ANTIBIOTIC

INTERNATIONAL REPORT

Antibiotic Resistance in Spain: What Can Be Done?

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The document Antibiotic Resistance in Spain: What Can Be Done? was prepared in 1994 by an ad hoc Task Force under the auspices of the Spanish Ministry of Health. The problem of the development of antibiotic resistance in community-acquired bacterial pathogens in Spain and its relation to antibiotic use and consumption has been of both national and international concern. This document analyzes the problem and provides general recommendations for limiting the emergence, evolution, and spread of resistant microorganisms. Particular emphasis is given to systems for surveillance of antibiotic resistance, the monitoring of patterns of antibiotic use and consumption, and strategies for influencing the producers (pharmaceutical industry), prescribers (physicians and veterinarians), dispensers (pharmacists), and consumers (patients) of antibiotics. Control of the emergence of antibiotic resistance requires a concerted effort on the part of all social and scientific agencies involved in health care.

In December 1994, a document entitled Antibiotic Resistance in Spain: What Can Be Done? was distributed by the Agency for Health Planning of the Spanish Ministry of Health. This document presents an integrated point of view from a panel of academic experts in the fields of clinical microbiology, infectious diseases (in both children and adults), internal medicine, clinical epidemiology, veterinary microbiology, and public health administration. The panel tried to write the final report in a simple style, making the information accessible to both health care workers and consumers.

See the editorial by Levy on pages 824–6

This document reflects the interest of the Spanish public health authorities in counteracting the worrisome problem of microbial resistance to antibiotics. In fact, resistance to antibiotics, particularly in agents of community-acquired infections, has caused concern among the general public in Spain. Moreover, the possibility that Spain may serve as a source of resistant strains for other areas of the world underscores the responsibility of the Spanish public health authorities to implement effective control measures. The objective of this document is to provide a comprehensive framework to support the necessary actions.

The Document

During treatment with antibiotics, hundreds of thousands of bacteria, most of which are unrelated to the etiologic agent of a particular infection and are frequently part of the normal human flora (that has evolved over millions of years), are destroyed. This selection pressure results in the emergence of resistant microorganisms. Spain is one of the countries where higher rates of antibiotic resistance have been documented, particularly among community-acquired bacterial isolates.

Antibiotic resistance is spreading across Spain's borders. It is therefore imperative that the Spanish health authorities and scientific societies make the solution of this problem a priority by encouraging and supporting specific programs to control the emergence of microbial resistance to antibiotics. Antibiotic Resistance in Spain: What Can Be Done? is aimed at all persons concerned with health policy, i.e., patients, doctors, nurses, pharmacists, veterinarians, executives of the pharmaceutical industry, and public health authorities, because a concerted effort on the part of everyone in Spain is required to control this increasingly menacing problem.

The Problem

Antibiotic Resistance

The prevalence of resistance in human bacterial pathogens. During the last decade, a well-developed network of hospital microbiology laboratories throughout Spain has collected data on antibiotic resistance patterns. Resistance rates for nosocomial bacterial isolates are well within the average rates observed throughout Europe; however, for community-acquired bacterial isolates, resistance rates are among the highest in the European Union.

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Consensus was reached by the Task Force as to the current resistance patterns in Spain. The figures are as follows for specific organisms and antimicrobial agents: 17% of *Streptococcus pyogenes* isolates in the Basque Region are resistant to macrolides; 40% of *Streptococcus pneumoniae* isolates are resistant to penicillins, and 18% are resistant to macrolides; 40% of *Haemophilus influenzae* isolates are resistant to aminopenicillins; 35% of *Neisseria meningitidis* isolates have diminished susceptibility to β-lactam agents; 25% of *Salmonella typhimurium* isolates are resistant to ampicillin; >50% of *Campylobacter jejuni* isolates are resistant to fluorquinolones; 50%–60% of *Escherichia coli* isolates are resistant to aminopenicillins, and 10% are resistant to fluorquinolones; and 25% of *Bacteroides fragilis* isolates are resistant to cefoxitin and/or clindamycin.

**Current patterns of resistance to antibiotics in animals and in the environment.** Resistant microorganisms that colonize animals may be important because these microorganisms may be capable of colonizing or infecting humans and because they may serve as reservoirs of resistance genes. Of *E. coli* isolates recovered from piglets with diarrhea, 80% were resistant to tetracyclines, 40% were resistant to ampicillin, co-trimoxazole, or neomycin, 21% were resistant to gentamicin, and 11%–23% were resistant to nalidixic acid.

