expertise, ReAct Latin America (RLA) has the opportunity to introduce the problem into broad social, political and health sectors that have not yet worked on the issue, while as part of ReAct Global, has at its disposal global expertise, information and opportunities for concerted action.

Purposes

- To make ReAct Latin America an active and creative network that promotes social and political awareness, mobilizes the community and health professionals to action, research and health promotion, aimed at containing bacterial resistance to antibiotics.
- To recover and develop a holistic vision of health that encompasses a harmonious relationship with the ecosystems.
- To emphasize the prevention and treatment of infections, including the appropriate use of antibiotics.

Objectives

- Promote awareness of the increase in bacterial resistance to antibiotics in Latin America.
- Boost the inclusion of ABR on the agenda of social and health networks in Latin America that have not previously worked in the problem.
- Build links with groups of experts in antimicrobial resistance, rational use of antibiotics, infectious diseases and pharmacology.

Causes, characteristics and difficulties related to ABR and its containment

ABR is one of the most worrying public health problems in the world. In Latin America, as well as in poor countries in other regions, it has become a major threat.

Undoubtedly, the misuse and abuse of antibiotics are the direct cause, but it is very important to recognize ABR as a multicausal problem of enormous complexity. All the following factors have contributed to the misuse and abuse of antibiotics and consequently the increase of resistance: the high prevalence of infectious diseases; the increase in poverty; the high cost of drugs; the fees for services; the absence of quality controls; the free sale of drugs in stores and pharmacies and advertising/promotion pressure by media.

The agriculture sector as well as the pharmaceutical industry holds considerable responsibility for the increase in consumption of antibiotics. The pharmaceutical industry contributes through its activities in the non-ethical promotion and distribution of medicines.

ABR is a community and hospital problem that is amplified by the frequency and speed of intra and

international travel. With the consequent 'export', let us say, of resistant organisms, arises the globalization of resistance to antibiotics. This is intensified given the ability of resistant bacteria to spread extensively through human, animal and plant populations and other elements of the environment, without respecting geographical or political limits.

It has been difficult to activate politicians, high-level health officers and other actors because ABR is not a visible problem[4] as are diseases such as HIV/AIDS or SARS which pose an obvious threat to everyone. In addition, due to the multicausality of ABR, tackling it is not the responsibility of a particular institution, authority or organization[5]. This requires the sensitization and participation of all in the search for solutions, in the short and long term, to enable the timely assimilation and internalisation of the ABR problem.

In the same way, it is complicated to measure the burden that bacterial resistance imposes on the population (diseases, death or costs) and to measure the short-term effects of efforts implemented to combat it.[6]

In any case, the key components of a strategy to tackle the problem have been widely identified, but nevertheless have not merited urgent action at the levels of political decision-making. Neither have the financing institutions shown interest.

While it is true that some countries have instituted their action plans at a national level, some of them have not succeeded in stopping the advancement of antiobiotic resistance due to a lack of coordinated multi-sectoral and global action.

Magnitude of the problem of bacterial resistance to antibiotics

"The golden era of antibiotics ended many years ago. Today in the whole world the increase in bacterial resistance to antibiotics is compromising the treatments for common diseases."[7] The specific burden of resistance in morbidity and mortality statistics at the global level, deserves particular attention of the health sector. In low and middle-income countries, 70% of neonatal infections acquired in hospital cannot be successfully treated using the recommendations of the World Health Organization (WHO)[7]. In a study released in 2009 in a parallel event to the World Health Assembly, it was reported that almost half of the patients in a hospital center in Uganda (28 of 62) did not respond to available antibiotics because of bacterial resistance (86% of newborns).[8]

These data, alarming in themselves, do not show the full magnitude of the problem, because ABR also prolongs disease and increases the cost of treatment. ABR is responsible for a consistent rising trend in mortality indicators. In England and Wales, the number of deaths caused by methicillin-resistant *Staphylococcus aureus* (MRSA) increased from less than 50 in 1993 to more than 1,600 in the year 2006.[9] In Southeast Asia, it is estimated that a child dies every two minutes due to the action of resistant bacteria.[10]

