Antimicrobial Resistance

An Ecological Perspective

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Antimicrobial Resistance: An Ecological Perspective
EXECUTIVE SUMMARY
A colloquium was convened by the American Academy of Microbiology to bring together leading scientists to review the fundamental relationships between the use of antimicrobial agents in humans, animals, agriculture, and aquaculture and their effects on humans, animals, and the environment. The colloquium was held in San Juan, Puerto Rico, on July 16-18, 1999.

Bacteria are everywhere and are inextricably linked to the lives of the organisms and larger environments they inhabit. Resistance to antimicrobial agents is inevitable and irreversible, a natural consequence of bacterial cell adaptation to exposure to antimicrobials. Multiple uses of antimicrobial agents in medicine, production of food animals, and crop protection have caused increasing resistance to those agents. Widespread use of disinfectants in household products may also be contributing to the development of resistance.

As existing antimicrobial agents decline in effectiveness, infections will be more difficult and expensive to treat and epidemics harder to control. The environmental consequences of the widespread use of antimicrobial agents are still little understood.

The medical community, governments, the World Health Organization, and other non-governmental international agencies have begun to institute policies to address the problem of antimicrobial resistance. However, there remains a lack of systematic and coordinated action. Surveillance—the collection, analysis, and reporting of data—is crucial. Different types of surveillance data are needed for each component of the biosphere, and data must be made available for treatment decisions, new drug development, and policy formation.

Further scientific research is required to determine the effects of antimicrobials on the environment, better assess the consequences of resistance to human health and ecology, and develop ways to detoxify antimicrobials. The possibilities for new diagnostic procedures, improved therapies, reintroduction of susceptible microorganisms, and reversal of resistance should be explored. Special efforts and innovative methods must be employed to investigate the global impact of antimicrobial resistance and find more effective ways to educate health care professionals, policy makers, and the public.

INTRODUCTION
Bacteria are an integral part of the world, inseparable from life on Earth. They are found everywhere in the environment, cover the skin and mucous membranes, and line the intestinal tracts of humans and animals. Most bacteria are harmless. Some bacteria are beneficial to their host and provide nutrients or protection from pathogens and disease by limiting the ability of more harmful bacteria to colonize. Because they have a short generation time—from minutes to hours—they can respond rapidly to changes in their environment. Thus, as antimicrobial agents were introduced into the environment, bacteria responded by becoming resistant to these agents.

Resistance develops as a natural consequence of the ability of the bacterial population to adapt. The increased use of antimicrobial agents increases selective pressure, and as the opportunity for bacteria to be exposed to the agents is extended, so is their opportunity to acquire mechanisms of resistance. Mechanisms of acquired resistance result from changes in the cellular physiology and structure of a microorganism due to alterations in its usual genetic makeup. They include genetic mutations, the acquisition of genes from other organisms via gene transfer mechanisms, and combinations of these two.
types of events. Whether particular bacteria become resistant to a particular antimicrobial agent may depend on many factors—the basic physiology of the bacteria, the characteristics of genetic mutations that occur, the prevalence of resistance genes that might be acquired, or the quantity and quality of exposure to the antimicrobial agent.

Rapid spread of genes resistant to antimicrobial agents can occur in a bacterial population and from one ecosystem to another. Particular antibiotic resistance genes first described in human specific bacteria have been found in animal specific species of microorganisms and vice versa, suggesting that bacterial populations can share and exchange these genes. The development of resistance in one bacterial population can, and does, spread to other populations over time.

Antimicrobial agents can be found in sewage effluents, especially in places where they are used extensively, such as hospitals, pharmaceutical production plants, and near farms where animal feed containing antimicrobial agents is used. The contaminated sewage can make its way to streams, lakes, and ultimately, the ocean. In a variety of interconnected ecosystems, antimicrobial agents can lead to the emergence of resistance, the reduction of microorganisms susceptible to the agents, and drastic alterations in the biodiversity of affected ecosystems.

The use of antimicrobial agents has increased dramatically in the past 50 years. Uses for humans include the treatment and prevention of infectious disease, as well as noninfectious applications, like acne. Antimicrobial agents are used extensively in the agricultural production of food animals for treatment and prevention of disease and the promotion of growth. In addition, bacterial diseases of plants are treated with antimicrobial agents, as are bacterial diseases affecting other food producers like honeybees and fish.

