Antibiotic Resistance: A Global, Interdisciplinary Concern

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Abstract
This article presents a brief overview of the impact that antibiotic use in clinical medicine and in other settings, such as agriculture and animal farming, exerts on antimicrobial resistance. Resistance has been described to all antibiotics that are currently in use, and resistant strains were sometimes reported as soon as months after specific antibiotics became commercially available. There are many examples in which the increasing prevalence of resistant microbial strains jeopardized the continuing effective use of the respective antibiotics in clinical medicine. In addition to resistant infections that occur in healthcare establishments, one of the recent challenges is the emergence of pathogens, such as MRSA, in the community, among individuals without any apparent risk factors for the infection. The transmission of resistant pathogens and antimicrobial resistance determinants across different components of the ecosystem transforms antibiotic resistance into a topic that extends beyond the scope of clinical medicine and needs to be visualized through an integrated global perspective. It should incorporate a broad range of disciplines, including molecular genetics, microbiology, food science, ecology, agriculture, and environmental science. Understanding this complex multi- and interdisciplinary framework will enable the implementation of the most appropriate interventions toward determining the dynamics of antimicrobial resistance, limiting the emergence and spread of resistant strains, and ensuring the ongoing effective and safe use of antibiotics.

Key Words: Antibiotic history; antibiotic resistance; antibiotic use and overuse; infectious diseases.

The Discovery of Antibiotics
Infectious diseases were among the leading causes of morbidity and mortality in the 1900s, and tuberculosis and bacterial pneumonia were some of the most frequent causes of death during childhood (Cohen, 1998). In 18th-century France, half of all children did not reach age 2; infant mortality in Bombay was ~50% between 1900 and 1920; and during the second half of the 19th century, up to one-third of the children in Western Europe and the United States did not reach their first birthday, with half of those deaths being caused by infectious diseases (Lee et al., 2007; Mulholland, 2000). Kohn and Weiner (1936) examined 1000 children admitted with non-tuberculous pneumonia to the pediatric services of Mount Sinai Hospital in New York between November 1926 and March 1933; they found overall mortality rates of around 20% and even higher rates, around 39%, among children younger than 1.

The discovery of penicillin marked one of the defining moments of the 20th century. In 1928, while studying the morphology of Staphylococcus aureus strains and preparing to leave for vacation, Louis Pasteur left several plates on a bench in his lab, and upon return, he discarded a few of them, which became contaminated with mold. As he was explaining his experiments to a colleague, he retrieved one of the discarded plates, which contained mold. Pasteur noticed that bacterial colonies on that plate had a different morphology and were undergoing lysis (Bentley, 2005; Davies & Davies, 2010, Kong et al., 2010). This observation marked one of the most important discoveries in the history of medicine and led to the development of penicillin.

The Emergence of Resistant Bacteria
In 1943, b-lactam antibiotics were introduced. Soon after, the first resistant strains – which had acquired the ability to hydrolyze the b-lactam ring of the antibiotic by using enzymes known as b-lactamases – threatened to compromise the effectiveness of this group of antibiotics (Abraham & Chain, 1940; Llarrull et al., 2010). The percentage of S. aureus strains that are resistant to penicillin increased from 6% in 1946 to 50% by 1950 and to 80–90% in recent years (Livermore, 2000; Deurenberg & Stobberingh, 2008). But the ability of some bacterial strains to hydrolyze and inactivate the antibiotic was reported in 1940, several years before penicillin became commercially available, which has prompted the question of which emerged first – the antibiotic or the resistance (Abraham & Chain, 1940; Davies & Davies, 2010). This question becomes particularly intriguing in light of a recent report describing b-lactamases in remote Alaskan soils that lack known antibiotic exposure and, except for researchers, were not visited by others (Allen et al., 2009).

