

A REPORT FROM THE AMERICAN ACADEMY OF MICROBIOLOGY

ANTIBIOTIC RESISTANCE: AN ECOLOGICAL PERSPECTIVE ON AN OLD PROBLEM



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Antibiotic Resistance: An Ecological Perspective on an Old Problem



ANTIBIOTIC RESISTANCE:
AN ECOLOGICAL PERSPECTIVE ON AN OLD PROBLEM

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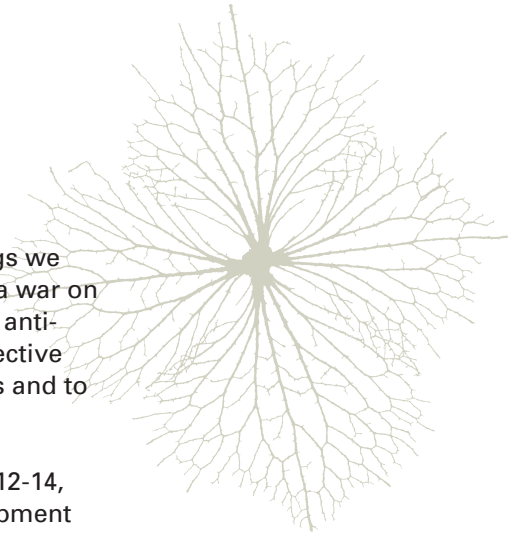
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EXECUTIVE SUMMARY



Antibiotic resistance is never going to go away. No matter how many drugs we throw at it, no matter how much money and resources are sacrificed to wage a war on resistance, it will always prevail. Humans are forced to coexist with the fact of antibiotic resistance. Public health officials, clinicians, and scientists must find effective ways to cope with antibiotic resistant bacteria harmful to humans and animals and to control the development of new types of resistance.

The American Academy of Microbiology convened a colloquium October 12-14, 2008, to discuss antibiotic resistance and the factors that influence the development and spread of resistance. Participants, whose areas of expertise included medicine, microbiology, and public health, made specific recommendations for needed research, policy development, a surveillance network, and treatment guidelines. Antibiotic resistance issues specific to the developing world were discussed and recommendations for improvements were made.

Each antibiotic is injurious only to a certain segment of the microbial world, so for a given antibacterial there are some species of bacteria that are susceptible and others not. Bacterial species insusceptible to a particular drug are “naturally resistant.” Species that were once sensitive but eventually became resistant to it are said to have “acquired resistance.” It is important to note that “acquired resistance” affects a subset of strains in the entire species; that is why the prevalence of “acquired resistance” in a species is different according to location.

Antibiotic resistance, the acquired ability of a pathogen to withstand an antibiotic that kills off its sensitive counterparts, originally arises from random mutations in existing genes or from intact genes that already serve a similar purpose. Exposure to antibiotics and other antimicrobial products, whether in the human body, in animals, or the environment, applies selective pressure that encourages resistance to emerge favoring both “naturally resistant” strains and strains which have “acquired resistance.” Horizontal gene transfer, in which genetic information is passed between microbes, allows resistance determinants to spread within harmless environmental or commensal microorganisms and pathogens, thus creating a reservoir of resistance. Resistance is also spread by the replication of microbes that carry resistance genes, a process that produces genetically identical (or clonal) progeny.

Rapid diagnostic methods and surveillance are some of the most valuable tools in preventing the spread of resistance. Access to more rapid diagnostic tests that could determine the causative agent and antibiotic susceptibility of infections would inform better decision making with respect to antibiotic use, help slow the selection of resistant strains in clinical settings, and enable better disease surveillance. A rigorous surveillance network to track the evolution and spread of resistance is also needed and would probably result in significant savings in healthcare.

Developing countries face unique challenges when it comes to antibiotic resistance; chief among them may be the wide availability of antibiotics without a prescription and also counterfeit products of dubious quality. Lack of adequate hygiene, poor water quality, and failure to manage human waste also top the list. Recommendations for addressing the problems of widespread resistance in the developing world include: proposals for training and infrastructure capacity building; surveillance programs; greater access to susceptibility testing; government controls on import, manufacture and use; development and use of vaccines; and incentives for pharmaceutical companies to supply drugs to these countries.