More than 50% of *Campylobacter* species are resistant to fluorquinolones. A rate of resistance to gentamicin has been observed among urinary *E. coli* isolates from dogs, and 20% of *Staphylococcus aureus* isolates have been found to be resistant to methicillin by members of the Task Force. Enterobacteriaceae and *Enterococcus* isolates from sewage have resistance rates similar to those of isolates from humans and animals.

**Antibiotic Consumption in Spain**

**Consumption by humans.** Antibiotic consumption by outpatients accounts for 90% of the total consumption of these drugs and may be related to the emergence of microbial resistance. The peak of antibiotic consumption by outpatients occurred between 1966 and 1976. In 1976, the total number of antibiotic units (boxes) supplied through drugstores was nearly 110 million, equivalent to 31 defined daily doses (DDD) per 1,000 persons per day (i.e., ~366 tons per year, or 1 ton per day). From 1976 onward, the total consumption of antibiotics in Spain decreased: 104 million units were purchased in 1978, whereas 92 million units were purchased in 1983, and 76 million units were purchased in 1988.

This latter level has been maintained in recent years: in 1993, the consumption was 19 DDD per 1,000 inhabitants. About 50% of the currently consumed antibiotics are aminopenicillins; other frequently used antibiotics include macrolides (17%), oral cephalosporins (13%), and fluorquinolones (6%).

**Antibiotics used in animal feed and veterinary medicine.** Spiramycin, tilosin, and virginiamycin (macrolides/streptogramins) and avoparcin (glycopeptide) are among the antibiotics accepted as feed additives for animals. Members of the Task Force have estimated that in 1984, ~250 tons of antibiotics (roughly two-thirds the amount consumed by humans) were used as growth promoters in chickens and pigs. The addition of antimicrobials (including most classes used in humans) in feed or water for therapeutic or prophylactic purposes remains uncontrolled, and the volume of drugs used is high (kilograms per ton are administered). In addition, the use of “human” antibiotics for the treatment of infections in pets should not be underestimated since the pet population in Madrid is estimated at ~0.5 million.

**Use of Antibiotics**

According to the results of a recent study carried out by the Spanish Society of Chemotherapy, 81% of the consulted general practitioners prescribe antibiotics every day. In a recent 1-day national survey conducted in the spring of 1994, it was determined that of 48,076 outpatients seeking care at primary care clinics, 22% had infections diagnosed, and most (14.4%) of these infections were respiratory. Antibiotics were prescribed in two-thirds (66.9%) of the cases; however, the drugs prescribed were considered inadequate in 36.5% of cases.

**The bases for prescribing antibiotics.** Why are antibiotics prescribed so extensively in Spain? Patients urge physicians to give them “strong, effective antibiotic treatment.” In busy practices, physicians may not have the time to make an appropriate differential diagnosis or to explain the risks of unjustified antibiotic therapy to patients and adopt a defensive attitude towards prescribing these drugs. The marketing procedures of the pharmaceutical industry may also play an important role in the over-prescription of antibiotics.

**Appreciation of the problem by clinicians.** With respect to the treatment of infectious diseases, the clinical importance of microbial resistance to antibiotics remains unclear to many Spanish physicians—even some who are experts in antimicrobial chemotherapy.

**Demographics and attitudes of the patients and consumers.** In 1993 the population of Spain was 39,402,000. In 1989 the total number of outpatient consultations in Spain was 465 million (International Medical Services [IMS]), and 80% of these consultations resulted in at least one prescription. Acute respiratory infection was the most common reason for consulting a physician, accounting for 10.6% of office visits (1,268 consultations per 1,000 inhabitants); this rate is much higher than the mean rate for the general European Community (i.e., 6.4% or 556 consultations per 1,000 inhabitants).

In a recent pan-European survey, the “demand index” for antibiotics among patients in Spain was 1.7, only surpassed by that in France (2.2); however, this figure was higher than that in Belgium or the United Kingdom (1.5) or in Italy (1.3). In Italy, 44% of interviewees considered antibiotics “dangerous for children”; in Spain, only 14% (the lowest score) of respon-
dents held this belief. The compliance rate among Spanish patients is low: only 58% of these patients complete the scheduled treatment, whereas in France or the United Kingdom, 84% and 91% of patients, respectively, complete therapy.