The 1960 introduction of methicillin, a semisynthetic penicillin derivative, overcame the problem of penicillin resistance, but bacterial strains resistant to methicillin emerged rapidly, by a new mechanism:
they acquired a new gene, encoding a protein with a lower ability to bind the antibiotic, but capable of continuing bacterial cell-wall synthesis even in the presence of the antibiotic (Llarrull et al., 2010). The first methicillin-resistant strains were reported in 1961, less than a year after the antibiotic was introduced commercially (Jevons, 1961; Palumbi, 2001; Lowy, 2003), and, in some countries, 40–50% of all S. aureus isolates are currently resistant (Lowy, 2003; Grundmann et al., 2006). Between 1999 and 2005, the number of admissions for MRSA infection in U.S. hospitals more than doubled, from approximately 127,000 to 278,000 (Klein et al., 2007).

Recently, Rice (2008) identified a group of pathogens that he refers to as “ESKAPE,” which includes Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. These are pathogens that, through their ability to escape susceptibility to antimicrobials, have become public health concerns in both the developing and the developed worlds. As Rice emphasizes, these pathogens stand out not only for the vast number of nosocomial infections that they cause worldwide, but also for their ability to serve as models for understanding bacterial pathogenesis, transmission, and antimicrobial resistance in other pathogens (Rice, 2008).

Hawkey (1998) describes four major mechanisms to explain how a bacterial cell may become resistant to an antibiotic. Antibiotic modification, the most frequent one, occurs when a resistant bacterium modifies and inactivates the antibiotic, which does not affect its cellular target any longer. The enzyme β-lactamase, which cleaves the β-lactam ring of the antibiotic, provides a relevant example. The second mechanism occurs when a bacterium prevents the antibiotic from entering the cell or removes the antibiotic from the cell by efflux pumps, and is illustrated by the tetracycline efflux system that was first described in Escherichia coli. Efflux pumps were subsequently reported for different antibiotics in other bacteria (McMurry et al., 1980; Poole, 2005). The third mechanism involves altering the antibiotic target site: the antibiotic is able to enter the cell and to reach its target, but the target is not affected any longer because it underwent structural changes. For example, a recently described fluoroquinolone acetyl transferase can acylate and reduce the activity of certain fluoroquinolones, conferring resistance (Robicsek et al., 2005). The fourth mechanism, called “bypass,” occurs when the bacterium retains the sensitive target but makes an alternative, additional target that is able to bind the antibiotic and confer resistance. The best example is provided by some S. aureus strains that acquire a gene that encodes a new penicillin-binding protein, PBP2a or PBP2β. Penicillin binding proteins (PBPs) are a group of enzymes that insert peptidoglycan precursors into the bacterial cell wall. Staphylococcus aureus has four such enzymes: PBP1, PBP2a, and PBP2β, whereas the product of the mecA gene, acquire reduced affinity for methicillin and can continue cell wall synthesis, despite inhibitory concentrations of the antibiotic and even though the other PBPs are blocked by the antibiotic. These are known as the methicillin-resistant S. aureus (MRSA) strains currently represent an emerging public health concern (Katayama et al., 2000; Chambers, 2003; Guignard et al., 2005).

Bacteria have developed resistance to all known classes of antibiotics discovered to date (Alanis, 2005), and often within years after individual antibiotics were commercialized (Palumbi, 2001), in many situations threatening the effective use of the respective antibiotics. Resistance was initially observed in health-care settings, but it soon emerged in the community, an even more worrisome trend that was described worldwide for several microorganisms (Furuya & Lowy, 2006). In addition, some bacteria, also known as “multi-drug resistant strains” or “superbugs,” became resistant to multiple antibiotics (Alanis, 2005). Infections with resistant pathogens are associated with higher morbidity and mortality, increased costs, and longer hospital stays (Cosgrove, 2006; Heymann, 2006). For example, mortality from MRSA is approximately double that from MSSA, its methicillin-sensitive counterpart (Gould, 2006).

Coupled with the increasing number of new antibiotics that are developed and approved, the increasing prevalence of antimicrobial resistance raises well-founded concerns about whether we may already have entered the post-antibiotic era (Alanis, 2005).