The problem is becoming much more serious, however, due to the emergence of new mechanisms of bacterial resistance, making these virtually immune to antibiotic action. Bacteria carrying NDM-1 (New Delhi metallo-betalactamase) were reported between 2007 and 2009 in bacterial samples collected from hospitalized patients in two areas of India (Chennai, and Haryana), and in patients referred to the national laboratory of the United Kingdom. From these samples they found 44 infected with NDM-1in Chennai, 26 in Haryana, 37 in Britain and 73 elsewhere in Bangladesh, India and Pakistan. Several of the infected British patients had recently travelled to India or Pakistan to receive hospital treatment, including cosmetic surgery. NDM-1 confers a high resistance to most antibiotics including carbapenems but not to colistin and tigecycline. This greatly limits the possibilities for successful treatment of patients with multi-resistant bacteria. NDM-1 is found primarily in *Escherichia coli* and *Klebsiella pneumoniae*.[11]

During January to June 2010, the Center for Disease Control (CDC) in the United States identified the first report of three isolates of *enterobacteriaceae* carrying NMD-1. The isolates were from *Escherichia coli, Klebsiella pneumoniae,* and *Enterobacter cloacae*.[12] From September 26 to October 10 of 2010, NDM-1 was detected in 2 of 50 samples of drinking water and 51 of 171 samples of water seepage (i.e. water pools in streets or rivulets) in New Delhi. NMD-1-carrying bacteria that were cultured included 11 species in which NMD-1 has not been previously reported, including *Shigella boydii* and *Vibrio cholerae*.[13]

Bacterial resistance to antibiotics in the countries of the andean region

In Latin American countries, the problem of antibiotic resistance is increasing rapidly. Based on the epidemiological profile of the region, this portends a terrible scenario. In the last two decades the expansion and the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased significantly, becoming one of the nosocomial pathogens of greatest importance. In recent years MRSA strains from the community with epidemiological characteristics and different genetics to those found in hospitals have been detected.

Re-emerging diseases are maintaining an upward trend, despite variations especially in impoverished nations and in social strata. In 2009 at the global level there were 5.8 million reported cases of tuberculosis with 1.7 million deaths corresponding to a rate of 20 deaths per 100,000 inhabitants. It was estimated that 250,000 patients had multi-drug resistant tuberculosis (MDR-TB), with only 12% being diagnosed and notified.[14] In 2008, 963 cases of extremely drug-re-

Table 1. Percentage of antibiotic resistance in bacteria reported at the community level in countries of the andean region

COUNTRY	*Salmonella typhimurium*		*Shiguella flexneri*		*Staphylococcus aureus*		*Neisseria gonorreae*		*Streptococcus pneumoniae (no meningitis)*		*Escherichia Coli*	
Venezuela	AMP	77,7%	AMP	100%	OXA	27%	PEN	100%	-------	-------	-------	-------
	-------	-------	-------	-------	ERI	34%	CIN	100%	-------	-------	-------	-------
Colombia	AMP	42%	AMP	84%	-------	-------	PEN	90%	OXA	47%	-------	-------
	TCY	89%	-------	96%	-------	-------	-------	-------	-------	-------	-------	-------
Perú	-------	-------	AMP	88%	-------	-------	-------	-------	OXA	44%	-------	-------
	-------	-------	-------	-------	OXA	24%	-------	-------	-------	-------	AMP	62%
Bolivia	AMP	87%	CTX	55%	OXA	61%	GEN	82%	CIP	46%	CTX	59%
	-------	-------	-------	-------	-------	-------	CAZ	81%	GEN	43%	-------	-------