The pharmacies. There is a network of pharmacies that are associated with the national health system in Spain; these pharmacies (roughly one pharmacy per 2,000 inhabitants) are located throughout the country. It is believed that ~7% of all drugs are illegally dispensed, without the required prescription form. Of these, almost 35% are antibiotics.

The pharmaceutical industry. Continuous research and development of new antimicrobial agents are essential in the fight against microbial resistance to antibiotics. Nevertheless, only rarely is the role of the pharmaceutical industry in the development of resistance considered. Overprescription of antibiotics may be an undesirable effect of successful marketing strategies.

The government. In Spain, the Ministry of Health is involved in the approval of any new drug, as well as in surveillance for undesirable effects. With respect to antibiotics, undesirable effects should be considered as both the effects of the drug on the patient (toxicity) and on the community (development of resistance in microbial pathogens or in the normal flora).

What Can Be Done?

Data on Antibiotic Resistance

Continuous collection of data on antibiotic resistance in human isolates. Continuous surveillance for the emergence of antibiotic resistance among sentinel bacteria should be performed. Isolates should be obtained and studied by a permanent network of laboratories specifically established for this purpose and selected from among hospital-based or community-based microbiology laboratories. In the community, surveillance should focus on infants and children in nurseries; elderly persons in day care centers; students in primary schools, high schools, and universities; immigrants; recruits entering military service; and internees in prisons. Surveillance of antibiotic resistance should be based on determination of MICs, ensuring that the data obtained from all the centers performing susceptibility tests are compatible.

Continuous collection of data on antibiotic resistance in isolates from animals and food of animal origin. A similar network of laboratories should be established for surveillance of bacterial antibiotic resistance in animals and animal products. The microbiology laboratories in veterinary faculties and in some farming industries may be involved in this task.

Detection of antibiotics and antibiotic resistance in the environment. Environmental laboratories at the University or the Ministry of Health or, in some cases, hospital laboratories and laboratories of industries whose activities result in the liberation of pollutants should be encouraged to be involved in this surveillance task since it is possible that the activities (e.g., fermentation, pharmaceutical research, and use of heavy metals) at these facilities result in selection for antibiotic resistance.

Continuous collection of data on human consumption of antibiotics. The Ministry of Health regularly obtains reliable data on all antibiotics received by nonhospitalized patients; these data include consumption per antibiotic, pharmaceutical specialty, geographic location, and identity of the prescriber. These data should complement those that originate from market-research surveys (such as those obtained by the IMS) in order to evaluate the rates at which antibiotics are prescribed by private practitioners as well as the rates at which antibiotics are purchased without prescriptions.

Regular estimation of direct, uncontrolled procurement of antibiotics by the public. This estimate should be based on regular inquiries to determine the rate of self-prescription among members of the general public (this rate should also reflect antibiotics kept in the home). This same research should be applied to day care centers, nurseries, nursing homes, veterinary clinics, and farms.

Physicians (the Prescribers)

Periodic collection of pharmacotherapeutic antimicrobial profiles. The pharmacotherapeutic profiles of office-based physicians who work for the public health system are now available in Spain. Profile forms are regularly submitted to each of these physicians. The goal of this process should be self-analysis on the part of the physician, with eventual self-regulation of prescription habits.

Periodic updating of physicians with regard to consensus recommendations on clinical and laboratory diagnosis of the most common community-acquired infections and possible treatment protocols. Alternative therapeutic possibilities for the most common community-acquired infections should be offered by groups of well-recognized, independent experts, and these possibilities should be published in independent brochures like those that are already published by the Social Security.

Assurance of easy access for community-based clinicians to microbiology laboratories and data on local antibiotic resistance patterns of the more frequent pathogens. Community-based physicians should be aware of the clinical situations that require accurate microbiological diagnosis. Physician access to specialized laboratories should be guaranteed.

Promotion of teaching the rational use of antimicrobials. Seminars on the use of antibiotics and antibiotic resistance should be encouraged in the Schools of Medicine, Pharmacy, Veterinary Medicine, and Agriculture. Promotion of continuing postgraduate education on the subject of antibiotic resistance is needed.