### MRSA in Hospitals & in the Community

By the end of the 1940s, half of the S. aureus strains in British and U.S. hospitals were resistant to penicillin (Grundmann et al., 2006). Methicillin, a new β-lactam antibiotic that is not degraded by β-lactamases, was commercially introduced in October 1960; approximately 6 months later, the first methicillin-resistant strains were already being described (Jevons, 1961). Since then, MRSA has become the most frequently identified antibiotic-resistant pathogen in many countries and has created a public health emergency of global concern (Grundmann et al., 2006). It is estimated that among the ~2 billion individuals worldwide who carry S. aureus, between 2 and 50 million carry MRSA (Grundmann et al., 2006). In addition to the increased mortality and morbidity associated with MRSA infections, some authors found that MRSA strains do not replace MSSA strains but, instead, cause additional disease (Gould, 2009).

MRSA infections were increasingly reported in health-care facilities, and hospitalization, dialysis, catheters, and long-term antibiotic use emerged as some of the main risk factors. In addition to the hospital-acquired MRSA (HA-MRSA), a new phenomenon in recent years is MRSA infections that occur in the community, in apparently healthy individuals who lack the known risk factors for the infection, and this has become known as “community-acquired” or “community-associated” MRSA (CA-MRSA) (Naimi et al., 2003). After 1980, when CA-MRSA was first reported in the United States (Saravolatz et al., 1982), this pathogen was increasingly described throughout the country and worldwide, and in 2007 it was estimated to represent the most frequent cause of skin and soft-tissue infections in U.S. emergency departments (Klevens et al., 2007).

The Centers for Disease Control and Prevention propose that the CA-MRSA definition be applied when the MRSA infection occurs in an outpatient setting, or within 48 hours after hospital admission, in an individual who lacks MRSA colonization or infection, hospitalization or residence in a long-term health care facility, surgery, or dialysis in his or her medical history (Nastaly et al., 2010). It is important to note that this classification is not based merely on the place where the infection occurs, as the name would imply, but HA-MRSA is different form CA-MRSA in several respects, which include molecular and epidemiologic characteristics, clinical manifestations, risk factors, risk groups, and the antibiotic resistance profile (McCarthy et al., 2010; Nastaly et al., 2010). CA-MRSA strains differ from HA-MRSA at the molecular level and often harbor several virulence factors, such as the Panton-Valentine leukocidin gene, which is responsible for producing cytoxins associated with tissue necrosis (Weber, 2005; Klevens et al., 2007; Deurenberg & Stobberingh, 2008; Guibbou & Broussard, 2010). Although HA-MRSA strains are often resistant to multiple antibiotics, CA-MRSA is often found to be susceptible (Huang et al., 2006; Nastaly et al., 2010). HA-MRSA occurs more frequently in hospitalized patients, the elderly, and health-care workers, whereas the CA-MRSA risk groups include patients in competitive sports, athletes, soldiers, prisoners, and drug users (CDC, 2003, Nastaly et al., 2010) and the infection often affects young, healthy individuals (Naimi et al., 2003).
As HA-MRSA enters the community and CA-MRSA emerges in health-care facilities, distinguishing these two strains is becoming increasingly difficult (McCarthy et al., 2010). Some authors suggest that CA-MRSA replaces HA-MRSA in hospital settings (Popovich et al., 2008), whereas others have found that, instead, CA-MRSA adds to the existing HA-MRSA burden (Klein et al., 2009). It is important to remember that the worldwide incidence of MRSA is on the rise, its epidemiology is changing, and this pathogen is an increasingly significant public health concern in health-care facilities and in the community. In recent years, MRSA was associated with ~19,000 deaths annually among hospital patients in the United States, a figure that is higher than the combined number of deaths caused by HIV/AIDS and tuberculosis (Boucher & Corey, 2008).