AMP: ampicilin; TCY: tetracycline; OXA: oxacilin; PEN: penicilin; ERI: erithromycin; NIT: nitrofurantoin; CIP: Ciprofloxacin.
Fuente: Red de Monitoreo/Vigilancia de la Resistencia a los Antibióticos 2008. OPS/OMS.

sistant tuberculosis (TB-XDR) were reported in 33 countries contrasting with 772 cases from 28 countries in 2007. It is believed that many cases of TB-XDR are not diagnosed due to the fact that laboratories do not have the capacity to determine resistance to second-line drugs.[15] In the region of the Americas it is estimated that in 2008, there were 8,200 new cases of MDR-TB.[16] The highest rates of MDR-TB were observed in the Dominican Republic (6.6%), Peru (5.3%), Ecuador (4.9%) and Guatemala (3.0%).[17] The average cure rate at the regional level has been 59%, but with large variations between countries, within the same countries and throughout the different years.

There is no updated data with regard to *Vibrium cholerae*, which was the cause of various epidemics in recent decades. In 1996 in Nicaragua, the resistance to trimethoprim sulphamethoxazole and ampicillin reached 29.3%. In Ecuador, in 1998, isolated strains were identified that had a resistance of 5.6% to erythromycin, and the only strain resistant to amoxicillin was multiresistant.[18] In Peru between 1997 and 1999 *V. cholerae* showed average resistance of 19% to trimethoprim sulphamethoxazole, 12.1% to tetracycline and 10.2% to ampicillin.[19] According to the 2002 report of the bacterial resistance surveillance monitoring network, in Peru there was up to 50% resistance to ampicillin (5/10), in Brazil up to 52% resistance, and in Cuba up to 14% resistance to ampicillin. For that year Ecuador had not submitted isolates.[20]

Table 2. Percentage of antibiotic resistance in bacteria reported at the hospital level in countries of the andean region .

COUNTRY	*Escherichia coli*		*Klebsiella penumoniae*		*Staphylococcus aureus*		*Acinetobacter baumanni*		*Pseudomona aeruginosa*		*Enterobacter spp*	
Venezuela	AMP	70%	AMP	96%	PEN	90%	TZP	86%	CFP	34%	-------	-------
	-------	-------	-------	-------	OXA	29%	SXT	82%	CIP	33%	-------	-------
Colombia	AMP	65,4%	AMP	93,5%	PEN	93,5%	CIP	72%	-------	-------	FOX	100%
	-------	-------	-------	-------	OXA	38%	GEN	71%	-------	-------	CEP	93,1%
Perú	AMP	82%	AMP	100%	PEN	95%	-------	-------	GEN	55%	AMP	95%
	-------	-------	-------	-------	OXA	72%	-------	-------	CAZ	54%	CEP	97%
Bolivia	AMP	87%	CTX	55%	OXA	61%	GEN	82%	CIP	46%	CTX	59%
	-------	-------	-------	-------	-------	-------	CAZ	81%	GEN	43%	-------	-------

AMP: ampicilin; CTX: cefotaxime; OXA: oxacilin; PEN: penicilin; SXT: trimetroprim+sulfamethoxazole; CIP: ciprofloxacin; GEN: gentamicin; CAZ: ceftazidime; TZP: piperacilin-tazobactam; CFP: cefoperazone; FOX: cefoxitine CEP: cefalotine.
Fuente: Red de Monitoreo/Vigilancia de la Resistencia a los Antibióticos 2008. OPS/OMS.

Nosocomial infections associated with devices

Device-associated infections (DAI) constitute one of the main causes of extra days of hospital stay (EDHS) and mortality in intensive care units (ICU). In a study conducted in hospitals affiliated with INICC (International Scientific Community for the Control of Nosocomial Infections), it was found that the total rate of nosocomial infection (NI) was 13.9 per cent and 21.6 per 1000 bed days.

Respirator-associated pneumonia (RAP) accounted for 41.2% of all DAI; bloodstream infections associated with central venous catheters accounted for 31.0% and cather-associated urinary tract infections associated accounted for 27.8%.