Regulation of antimicrobial agents varies from place to place and according to intended use. In much of the industrial world, antimicrobial agents ingested by humans are available only by prescription, but topical agents are increasingly being made available over-the-counter. In many other countries, a prescription is not required for the purchase of antimicrobial agents. Whether or not a prescription from a medical professional is required, there is no guarantee that antimicrobial agents will be used properly. Taken for nonbacterial infections, in ineffective doses, or for an inadequate or inappropriate length of time, antimicrobial agents can not only be ineffective, but lead to the development of resistance.

There is increasing concern about the medical and public health problems directly associated with the development and spread of antimicrobially resistant microorganisms in hospitals, communities, and the environment. Resistant bacteria cause infections that are more difficult to treat, requiring drugs that are often less readily available, more expensive, and more toxic. In some cases, strains of bacteria have become resistant to all available antimicrobial agents. Without effective agents to hold them in check, these infections spread through hospitals and communities, causing epidemics that are difficult to control. Outbreaks of dysentery in Africa, cholera in South America, and enterococci in the United States are examples. It is estimated that resistant bacterial infections increase health care costs by $4 billion per year in the United States alone. Antimicrobial resistance is becoming an economic, as well as a medical problem.

Resistance to penicillin in *E. coli* was first recognized in 1940 (Abraham and Chain, 1940), and the ability of bacteria to transfer the genetic information responsible for resistance to other bacterial species was described in 1952 (Lederberg and Lederberg, 1952). Despite this, often unrestricted and indiscriminate use of antimicrobial agents in humans, animals, fish, and on plants over a relatively long period of time has...
resulted in an environment that has encouraged the development of resistance in many bacterial species. Relatively few new classes of antimicrobial agents are being developed, and the absolute need for the prudent use of the agents we have is becoming increasingly apparent. A broad, multidisciplinary, and multi-tiered approach to stemming antimicrobial resistance—not only in bacteria, but also among fungi, viruses, and parasites—and controlling the spread of already resistant microorganisms is required.

**THE ISSUES:**

**THE NATURE OF THE PROBLEM**

Resistance is a consequence of both appropriate and inappropriate use of antimicrobial agents. While overuse and misuse of antimicrobial agents is doubtless an important cause of existing and emerging problems, use deemed appropriate for humans, animals, and plants may have effects that are unintended or not immediately recognized on other species, their immediate environment, or the ecosystem as a whole. A complex set of interrelated processes, progressing in the bacteria of humans, animals and the environment for the past sixty years, has resulted in a decline in the effectiveness of antimicrobial agents for human, animal, aquacultural, and agricultural use.

Relatively new findings in the fields of molecular biology and population biology have emphasized the fact that resistance is both inevitable and irreversible, a natural consequence of the use of antimicrobial agents on bacterial evolution. Non-antimicrobial agents, like disinfectants, sterilants, and copper and other heavy metals used to kill bacteria on plants, can also contribute to the development of antimicrobial resistance. Bacteria are more likely to become resistant to these other agents as well because mechanisms that determine resistance, such as efflux systems, are often not drug specific. The antibacterial, non-antibiotic substances and products that proliferate in soap, toothpaste, baby clothes, and bed linens increase selective pressure on microorganisms to develop resistance to these agents. While it is never possible to create a sterile environment free of bacteria, it is certainly possible to alter the normal flora of the home environment, killing harmless bacteria and contributing to the selection for resistant organisms. Few studies have yet been conducted to determine the extent of changes that may be caused by these agents.

Other classes of microorganisms—fungi, viruses, and parasites—have also been shown to develop resistance in response to selective pressure from the use of anti-infectives. Resistant strains can be passed to other patients, causing treatment failures when the same anti-infective agent is used, as has occurred with failures of anti-malarial drugs. As with bacteria, however, development of resistance may not occur in an individual patient, but may contribute to the spread of resistance as selective pressure is exerted on a larger population of microorganisms present in the patient or the environment.

**FACTORS CONTRIBUTING TO THE PROBLEM**

Medical Practices: In order for the use of an antimicrobial agent to be described as appropriate or proper, it should be prescribed and administered as early as possible in the infection process and at the correct dosage. Just enough of the drug should be used to kill the infectious agent without increasing the selective pressure for resistant strains. What is appropriate use in one patient may, however, affect the patient in the next bed differently.