The Spread of Pathogens & Resistance

The use of antimicrobial agents increasingly emerges as a selective force that promotes the emergence of resistant microbial strains (Lipsitch & Samore, 2002). A bacterial strain can become resistant to antimicrobials in two major ways. The first mechanism involves the introduction of new mutations into existing genes, such as a mutation in a gene encoding an antibiotic target, which leads to the inability of the antibiotic to bind its target. For example, resistance to quinolones can be acquired by mutations in the genes encoding DNA topoisomerases (Drlca & Zhao, 1997; Blázquez, 2003). In addition, it is important to appreciate that drug resistance is mobile and that bacteria may acquire new resistance genes from other bacteria by means of plasmids, naked DNA, bacteriophages, or transposons (Levy & Marshall, 2004; Boerlin & Reid-Smith, 2008). The acquisition of new resistance genes can be intracellular, such as the transfer of a gene from a plasmid to the chromosome, or intercellular, which is often called “lateral” or “horizontal” gene transfer (Boerlin & Reid-Smith, 2008). As a result of horizontal gene transfer, antimicrobial resistance may be transferred between bacteria from the same species or between different bacterial species (Barlow, 2009). This process can be accomplished by different mechanisms, which include transformation, in which bacteria take up DNA from the environment and incorporate it into their genome; conjugation, which involves the transfer of DNA by direct contact between a donor and a recipient bacterium; and transduction, when bacterial viruses, also known as bacteriophages, transfer genetic information between bacteria (Boerlin & Reid-Smith, 2008; Juhás et al., 2009).

One of the most elegant examples to illustrate how antibiotic resistance can spread from one species to another was provided by Levy et al. (1976), who showed that in chickens fed with tetracycline, antibiotic-resistant plasmids were transferred from chickens to chickens and from chickens to humans. More recently, Brody et al. (2008) performed a whole-genome analysis to compare several S. aureus strains and found over 14 different DNA regions that were shared between a human MRSA isolate that is endemic in hospitals and strains that cause bovine mastitis, which indicates that horizontal gene transfer may have occurred between various strains. Bates et al. (1994) reported that vancomycin-resistant enterococci are present in nonhuman sources, including farm animals, uncooked chicken, and sewage. When the authors performed ribotyping for 42 of the 62 strains with high-level vancomycin resistance that they had isolated, they distinguished 12 ribotypes, two of which, found in nonhuman sources and in humans, were indistinguishable: a sewage isolate was identical to a human blood and urine isolate, and a pig isolate was identical to a human stool isolate. This study found, for the first time, clinical isolates and strains identified from nonhuman environmental sources that have indistinguishable ribotypes.

Resistant pathogens can be transmitted from animals to humans. Manian (2003) reported that a diabetic patient developed recurrent MRSA infection of the leg, and his wife had cellulitis. MRSA isolated from the couple’s dogs’ nostrils had the same antibiotic resistance pattern as the one cultured from the couple’s nostrils and wounds, and the strains showed indistinguishable patterns by PFGE typing. The couple confirmed that the dog slept in the same bed, and often licked their faces. Recurrences of the infection in the couple were stopped only when the dog was also treated with antibiotics. This and several other studies have revealed that resistant microorganisms can be transmitted between animals and humans. Rwego et al. (2008) collected fecal samples from humans, livestock, and mountain gorillas from the Bwindi Impenetrable National Park in southwestern Uganda, between May and August 2005. The authors reported that a particular group of gorillas, which were the focus of tourism activities and ventured into areas used by humans, harbored E. coli strains that showed genetic and antibiotic resistance similarities with human and livestock bacterial isolates, illustrating that habitat overlap could facilitate the cross-species transmission of microbial pathogens.

An important emerging concept, relevant to the spread of resistant microorganisms between different environments and species, is the idea that the medical and scientific communities have mostly focused on antimicrobial resistance in bacteria that are pathogenic, but that a broader view is needed, to incorporate resistance genes from pathogenic as well as nonpathogenic bacteria that together reflect the sum of all the microbial genomes. The resistance genes found in all these microorganisms, pathogenic and nonpathogenic, have been termed the “resistome,” a concept that promises to advance our understanding of the global ecology of bacterial resistance (D’Costa et al., 2006; Wright, 2007). To illustrate the large number of resistant bacteria that exist in addition to the medically relevant ones, D’Costa et al. (2006) tested 480 bacterial isolates from soil samples for sensitivity to 21 different antibiotics, and they reported that every strain was resistant to seven or eight antibiotics, on average. In light of the wealth of antibiotic-resistant bacteria that exist in nonclinical samples, and the established mechanisms that allow pathogens and resistance determinants to be transmitted between ecosystems, it is imperative to consider antimicrobial resistance not simply as a clinical issue but as a global, ecological concern.