83.8% of DAI were caused by methicillin-resistant *Staphylococcus aureus*. Other organisms of importance are: *enterobacteriaceae* species resistant to ceftriaxone (51.3%); *Pseudomonas aeruginosa* resistant to fluoroquinolones (58.3%); and *Enterococcus sp* resistant to vancomycin (3.3%).[21]

Bacterial resistance to antibiotics in Ecuador

The Bacterial Resistance National Network of Ecuador (REDNARBEC), created in 1999, is the organization that presents data on bacterial resistance both at the community level and in the hospital setting in Ecuador.

The most recent data available for the year 2008 reported that at the community level the resistance of *Shigella spp* to tetracycline was 96% and to ampicillin was 93%. *Salmonella spp* were 30% resistant to tetracycline. *Escherichia coli* was71% resistant to ampicillin and tetracycline, *Staphylococcus aureus* was 30% resistant to erythromycin and 25% to oxacillin.

At the hospital level: *Escherichia coli* was 77% resistant to ampicillin; *Klebsiella pneumoniae* was 65% resistant to cefotaxime; *enterobacter* showed up to 67% resistance to ampicillin sulbactam; *Staphylococcus aureus* was 41% resistant to oxacillin; *Acinetobacter baumannii* was 68% resistant to trimethoprim + sulfamethoxazole and 64% resistant to ciprofloxacin. *Pseudomonas aeruginosa* was 55% resistant to gentamicin and 54% resistant to ciprofloxacin.[22]

The use of antibiotics in animal production and the ecological, social and economic impact

After their success in human medicine, antibiotics were gradually introduced into the treatment and prevention of diseases in animals, fish and plants. In addition, once the effects of subtherapeutic doses of antibiotics in accelerating growth was demonstrated, they have been used intensively for decades in animal husbandry.[23]

In the year 1946, US researchers showed that streptomycin and sulfasuxidine (a sulfonamide drug used for treatment of enteric infections in chickens) accelerated the growth of chickens, an observation that largely went unnoticed at the time. This was subsequently confirmed by proving that waste from the fermentation of tetracycline increased growth, an effect which was initially attributed to vitamin B12. It is not yet known exactly how growth promoters exert their action, but there are three accepted explanations. The subtherapeutic dose of the antibiotic:

a. Controls infectious diseases;

b. Maintains a gut lining that absorbs nutrients more effectively;

c. Eliminates commensal bacteria so that they do not divert some nutrients from the host.

The maximum impact of growth promoters occurs in the early stage of life. It is interesting to note that the effects of some antibiotics on growth are most noticeable in unhygienic conditions than when animals are kept in new premises or in completely clean establishments, which suggests that the suppression of intestinal microbes is an important effect.[24]

In the mid 1990s, the spread of *Enterococcus* strains with high level resistance to vancomycin in food samples, sewage and feces from humans and healthy animals was observed in various European countries. However, these type of drug-resistant strains were uncommon in clinical samples. The situation in the USA was the opposite, where strains of *Enterococcus* resistant to vancomycin in human clinical samples was detected in a relatively high proportion but not in environmental, food and intestinal samples, It is thought that the use of avoparcin (a molecule with structure and mechanism of action similar to vancomycin thereby generating cross-resistance) used for animal growth and authorized for this purpose in