Controlling antibiotic resistant bacteria and subsequent infections more efficiently necessitates the prudent and responsible use of antibiotics. It is mandatory to prevent the needless use of antibiotics (e.g., viral infections; unnecessary prolonged treatment) and to improve the rapid prescription of appropriate antibiotics to a patient. Delayed or inadequate prescriptions reduce the efficacy of treatment and favor the spread of the infection. Prudent use also applies to veterinary medicine. For example, antibiotics used as “growth promoters” have been banned in Europe and are subject to review in some other countries.

There are proven techniques for limiting the spread of resistance, including hand hygiene, but more rapid screening techniques are needed in order to effectively track and prevent spread in clinical settings. The spread of antibiotic resistance on farms and in veterinary hospitals may also be significant and should not be neglected. Research is needed to pursue alternative approaches, including vaccines, antisense therapy, public health initiatives, and others.

The important messages about antibiotic resistance are not getting across from scientists and infectious diseases specialists to prescribers, stakeholders, including the public, healthcare providers, and public officials. Innovative and effective communication initiatives are needed, as are carefully tailored messages for each of the stakeholder groups.

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INTRODUCTION

The struggle against antibiotic resistance is a war we will never win. The strength of trillions upon trillions of microorganisms, combined with the ancient force of evolution by constant, unrelenting variation, will inevitably overpower our drugs. Their spectrum is selected to include pathogenic bacteria; antibiotics always select naturally resistant bacteria and the strains which have acquired resistance (e.g., Methicillin resistant staphylococci which acquire resistance readily and *Burkholderia cepacia* which is naturally resistant).

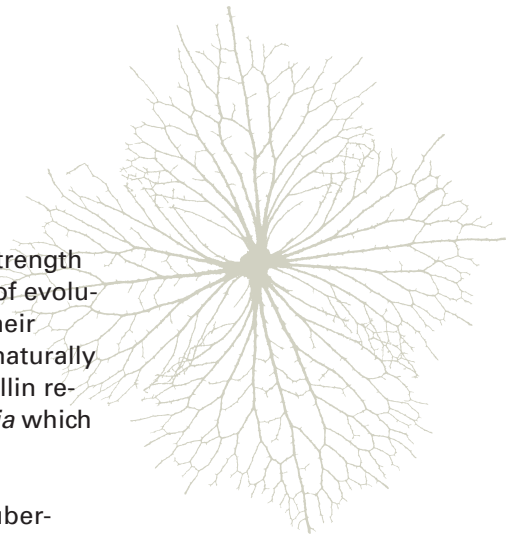
Tuberculosis illustrates just how lopsided the battle with resistance is. Tuberculosis (TB) is a disease we should have well in hand; effective antibiotics for this condition have been available for decades. In developing countries, TB should be considered a thing of the past. However, largely because of antibiotic resistance, TB is on the march.

The treatment regimen for TB lasts as long as six months, and if a patient discontinues treatment or takes prescribed antibiotics sporadically, resistance can get a foothold. Once a patient has acquired a resistant form of TB, re-starting them on the same therapy no longer works. Antibiotic resistant TB is curable, but treatment requires lengthy and expensive regimens of chemotherapy—something many patients, particularly those in developing countries, cannot afford. Strains resistant to the two most powerful anti-TB drugs and multidrug-resistant TB have become more common. Now, extensively drug-resistant (XDR) TB strains, which are resistant to all major TB drugs, have arrived on the scene. TB is finding a way around all of the best antibiotics, and, at the present time, the World Health Organization (WHO) estimates that 30% of the world's population is infected with the tuberculosis bacterium. This is an impressive statistic for a disease that should be treatable with antibiotics.