Antibiotics in Agriculture

In addition to antibiotic use in clinical medicine, huge amounts of antibiotics are being used in agriculture, aquaculture, and animal farming. These environments are in a dynamic state with one another and also with other ecosystems, and resistant microorganisms or genetic determinants of resistance can be transmitted between them. In the early 1940s and 1950s, it was noticed that supplementing the food of healthy animals with antibiotics contributes to their growth rate (Hammerum et al., 2010). Soon, this became a worldwide practice, and in addition to the antibiotics used in farm animals for therapeutic purposes, to treat infections, large amounts of antibiotics started to be used as growth promoters at subtherapeutic concentrations (van den Bogaard et al., 2000; Nikaido, 2009). Approximately 48% of the >10,000 tons of antibiotics used in the European Union and Switzerland in 1997 was used in animals. From this amount, 33% was for therapeutic and prophylactic purposes and 15% for growth promotion, with large country-to-country variations (van den Bogaard & Stobberingh, 2000). Antibiotic additives as growth promoters were banned in the European Union on 1 January 2006 (Castanon, 2007). In the United States, between 50% and 80% of the antibiotics that are manufactured are being used in agriculture (Lipsitch et al., 2002; Smith et al., 2002). The Union of Concerned Scientists estimated that, annually,
–24.6 million pounds of antimicrobials are given to animals in the absence of disease, for nontherapeutic purposes (Mellon et al., 2001), and the Institute of Medicine (1989) reported that over half of the ~31 million pounds of antibiotics produced annually are being directed to farm animals. Teuber (2001) estimated that approximately half of the >1 million tons of antibiotics released into the biosphere during the past 50 years was for veterinary and agricultural purposes.

○ The Example of Avoparcin

In 1975, avoparcin was approved as a food additive and growth promoter in many countries worldwide, including the European Union, but not in Sweden, the United States, or Canada (van den Bogaard & Stobberingh, 2000; Hammerum et al., 2010).

Cross-resistance between avoparcin and vancomycin occurs because the same gene, vanA, carries the resistance determinant to both antibiotics (Bager et al., 1999). In 1995, Aarestrup revealed that the agricultural use of avoparcin could select for vancomycin-resistant enterococcal strains in humans (Aarestrup, 1995). To compare conventional poultry farms with ecological ones (which did not use antibiotics therapeutically or as a feed additive) in Denmark, the authors examined fresh fecal samples and detected vancomycin- and avoparcin-resistant strains on five of eight conventional farms, but no resistance was observed among strains isolated from ecological farms.

In The Netherlands, it was reported that approximately 1500 kg and 1260 kg of vancomycin were used for human therapy in 1996 and 1998, respectively, and an estimated 80,000 kg of avoparcin was used annually in farming until 1997 (van den Boraard et al., 2000). Avoparcin use was discontinued in Denmark and Norway in 1995, in Germany in 1996, in the rest of the European Union and Korea in 1997, and in New Zealand and Taiwan in 2000 (Lauderdale et al., 2007; Hammerum et al., 2010). After this ban, a reduction in vancomycin-resistant bacteria from animals and humans in the community was recorded in many of these countries (Witte, 2000).

Aarestrup et al. (2001) found that between 1995 and 2000, the proportion of vancomycin-resistant E. faecium isolates in Denmark decreased from 72.7% to 5.8% in broilers, and from 20% to 6% in pigs. Similar findings were reported from other countries, such as The Netherlands, where van den Bogaard et al. (2000) revealed, in addition, that within 2 years after the avoparcin ban, the prevalence of vancomycin-resistant enterococci in the flora of healthy humans decreased from 12% to 6%. In Germany, Klare et al. (1999) reported that in the Saxony-Anhalt state, the prevalence of vancomycin-resistant enterococci in the intestinal flora of healthy persons decreased from 12% in 1994, when avoparcin was still in use, to 6% in 1996 and 3% in 1997, after the antibiotic was banned. The authors also showed that by the end of 1997, which marked almost 2 years from the avoparcin ban in Germany, the prevalence of vancomycin-resistant enterococci in fresh and frozen poultry meat from German producers decreased as compared to the previous years, when the antibiotic was still in use.