Europe until 1997 but never allowed in the US, could have contributed to the selection of strains of *Enterococcus* resistant to vancomycin in animals...[25] The first authorizations of antibiotics as growth promotion additives totalled 13 substances and rose to a maximum of 24 in December 1998. This list has progressively reduced since the Council of the European Union banned the use of most of them, only authorizing the use of four: flavophospholipol, monensin sodium, salinomycin sodium and avilamycin. A ban was proposed on these by the Commission of the European Union in January 2006. The prohibition of the use of growth promoters in animal feed was based essentially on the danger posed by the ability of these substances to create cross-resistance to the antibiotics used in human medicine. However, some sectors point to other reasons, such as commercial interests and the ability to block the import of animal products from countries in which the use of these substances is allowed.[26] The situation in the US in regard to growth promoters has been and is very different. Currently approved as growth promoters are: penicillin, chlortetracycline, erythromycin, spectinomycin (all these antibiotics are of use in humans), tylosin and virginiamycin (antibiotics with structures similar to others used in humans).[25]

In the 2001 report *Hogging it¡ Estimates of antimicrobial abuse in livestock*, it was estimated that "70% of all antibiotics used in the United States - more than 24 million pounds a year - are added daily to food and water of healthy livestock"...and often are excreted without alteration. According to a study by J. C. Chee-Sanford and collaborators in 2001, up to 75% of tetracycline given to pigs was excreted without alteration. These drugs may persist in the environment, which creates an opportunity for the selection of resistance within bacterial populations. Animal waste management practices include "application to the earth": the spreading of waste on the soil surface by way of fertilizer which can result in contamination of the soil and surface water or groundwater. Many

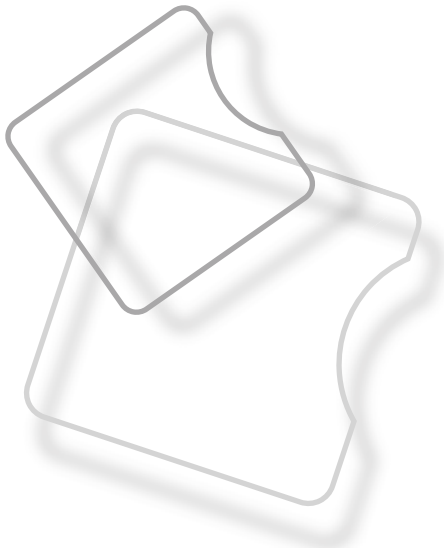

El agua es el vehìculo de la naturaleza hoy, no la contamines ni desperdicies, porque mañana, podria ser tarde.

conventional breeding operations also used waste gaps, which provide an alternative route by which birds and insects can receive bacteria resistant to antibiotics.[27]

In Latin America irresponsible aquaculture constitutes a serious danger. Aquaculture countries such as Chile consume large quantities of antibiotics. In the year 2000, consumption was approximately 500 tonnes[28], using antibiotics essential for human health including: quinolones such as nalidixic acid and oxolinic acid; amoxicillin, ampicillin, cefotaxime, chloramphenicol, erythromycin, furazolidone, gentamicin, kanamycin, streptomycin, tetracycline, trimethoprim-sulfa, among others.[29]

All the above-mentioned data show us that the food security of peoples and communities is in serious danger, because many of their traditional foods are reporting high levels of metabolites of antibiotics. Residues of antibiotics in food can cause an anaphylactic reaction and other allergic manifestations in the gut, skin and respiratory tract.[30] Therefore the prohibition of antibiotics as growth promoters must be understood as a security measure in public health, not as a purely political measure.[25]

Infectious diseases, environment and society



To understand the gravity of the problem, it is necessary to take into perspective that environmental changes have multiple direct and indirect effects on human health. By way of evidence, the rise in temperature and humidity influences the abundance and distribution of vectors and host intermediaries, and therefore, the spread of infectious diseases. Today we see a resurgence of diseases which we thought were defeated, such as zoonoses from host animals that have entered in concentrated human populations after significant climate changes.

There is an urgent need to integrate knowledge on bacterial resistance and infectious diseases with reference to climate, environmental, migration and demographic change. All are linked inextricably and involved in the modified patterns observed today in infectious diseases. Another key element is to accept that the phenomenon is not local but global, and to confront it needs scientific, political, social and economic responses by all countries.[31]

At the level of governments, authorities, health agencies and communities there has been no action contemplated against ABR as a priority in health policies, with a comprehensive and holistic approach, which involves social dimensions, economic and environmental concerns, and that can be applied in all localities, countries and regions, toward the objective of restoring the harmony of ecosystems.