Optimization of the medical consultation (time spent per patient) in community clinics. Patients frequently ask for drugs rather than investing additional time during consultation with a physician.
Establishment of committees on antibiotic policy at the national, regional, and local levels. Committees on antibiotic policy are established by law in hospitals, and the activities of such committees are considered important. Similar activities should be assured in the area of the community that corresponds with each hospital.

Patients and Consumers

Dissemination of information to patients about antibiotic resistance. The dissemination of simple messages to consumers of antibiotics via direct mail, posters (particularly in community clinics), and radio and television on the problems related to overuse of antibiotics will be useful.

Dissemination of information to the food industry on the dangers of uncontrolled use of antibiotics in feed or water for therapeutic or prophylactic purposes.

Pharmacists (the Dispensers)

Promotion of pharmacists as agents of the rational use of antimicrobials. At least 25% of the customers in pharmacies receive information on their prescriptions from the pharmacists. The pharmacists’ knowledge of local antibiotic use and antibiotic resistance patterns should be tapped to discourage self-prescription habits.

Continuous inspection of pharmacies to prevent the delivery of antimicrobials to customers without prescriptions from physicians. According to Ministry of Health regulations, all antimicrobials should be dispensed by prescription. Delivery of antibiotics without prescription should be controlled and prosecuted through regular inspections.

Use of Antibiotics in Animals

Standardization of veterinarians’ prescription forms for the therapeutic use or prophylactic use of antimicrobials in animals. Current Spanish legislation on veterinary drugs requires a veterinarian’s prescription, both for pharmaceutical products and medicated feed. The detection of unacceptable quantities of an antibiotic or its metabolite may contribute to the detection of transgressions.

Encouragement of the rational use of antimicrobials in veterinary medicine and as growth promoters. A curriculum that covers appropriate use of antibiotics and resistance is urgently needed in veterinary schools. The livestock industry should be monitored for the use of unacceptable antibiotics as growth promoters. A reevaluation of the current list of approved antimicrobials is urgently required.

The Pharmaceutical Industry

A provision of support to the pharmaceutical industry to enable continuous research and development of innovative drugs and strategies for counteracting antibiotic resistance. Promising innovative research for new antibiotics should be publicly financed and supported.

Provision of support to the pharmaceutical industry for obtaining data on the development of antibiotic resistance during clinical trials with new antimicrobials. The ability of a given drug to select for resistant variants should be routinely explored by analyzing the normal flora of treated patients. It is essential to obtain data from clinical and microbiological treatment failures and correlate these data with decreases in susceptibility.

Encouragement of analysis of the potential for cross-resistance between antimicrobial products used as growth-promoting agents with antibiotics used in humans.

Provision of incentives to pharmaceutical companies to regularly perform well-controlled surveys on antibiotic resistance. Companies that support the general philosophy of preventing the spread of antibiotic resistance should have a privileged relationship with the Health Administration.

Provision of recommendations to the pharmaceutical industry on establishing self-regulatory procedures to counteract local increases in antibiotic resistance. Such procedures could be devised to temporarily regulate the marketing and promotional pressures in a given area.

The Health Administration

Consideration of the potential impact on antibiotic resistance should be incorporated into the evaluation of new antimicrobials.

Provision of better information in package inserts. It would be useful if the package inserts were clear regarding the risk of the emergence of resistance because of inappropriate use. Warnings directed at patients, on the box or the package insert, which remind them that “the use of this drug without a prescription is prohibited,” could be useful.

Establishment of programs for rational use of antimicrobial agents in humans. The Administration should encourage the establishment of surveillance programs directed at implementing the above proposed recommendations; these programs should be assigned the necessary priority with respect to epidemiological research grants.

National committees’ reevaluation of the products used as feed additives and of the antibiotics used in veterinary medicine.

Organization of local or regional committees for identifying outbreaks of resistant organisms and for analyzing and instituting control procedures.

Evaluation of the role of vaccines in the control of bacterial antibiotic resistance. The use of vaccines should contribute to a decrease in the number of antibiotics required by both humans and animals. Vaccines directed against the more-resistant bacterial subtypes may have a bioremediating effect.
The Environment

Because of the effect of microorganisms on human health, antibiotics should be included among the products that have an environmental impact on health.

Final Note

This English-language version of the document *Antibiotic Resistance in Spain: What Can be Done?* is a comprehensive summary of the original document in Spanish. The entire report is available either in English or Spanish from the main author.

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