Lauderdale et al. (2007) conducted a nationwide surveillance of 300 chicken farms in Taiwan, between 2000, when avoparcin was banned, and 2003, and revealed that the proportion of vancomycin-resistant enterococci decreased from 13.7% to 3.7% and the proportion of E. faecium from 3.4% to 0%, whereas resistance to several other antibiotics tested remained similar between the 2 years.

○ Resistant Bacteria in Food Products

Reports from several countries increasingly reveal the occasional presence of resistant bacteria in commercial food products. Warren et al. (2008) found CTX-M β-lactamase genes, which represent a new family of plasmid-mediated extended-spectrum β-lactamases that raise significant public health challenges worldwide (Bradford, 2001), in imported chicken breasts, opening concerns that they could colonize the intestinal tract of humans. Only one of 62 breasts reared in the United Kingdom was resistant to fluoroquinolones, whereas 9 of 27 samples that were imported harbored the resistance gene. In a study that analyzed meat products from Dutch supermarkets and butcher shops, van Loo et al. (2007) found MRSA in 2 of 79 raw meat samples (2.5%). Kitai et al. (2005) provided the first evidence of MRSA in commercial raw chickens in Japan, when they detected the pathogen in 2 of 444 commercial samples collected from retail locations. MRSA was also detected in 5 of 318 (1.6%) meat samples collected between November 2007 and March 2009 in La Rioja, Spain (Lozano et al., 2009). The first survey to examine MRSA prevalence and characteristics in retail meat products from the United States was conducted by Pu et al. (2009), who randomly collected 120 samples from 30 grocery stores belonging to seven supermarket chains in Baton Rouge, Louisiana, and isolated MRSA from one beef and five pork samples.

Even though cooking destroys bacteria in food products, pathogens pose a significant threat under several circumstances, such as during the consumption of raw food. In addition, resistant pathogens may be transmitted to processing-plant personnel or food handlers and colonize their skin, nostrils, and gastrointestinal tract (de Boer et al., 2009). Another place where contamination can occur is in the kitchen, during food preparation, when cross-contamination of utensils, clothes, fingers, and kitchen surfaces can facilitate pathogen dissemination. Kusumaningrum et al. (2003) reported that the rate of S. aureus transfer from artificially contaminated sponges to stainless steel surfaces immediately after contamination was ~40%, and some bacteria remained on sponges after the transfer, enabling additional cross-contamination. Staphylococcus aureus was detected on dry stainless steel surfaces for at least 96 hours when contamination was moderate or high, thus illustrating its ability to survive and cross-contaminate other surfaces. Scott and Bloomfield (1990) reported that S. aureus survives on laminated surfaces and clothes, from which significant numbers can be transferred to fingertips or inanimate surfaces even after a brief contact, posing an infection hazard upon contact with food. A study conducted in Ireland that examined the secondary dissemination of pathogens from contaminated food in the kitchen described the cross-contamination of multiple test sites with S. aureus, including preparers’ hands, refrigerator and oven handles, counter-tops, and draining boards (Gorman et al., 2002).

○ Ecosystems

For a long time, antibiotic resistance has been viewed as only a clinical concern but, in reality, the topic is much more complex and emerges as an environmental issue of global importance that is situated at the crossroads of several disciplines (Cassone & Giordano, 2009).

To visualize the changes in the antibiotic resistance pattern of environmental bacteria over time, Knapp et al. (2010) examined soil samples retrieved from the soil archive in Alterra, at the Wageningen University and Research Centre in The Netherlands, where samples have been regularly deposited since 1879. The authors found that microorganisms isolated from soil samples from 1940 through 2008 exhibited resistance to all classes of antibiotics that were tested, and the current abundance of some resistance genes is more than 15× higher than it was in the 1970s. This analysis identified some extended spectrum β-lactamase genes from periods that preceded their emergence in the clinic, which points toward the potential origin of these resistance determinants in soil bacteria (Knapp et al., 2010; Wright, 2010).