The specific meaning of “antibiotic resistance” depends entirely on context. The clinical definition used in this document refers to the ability of a microorganism—a bacterium, virus, fungus, or parasite—to survive concentrations of antibiotics that kill sensitive cells of the same strain. It is important to note that for every antibiotic, there are sensitive strains, which are killed or inhibited by the drug, and naturally resistant strains. When a sensitive strain gains the ability to withstand an antibiotic, it is “antibiotic resistant.”

In bioclinical terms, antibiotic resistance simply means that a pathogen is less susceptible than its counterparts and may not respond to the antibiotic administered. In genomics, organisms that possess a resistance gene are resistant. Like all other living things, the evolution of microorganisms is Darwinian: in the face of change, the fittest survive. Antibiotics represent an evolutionary challenge that microorganisms must surmount or perish.

Resistance is commonly considered simplistically—either an organism is resistant or it's not. In reality, resistance exists as a gradient that reflects phenotypic and



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genotypic variations in natural microbial populations. Among “wild type” strains, for example, the minimum inhibitory concentration of a given antibiotic can vary by four- or five-fold. Moreover, the genes in clinical isolates can be identical to those in “naïve,” unexposed populations. Different mechanisms of resistance confer different levels of resistance. Low levels of resistance are often overlooked but can play an important role in the expansion of resistance. The currently accepted definitions of antibiotic resistance do not take such diversity into account.

Resistance is often portrayed as an undesirable consequence of antibiotic abuse or misuse. This view is simplistic and inaccurate. The rate of antibiotic resistance emergence is related to all uses of these drugs, not just misuse, and the total amount of antibiotics used and the environment also play roles. The main driving factor behind resistance may actually be a lack of adequate hygiene and sanitation, which enables rapid proliferation and spread of pathogens.

Antibiotics have dramatically improved public health by enabling millions of people to live longer, more productive lives. They have dramatically lowered child and infant mortality rates, particularly in the developing world, and spurred accelerated population growth and an increase of seven years in the average human lifespan. The very success of these drugs has often resulted in a cavalier attitude toward prescribing them; since antibiotics can miraculously cure the most dreadful infections, their potential to develop resistance is often overlooked.

This leads to the question: Is resistance really a major clinical problem in terms of mortality and morbidity? As long as clinicians have one effective drug available, one could argue that there is no pressing problem in hospitals and clinics. However, this argument does not consider the recent emergence of pan-resistant bacteria (including *Mycobacterium tuberculosis*, *Klebsiella*, and *Acinetobacter*), which can overcome virtually any antibiotic used. What’s more, the perception that resistance is not a huge problem blunts awareness of the fact that we are obliged to keep seeking, testing, and validating new antibiotics.

The matter of antibiotic resistant bacteria (and infections due to them) shares features with other global issues, such as global warming. The concern for the individual patient is sometimes different than the general view on society. The problem with antibiotic use and resistance is not just too much use, but also too little use when access is limited, such as in rural areas and developing countries.

Resistant bacteria spread silently over the world and emerge through infections months or years later. Managing the problems of resistance cannot be undertaken by any single country; they are problems that must be addressed at the global level.

WHERE DOES ANTIBIOTIC RESISTANCE COME FROM?

Antibiotic resistance arises by chance through mechanisms that may represent the legacy of natural competition among microorganisms. The mechanisms, genes, and pathways of antibiotic production and resistance help microorganisms compete for niches in nature; therefore, they are fundamental components of microbial life and represent normal evolutionary phenomena.

Unfortunately, these phenomena are amplified by the use, appropriate or not, of antimicrobials. Although resistance emerges by chance, dissemination of antibiotic resistance could be delayed.

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Most organisms can be sources of resistance genes, but selection for antibiotic resistance most often takes place in non-pathogenic microorganisms, since they comprise the vast majority of the microbial world. Commensal organisms, which live on and in the body (or animal) without causing noticeable harm or benefit, as well as environmental organisms, can be the source of resistance. Resistance genes are often derived from existing essential genes. For example, there is evidence that beta-lactamase enzymes (which confer resistance to beta-lactam drugs like penicillin) are forms of penicillin binding proteins, suggesting that the enzymes that destroy antibiotics can be part of the existing machinery of wild type bacteria. Resistance genes may also originate from antibiotic-producing strains that use them to protect themselves from their own noxious products, or from natural protection mechanisms like efflux pumps, which carry unwanted materials out of the cell.