Development and maintenance of resistance have been affected by changes in patterns of medical use of antimicrobial agents. Medical professionals have emphasized different classes of drugs at different times. The 1970s and 1980s were the era of aminoglycosides and cephalosporins; by the early 1990s,
fluoroquinolones had become the antimicrobial treatments of choice. Variation in the ways that these diverse types of antimicrobial agents have been used also selects differently for resistance. The concept of cycling antimicrobial agents was tried with aminoglycosides in the 1980s, with variable success. Prophylaxis, or the preventative use of antimicrobial agents for surgery, transplantation, or other procedures, usually involves a shorter course or lower dose of the drug than is prescribed for definitive treatment.

There have also been changes in the nature of the threat and incidence of disease that have affected the development of resistance. In the United States, vaccination has virtually eliminated *Haemophilus influenzae* as a cause of meningitis, resulting in changes in empiric therapy, as the pathogen causing meningitis in children is much more likely to be pneumococci. Otitis media, the infection or inflammation of the middle ear so common in very young children, has increased dramatically in the United States and become the ailment for which antimicrobial drugs are most often prescribed.

Characteristics of the patient population can also produce changes in patterns of antimicrobial resistance. An increase in the number of immunocompromised patients due to diseases like AIDS, medical procedures like organ transplantation, or changing demographics like the aging of populations in the United States and Europe affect the need for and use of antimicrobial agents.

Medical practitioners may also use antimicrobial drugs to prevent more severe disease, even when the disease they are currently treating is not serious or is known to be self-limited. Doctors may prescribe antimicrobial agents as a preemptive measure and with the intention of avoiding more serious complications. Decisions can also be influenced by the guidelines of health maintenance organizations (HMOs) and managed care plans that encourage treatment before the completion of bacterial cultures that determine the presence of an infectious agent and other potentially expensive laboratory tests. The fact that many patients expect to have an antibiotic prescribed for them and the fear of litigation by the physician community should another disease develop may influence prescribing patterns. Further, physicians receive free samples of antimicrobial agents from pharmaceutical companies and are inclined to prescribe what is immediately available. In addition, physicians have little training in the prudent use of antimicrobial agents. Unlike some other classes of drugs, antimicrobial agents can be prescribed by all physicians, and often by physician assistants and nurse practitioners using an algorithm that requires little clinical training or skill.

Laws in many countries do not require that antimicrobial agents be prescribed by a medical professional. They can be purchased over-the-counter at pharmacies and drug and discount stores, often in large quantities. Some of these policies were instituted with the hope of providing medication for people who do not have access to a doctor or could not afford to see one, but the lack of regulation has contributed to other problems. Manufacturing standards vary widely in places with little regulation, and counterfeit antimicrobials may be sold at subtherapeutic doses with little, if any, quality control. Encouraging self-diagnosis and self-medication with antimicrobial agents can lead to resistance when agents are taken for viral or other illnesses for which they are not indicated, in doses too small or too large, or for time periods that are too long or too short. As bacteria continue to evolve in response to repeated exposure to agents, resistant strains that are difficult to treat can gain prevalence. These trends are especially dangerous in countries where newer classes of antimicrobial agents are not readily available and/or where large segments of the population cannot afford the newer alternatives.
Agriculture and Aquaculture: Use of antimicrobial agents for non-humans includes application for a variety of purposes in production of food animals (livestock, poultry), aquaculture, plant and crop protection, food production, and industrial use, such as the cleaning of oil pipes. At subtherapeutic levels of 10–100 ppm per kg of feed, antimicrobials are used for growth promotion in livestock and poultry, at various levels for prophylaxis, and at therapeutic levels for treatment.

Most of the classes of antimicrobial drugs used for humans are also used in animals, including compounds from classes that are considered drugs of last resort for specific human infections: glycopeptides, streptogramins, everninomycins, quinolones, aminoglycosides, and third generation cephalosporins. Reports from North America and Europe have estimated that about 40% of all antimicrobials produced are used in livestock, including poultry. Approximately 90% of that quantity was administered in and on feed at levels subtherapeutic for disease prevention and growth promotion—at 70% and 30% concentrations, respectively. In the European Union in 1997, an estimated 10,493 tons of active antimicrobial substance was used: 52% for humans, 33% for therapeutic use in animals, and 15% as feed additives for growth promotion. The largest amount of antimicrobials is administered to animal flocks and herds through feed or water. Inherent problems of imprecise dosage and the inevitable treatment of healthy animals contribute to problems of resistance.