Strategies

1. Establish a sustainable base for the work of ReAct Latin America (RLA) through existing networks:

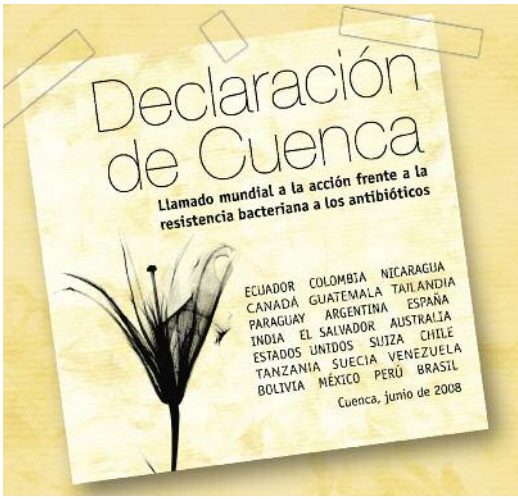
- Introduce the topic to the agenda of existing networks in the region such as the Latin American and Caribbean Women's Health Network and the Alegremia Network.
- Interlink networks of experts in Latin America in infectious diseases, antibiotic resistance, microbiology and pharmacology.
- Build slowly but firmly a movement that stirs the formation of groups that generate information, initiatives and ideas.
- Disseminate information on ABR, including local, national and regional data, within a holistic context, in order to raise social awareness.
- Develop and disseminate popular education material, facilitate its free printing and promote its use to group and community level.

2. Integrate technicians, experts and academic institutions in the network

- Activate and promote ties of cooperation and coordination in the network with academic institutions that know about and are interested in ABR.
- Encourage the action, participation and the exchange of experiences and information in the field of microbiology, pharmacology, infectious diseases and resistance to antibiotics.

3. Gradually establish links with other groups in Latin America

- Explore new contacts and encourage the integration into the network of professional and academic associations, such as the National Association and the Latin American Association of Faculties of Medicine, the Latin American Association of Social Medicine (ALAMES), and civil society and other organisations.



Lines of action

1. Educommunication:

- Compilation, editing and publication of a newsletter aimed at promoting the health of ecosystems, in connection with bacterial resistance.

- Production of popular education material based on regional evidence, including cartoons on resistance to antibiotics; dissemination via the Internet and printing for distribution to local organizations.

- Opening of a permanent forum for exchange of information among members of the different networks.

- Translation, synthesis and adaptation of ReAct Global documents, to the regional, national and local cultural context.

- Planning and development of activities in Ecuador, as a way to influence groups and authorities working locally and regionally within the country.

2. Construction, development and consolidation of an action network:

- Promote the participation of those who have the interest, knowledge and energy to work on the themes in different places and in different situations, and to stimulate action.

3. Promote research, training and capacity building:

- Promote research at local, national and regional levels as a mechanism to assess the situation and the search for determining factors in the development of ABR for understanding and action.

- Training at different levels of the population, starting with health professionals, through a training program at the postgraduate level related to Primary Health Care, Infectious Diseases, ABR and rational use of antibiotics. This process will be undertaken with inter-agency and international support.

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Summary

Bacterial resistance to antibiotics or more commonly referred to as Antibiotic Resistance (ABR) is a global health problem which occurs as much in low and middle income countries as in high income countries, as much in the hospital setting as in the community, with strong impacts in terms of mortality, morbidity and costs.

The inappropriate use and abuse of antibiotics in human medicines and agriculture and aquaculture are the direct cause of antibiotic resistance.

Our principal aim is to create an environment of alertness, awareness and commitment of professionals, authorities, academics and the community to contribute to dynamic regional, national and local action.

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