Developing resistance to antibiotics increases the cache of genes available to microorganisms and impacts many other genes as well, thereby contributing to the evolutionary possibilities available to them. Once a microorganism derives a genetic tool for resistance, it can pass that gene on to its progeny by clonal replication or to other microbes through horizontal gene transfer (see *Horizontal Gene Transfer*, below).

WHY ARE RESISTANCE GENES SO STABLE?

Although limiting the spread of antibiotic resistance has proven to be possible, efforts to eradicate antibiotic resistance ultimately prove futile. This failure may be due to many factors (e.g., compensatory mutations for fitness; killer plasmid; chromosomal integration).

Logic would say that once the selective pressure to maintain a resistance gene is removed, resistant bacteria will lose their ability to withstand an antibiotic. However, studies show that resistance does not disappear from a population after the antibiotic is no longer used. After all, many of these genes retain their original essential functions for survival in the environment, so shedding them is not possible.

Antibiotic resistance genes are ubiquitous, and gene flux in the environment and in the human gut is extensive, so resistance genes may be passed around from organism to organism like trading cards. Resistance genes carried on integrons are apparently more difficult to eliminate than other genes, perhaps because of a fitness cost associated with losing an integron. In general, resistance genes within a chromosome have different functions than genes on a plasmid.

TOPICS DISCUSSED IN THIS DOCUMENT

As the TB example demonstrates, the ability of pathogens to develop resistance to antibiotics is too powerful for us to confront directly. What's more, once an organism finds a way to tweak an existing gene to fend off an antibiotic, or pump the drug out of the cell, that gene will spread from organism to organism, magnifying the problem. The bottom line: development of antibiotic resistance cannot be stopped, and antibiotic resistant strains cannot be eradicated.

If science and medicine cannot win a war against antibiotic resistance, what CAN be done? We have to find a way to co-exist with resistance. To minimize the loss of life, we can develop strategies to prevent new resistance from spreading and, where resistance already exists, identify the strains we need to protect against, find ways to

treat resistant infections effectively in patients, and manage reservoirs of antibiotic resistant strains in the environment. Preventing development of new forms of resistance should rely, in part, on prudent use of antibiotics with an eye to the ecologies of pathogens and other microorganisms.

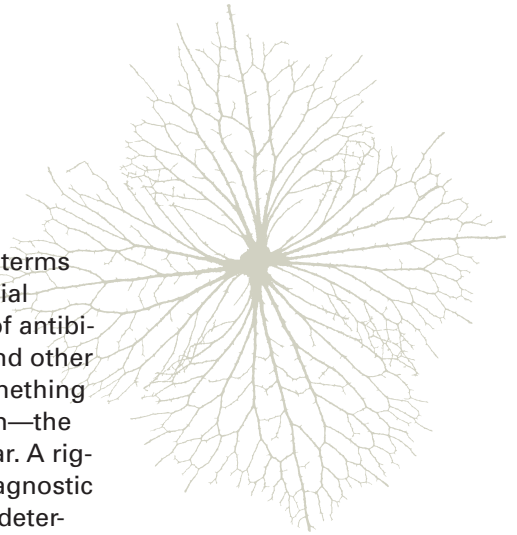
This report summarizes the current scientific understanding of antibiotic resistance, the scope of the problem, and methods at our disposal for detecting emergence and preventing spread. The knowledge gaps about the prevalence of resistant strains and resistant infections are highlighted, as is the need to fill these gaps with far-reaching surveillance efforts, rapid diagnostic tools, and other efforts. The resistance situation is necessarily different in developing countries, where lack of access to basic sanitation and over-the-counter antibiotics are often the norm, and the report details some of the more significant issues.