A wealth of epidemiological information indicates that food of animal origin is the source of a majority of foodborne bacterial infections caused by non-typhoid Salmonella, Campylobacter, Yersinia, E. coli 0157, and other pathogens. Bacteria can move between ecosystems, animals, and humans. When bacteria are themselves pathogenic or can transfer resistance genes to bacteria that are pathogenic, adverse health effects can result. In most settings, human-to-human transmission of these bacteria appears to play an inferior role, suggesting that the majority of antimicrobial resistant strains of these bacteria isolated in humans come from food animals. In addition, commensal bacteria—those that do not harm or benefit their animal host—can be transmitted to humans and may be pathogenic under certain circumstances. The rate at which this occurs is difficult to quantify. Documented examples include E. coli and enterococci, but it is likely true of almost any organism belonging to the micro-flora of a healthy animal.

There is direct evidence that antimicrobial use in animals selects for antimicrobially resistant non-typhoid Salmonella serotypes. These bacteria are transferred to humans through food or direct contact with animals. A small subset of cases of non-typhoid Salmonella infections requires antimicrobial treatment, and resistance limits available treatment options for these cases. A clone of the bacterium S. typhimurium DT 104 resistant to ampicillin, streptomycin, chloramphenicol, and sulphonamides has recently been found in humans and animals and has become prevalent in several countries. Potential problems are further suggested by the apparent relationship between the introduction of fluoroquinolones for use in food producing animals and the emergence of Salmonella serotypes with reduced susceptibility to fluoroquinolones in humans. Since the introduction of fluoroquinolones for use in poultry, there has also been a significant rise reported in the prevalence of fluoroquinolone-resistant Campylobacter jejuni isolated in live poultry, poultry meat, and humans in The Netherlands, United Kingdom, and United States.

The ability of resistance genes from animal bacteria to be transferred to human pathogens has not been sufficiently documented. However, horizontal gene exchange among animal bacteria and human pathogenic bacteria is suggested by the finding of identical resistance gene classes in sub-groups of bacterial populations from humans and animals. The use of avoparcin as a growth promoting feed additive in
animal husbandry has contributed to the reservoir of transferable genes resistant to glycopeptides. Vancomycin-resistant enterococci (VRE) from animals can reach humans through the food chain.

**Other Uses:**
Increasing use of disinfectants, in everything from soap to gym clothes to baby toys and toothpaste, sends the message that every attempt should be made to eliminate as many bacteria in our personal environment as possible. The result is that everyday household products put increasing selective pressure on the bacterial population to become more resistant in the homes that use these products. This change in the normal flora can have adverse consequences if and when the members of the household become ill with an infectious disease. The use of these products may reduce the number of harmless bacteria and increase the selection for antimicrobial resistance organisms. Unfortunately, few studies have been conducted in this area. Until data can be provided that antimicrobial agents do harm to beneficial bacteria, these products will continue to be heavily advertised, and consumers will believe they are helping raise the level of hygiene in the home.

**Policy and Practice:**
Government, Institutions, and Organizations: In general, governmental agencies in Europe and the United States have shown increasing recognition of the problem of antimicrobial resistance and have begun to respond with some new or changed policies. Total use of antimicrobials in Europe has been limited as the use of these agents for growth promotion in food animals is banned. In the U.S., recommendations issued by the Centers for Disease Control and Prevention (CDC) have changed patterns in the use of vancomycin. Other policy efforts include the establishment of practice guidelines and formularies to help control antibiotic use by public hospitals and the imposition by government agencies of additional taxes on imported drugs. There remains, however, a lack of coordinated, sectoral, and interagency policy on antimicrobial resistance at the national level.

On the international level, the World Health Organization (WHO) is focusing on strengthening the capacity of nations to detect, monitor, and respond to anti-infective drug resistance (including that which affects the treatment of malaria and tuberculosis). In response to pressure for action, WHO is also coordinating global efforts to assess and reduce the impact of anti-infective drug resistance. Currently, they are developing a global strategy for containment of antimicrobial resistance.