Antibiotic-resistant bacteria were found in some of the most remote locations on the planet. During a 2005 expedition organized by the
Swedish Polar Research Secretariat, Sjölund et al. (2008) examined 97 birds from three Arctic locations — northeastern Siberia, Point Barrow (Alaska), and northern Greenland — and found eight antibiotic-resistant strains, four of which were resistant to four or more antibiotics. Other studies found antibiotic-resistant bacteria in remote human populations that were not exposed to antibiotics. In September 1999, Bartoloni et al. (2004) examined a very remote rural community of Guaraní Indians in Bolivia, residing at ~1700 m altitude, having minimal exchanges with the outside world and minimal antibiotic consumption, and found that >67% harbored E. coli strains that were resistant to at least one antibiotic. Subsequently, the authors studied a very remote population from the Peruvian Amazonas, with minimal exposure to antibiotics and limited exchange with the outside world, and found some commensal E. coli strains that showed high levels of acquired resistance to some of the oldest antibiotics (Bartoloni et al., 2009).

Rhodes et al. (2000) provide direct evidence that a specific type of tetracycline-encoding plasmids, previously associated only with fish farms, have disseminated between Aeromonas species and E. coli and between aquaculture systems and human environments in at least four countries: Norway, England, Germany, and Scotland. The authors suggested that instead of thinking separately about the two compartments of the environment, the fish farm and the hospital, we should instead envision them as one interactive compartment in which the free exchange of genetic information can occur.

To illustrate the dynamics of antibiotic resistance among ecosystems, Baqueró et al. (2008) described four main “genetic reactors” where antibiotic resistance develops: the human and animal microbes, which involve >500 species that are exposed to prophylactic and therapeutic antibiotics; hospitals, long-term care facilities, farms, and other locations where overcrowding exposes individuals to bacterial infections; biological residues such as the products of wastewater and sewage treatment plants that originate in the secondary reactor; and where bacteria can mix and recombine; and the soil and ground water, where bacteria can mix and interact with other organisms.

The bacterial world is still filled with mysteries, and it is safe to assume that we are still mostly ignorant about the ecology of microorganisms on Earth. As Stephen Jay Gould pointed out, we live in the "Age of Bacteria," in which microorganisms, the "stayers and keepers" of life's history, exist in tremendous numbers and varieties and populate "every place suitable for the existence of life," from glaciers to hot springs (Gould, 1997). The number of bacterial cells that colonize our bodies exceeds that of our own cells by a factor of 10 (Blaser & Falkow, 2009). Studying bacteria and their interaction with other biological organisms becomes even more challenging in light of the fact that most bacteria do not grow under laboratory conditions, which historically represented the first step toward isolating and characterizing them. Lewis (2007) pointed out that >99% of microorganisms in nature cannot be cultured and, thus, cannot be characterized, while >99.9% of the professionals work on those microorganisms that can be cultured. This leads to a gap in our understanding of the microorganisms that inhabit our planet and interact with us and with other components of the various ecosystems. The abundance of previously unexplored bacterial populations recently started to emerge from metagenomic approaches, which involve the direct isolation and examination of DNA from a sample, without the need to culture the microorganisms. This ensures that DNA from bacteria that would not have grown in culture is also present in the sample and can be examined and characterized. By using a metagenomics approach, Venter et al. (2004) found, in surface water samples collected from the Sargasso Sea in Bermuda, an estimated 148 previously unknown bacterial phylotypes, illustrating the diversity of the microbial world that this powerful approach can unveil.