**Surveillance:**
Existing Systems: A critical element in addressing the environmental impact of antimicrobial resistance is effective surveillance. Surveillance involves the collection, analysis, and reporting of data. With respect to antimicrobial impact on the environment, surveillance involves not only data on bacterial pathogens, but also data on other microorganisms that are part of the affected ecosystem. Surveillance is undertaken to help direct antimicrobial use, particularly empiric therapy, based on resistance patterns of organisms in the community. From a public health perspective, it is used to identify points for interventions to control resistance, and afterward to assess the effects of interventions. Surveillance can serve as a base of information for infection control efforts in hospitals. Assessment may involve pathogens, commensals, indicator organisms, or the relative composition of an entire ecosystem. More than 100 international, national, regional, and local surveillance efforts are currently under way and have been reported to the World Health Organization. Much of the current surveillance is conducted by pharmaceutical companies to direct marketing efforts and to gather organisms for testing against new agents. Information on patients is rarely available. Special emphasis should be given to the resistance gene pool and to the emergence and spread of resistant clones.
Different types of surveillance are needed for each component of the biosphere. The first type is the collection of data that shows trends over time. This type of surveillance would be useful in advising prescribers what changes may be indicated in empiric therapy or prevention of various infections. For example, if pneumococci in a geographic area are showing increasing resistance to beta-lactam antimicrobials, alteration of the empiric therapy of serious invasive disease to include vancomycin may be indicated. This type of surveillance may also be helpful for those making decisions relating to the allocation of limited health resources.

A second type of surveillance system is the sentinel surveillance, or early warning system. Such a system is particularly useful for detecting rare or especially important events, such as the emergence of vancomycin-resistant *Staphylococcus aureus* or in identifying early changes in resistance that might foreshadow large, more significant changes. In contrast to traditional definitions of resistance that may predict clinical outcomes, these new surveillance systems might define resistance by so-called “thresholds” of change in susceptibility that would provide a selective advantage to a microorganism or risk for evolution toward greater resistance.

For those efforts involving patients, there are different methodologies for conducting surveillance. Existing types of surveillance can be divided according to how bacteria are sampled and where the testing of the bacteria is done. Some surveillance is conducted with prospectively defined populations, e.g., surveying pharyngeal carriage of pneumococci in a defined group of children. This is epidemiologically desirable, but expensive, since the survey has to pay for the culturing and testing. Most other surveillance is done on patient samples taken by clinicians in order to guide treatment; samples then are sent for testing to the local routine laboratory. These test results can comprise a local resistance database. A potential disadvantage with this type of patient surveillance is that the quality of the testing itself can vary. However, there are two great advantages. First, the data are rich in local epidemiological detail and costs very little. Second, the analysis of the resulting stream of test results can serve to continuously improve the quality of the laboratory sampling and testing.

A third type of patient surveillance sends a subset of local clinical isolates for retesting at a reference laboratory. The advantage is that the reference laboratory can do more elaborate testing of more uniform quality than the local laboratory. The disadvantage is that it is expensive and, by itself, may give little local epidemiological detail.

Such local antimicrobial resistance databases support management of resistance locally, where it is best interpreted and interventions best devised. If such databases reside in similar or compatible software, they may be aggregated for multi center, national surveillance. They may also be integrated with reference laboratory surveillance systems to gain the complementary advantages of each.

Use of Surveillance Information: One of the issues related to surveillance to be resolved involves getting the information into the hands of those who can use it. Those with the greatest need are local physicians to assist with therapeutic decisions. Pharmaceutical companies also need the information to identify needs for drug development. And finally, governments—local and national—and international organizations need the information to develop policy relating to the resistance problem.

Those working in animal husbandry, aquaculture, and plant microbiology also need information from surveillance. However, there is very little surveillance data currently. Monitoring systems should be
developed that are linked to allow for comparisons between ecosystems. Some of the new technologies, such as DNA probe hybridization and DNA chip technology, allow for screening of large numbers of isolates and multiple resistance genes in a short period of time.