What Can We Do?
Despite the initial success of antimicrobial treatments, infectious diseases at the beginning of the 21st century remained the third leading cause of death in the United States and the second leading cause of death worldwide (Spellberg et al., 2004). With costs between $400 and $800 million required for the research and development associated with one pharmaceutical compound (DiMassa et al., 2003), the number of new antibiotics approved by the Food and Drug Administration has seen a decrease, from an average of 2.9 drugs annually in the 1960s, to 2.2 in the 1990s, to 1.6 annually since 2000 (Powers, 2004). At the same time, antibiotic resistance has been on the rise, and implementing measures for the judicious use of antibiotics becomes a more urgent task than ever.

Goossens et al. (2005) examined outpatient antibiotic use in 26 European countries between 1997 and 2002 and showed that while antibiotic use varied widely among participating countries, resistance rates were proportional with the amount of antibiotics being used. Another study that involved 11 European countries found a linear relationship between macrolide and β-lactam antibiotic use and the prevalence of penicillin-resistant S. pneumoniae isolates (Bronzwaer et al., 2002).

One of the most important factors contributing to antimicrobial resistance is the over-prescription of antibiotics and their inappropriate prescription for conditions that do not respond to antibiotics, such as viral infections. A survey conducted in 1992 that included ~28,000 visits at >1500 office-based physicians' offices found that ~12 million antibiotic prescriptions, or 21% of the total antibiotic prescriptions for adults, were made for colds, upper-respiratory-tract infections, and bronchitis, conditions that normally do not benefit from antibiotics (Gonzales et al., 1997). Similarly, a survey of >530 pediatric office visits found 6.5 million antibiotic prescriptions, or 12% of the prescriptions written for children in 1992, were for conditions that do not benefit from antibiotics (Nyquist et al., 1998).

It was estimated that eliminating up to 50% of the human antibiotic use and up to 80% of the veterinary antibiotic use, could be possible without major consequences (Dryden et al., 2009). Reducing antibiotic use is one of the most promising interventions to prevent the emergence of resistant isolates. In 1970, Price and Sleigh (1970) reported that in a study that involved 11 European countries found a linear relationship between macrolide and β-lactam antibiotic use and the prevalence of penicillin-resistant S. pneumoniae isolates (Bronzwaer et al., 2002).

The risk of infection with a resistant microorganism depends not only on individual antibiotic use but also on the presence of resistant strains in the community. Walson et al. (2001) examined individuals from three villages in Nepal and found that antibiotic use in the community contributes to the presence of resistant bacteria in a person's fecal flora to a larger extent than the person's individual antibiotic consumption. This suggested that in addition to the individual consumption of antibiotics, an individual's exposure to others in the community who harbor resistant bacteria has an even greater effect.

Antibiotic resistance takes on new dimensions in the current era of global mobility, when any remote part of the planet can be reached within hours, enabling the transcontinental and intercontinental spread of resistant pathogens. This is vividly illustrated by multidrug-resistant S. pneumoniae isolates that were collected in a Cleveland daycare and shown, by molecular analyses, to be identical to a strain previously characterized in Spain (Muñoz et al., 1991).

The importance of good hygiene practices cannot be overstated. Rahuma et al. (2005) examined 150 houseflies collected from
streets, the hospital, and an abattoir in the city of Misurata, Libya, and showed that they are competent vectors enabling the transfer of antibiotic-resistant microorganisms among communities. Elgderi et al. (2006) collected 403 cockroaches from hospitals and households surrounding hospitals in Tripoli, Libya, and, among the ones isolated from the hospital setting, the authors described some that were resistant to six or more antibiotics.

No consensus exists on how best to address the increasing threat of antibiotic resistance. Some of the most frequent, and sometimes conflicting, recommendations propose to reduce the number of prescriptions, limit antimicrobial use in hospitals, decrease the use of prophylactic antibiotics, rotate different classes of antibiotics in time, reduce antibiotic use in agriculture and aquaculture, and implement measures to control pathogen transmission among ecosystems (Lipsitch & Samore, 2002; Bal et al., 2010). Most importantly, there is an urgent need to implement educational activities that raise awareness about the consequences of medical and nonmedical antibiotic use, in an attempt to prevent, as Gould (2009) wrote, an “ecological disaster of unknown consequence.”

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