OUTLOOK AND RECOMMENDATIONS FOR THE FUTURE:

SCIENTIFIC RESEARCH

Based on the issues described in the sections above, a number of research areas have been identified. A better understanding of the ecology of resistance should help us to design new intervention strategies. For example, if agricultural use of antimicrobial agents proves to have an effect on resistance in human pathogens, it would be appropriate to develop special antimicrobials or design new agricultural practices that would minimize the use, release, and transfer through the food supply of antimicrobials and antimicrobial resistant bacteria. In other cases, such as multi drug-resistant pneumococci, vaccines may prove to be a more effective preventive strategy. Information about how far antimicrobials move after they are released into the environment and what impacts they have on environmental sites could aid in the design of more antimicrobials more amenable to biodegradation. Significant gaps in scientific knowledge surrounding the development and effects of antimicrobial resistance exist, and we recommend that future research efforts be directed toward the following goals:

• Determine the fate of antimicrobials released into the environment. Use chemical analysis to establish what happens to antimicrobial agents that are released into the environment after therapeutic, prophylactic, or other uses. Determine which antimicrobials are stable in the environment, including the intestinal environment, and how far antimicrobials that enter the food and water supply travel from the original point of entry. Use biological approaches to determine the biological selectivity of an environment by introducing bacteria as environmental sensors.

• Determine the environmental impact of antimicrobial agents in relation to amount and duration of exposure. Determine the effects of use-level and period of administration of an antimicrobial agent on resistance development and establish whether resistance arises during or after treatment. Identify bacterial species that can function as sentinel species for detecting effects of antimicrobials in the environment. Investigate the possibility of establishing thresholds for ecological effects of antimicrobial agents. Develop a population biology model of antimicrobial resistance development, including mathematical modeling of resistance emergence and decline. Such studies should be done on the extent of resistance gene transfer in different ecosystems.

• Develop ways to contain or detoxify antimicrobials. Determine how antimicrobial agents may be rendered less active or prevented altogether from entering areas such as the water supply. Identify practices that might limit dissemination of antimicrobials and antimicrobial-resistant bacterial from hospitals, agriculture, and aquaculture.

• Assess the role of non-antibiotic antimicrobial substances on the development of resistance. Determine how widespread are clusters of genes that contain both antimicrobial resistance and other types of resistance genes, such as heavy metal resistance genes, and what conditions favor their formation. Look for novel mechanisms other than integrons for development of such resistance units. Establish the extent to which non-antibiotic antimicrobial substances co-select for antibiotic resistance under field conditions.
• Evaluate the effects of antimicrobial resistance on human morbidity and mortality. Establish how the administration (timing and dosage) of antimicrobial agents affects outcomes, such as human morbidity and mortality. Determine quantitatively the impact of resistant bacteria on human morbidity and mortality. Develop measures for quantitative scoring to define such outcomes.

• Evaluate connections between human ecology and antimicrobial resistance development. Identify human practices, such as those in agriculture, aquaculture, travel, hygiene, and food processing, that affect (or could affect) the development of antimicrobial resistance. Establish the influence of demographic factors, such as the age structure on development of antimicrobial resistance. Determine the extent to which resistant bacteria in the food supply contribute to the development of resistance of human pathogens.

• Determine the global impact of resistance. Develop new approaches to preventing resistance transmission from one locale to another. Investigate in more detail the patterns of resistance emergence in the developing world. Examine resistance development in isolated environments, such as space shuttles or interplanetary travel vessels.

• Evaluate the potential benefits of rapid diagnostic procedures and develop improved therapies. Explore ways in which effective diagnoses may be made in the shortest time and determine how feasible these would be in real-life clinical settings. Investigate the possible role of molecular methods in clinical diagnosis. Find ways to improve therapeutic strategies to prevent resistance emergence.

• Reassess the possible reversal of resistance due to reintroduction of susceptible bacteria into selected environments. Explore the possibility that affected microbial populations, including those found in or on the bodies of humans and animals, can be bioremediated by reintroducing members of the natural populations that were displaced. Find ways to use bacteria to prevent the emergence and maintenance of resistant bacteria in an environment.

• Develop new strategies for educating policymakers, consumers, health care professionals, etc. Find more effective means of educating various groups about appropriate use of antimicrobial agents and the dangers of misuse. Find ways to reduce the differences in perception between physicians and patients about what patients really want and need.
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