There are some proven tactics for preventing resistance spread in hospitals and elsewhere, but more and better approaches are needed, and the report describes research areas that require further study. Again, the developing world has distinct circumstances with respect to antibiotics and resistance; the report includes specific recommendations for addressing problems in these countries.

Finally, this report makes recommendations for addressing the widespread ignorance of the facts about antibiotic resistance that exists among the public, public officials, and clinicians. Conveying information to stakeholders will require innovative communication approaches and tools, as well as specifically tailored messages that deliver the facts each group needs to hear.

DETERMINING THE SCOPE OF THE PROBLEM

In order to effectively manage antibiotic resistance, we must first come to terms with the scope of the problem. The use of antibiotics in agriculture, antimicrobial products, and release into the environment all play roles in the development of antibiotic resistance, and horizontal gene transfer, travel by humans and animals, and other factors all have a hand in the spread of that resistance. Although we know something about these various roles, the actual scope of the antibiotic resistance problem—the number of cases per year, the mechanisms of resistance, etc.—is not at all clear. A rigorous, coordinated surveillance effort, better models of transmission, rapid diagnostic tools, and standardized, easy-to-use susceptibility tests are all needed to help determine the patterns of resistance in different parts of the world so that we may better treat patients and prevent new infections.



PREDICTING THE EVOLUTIONARY POTENTIAL OF RESISTANT PATHOGENS

To some extent, it is possible to estimate the evolutionary potential of individual antibiotic resistant clones. However, it is difficult, if not impossible, to predict how resistance will arise in a patient or animal model, since resistance arises *in vivo* differently than it does in the laboratory. There are several tests that can predict whether a drug will incite resistance, and in the process of developing new antibiotics, attempts are often made to develop resistance in the laboratory based on the argument that if it is easy to force resistance under lab conditions, it will be even easier to force resistance in the clinic. Once these drugs are used for therapy, however, resistance develops more frequently and often by different mechanisms than observed in the laboratory. There are many more factors involved in the selection of resistance in a complex *in vivo* setting, including biofilm growth, host factors, and pharmacokinetics of antibiotic levels, than in a simple laboratory experimental system. Moreover, in many pathogens, it appears that the number of resistance genes that a bacterium can acquire and retain is practically unlimited.

Selection for antibiotic resistance takes place anywhere an antibiotic is present: in the skin, gut, and other areas of the bodies of humans and animals and in the environment, particularly in sewage and sediments (see *Environmental Fate*, below).

The following factors most likely play significant roles in increases and decreases in the prevalence of resistant strains:

- Host and clone specificity,
- Plasmid and clone specificity,
- Virulence,
- Interactions with other commensal flora,
- Duration of the selection pressure, and
- Variable gene expression.

Many markers of antibiotic resistance are apparently neutral with respect to selection pressure—that is, a bacterium that carries the marker suffers no loss of fitness because the bacterium has developed a compensatory mutation. In the presence of an antibiotic, developing resistance helps a pathogen spread, outcompete its competitors, and increase transmission from host to host. In the worst case infection scenario, a fit, clinically-successful, and virulent strain will develop resistance, but for long-term success can we speculate that a bacterium that becomes less virulent (and therefore less likely to kill its host before it transmits the disease to another person) may have an advantage? In fact, the factors that contribute to making a clone or a resistance gene “successful” are mostly unknown.

It is interesting to note that in a species the proportion of strains resistant to an antibiotic after the early rise reach more slowly a quite stable plateau different for the different antibiotics, never reaching 100%. Factors involved in the stability of prevalence are also poorly known.

HORIZONTAL GENE TRANSFER

Horizontal gene transfer—the movement of genetic material from one organism to another—is the primary mechanism by which bacteria acquire antibiotic resistance. Antibiotics promote this genetic exchange by inducing the transfer of conjugative elements. In this way, antibiotics can be viewed as ecological effectors—simply another of many pressures that can drive evolution of individual clones and communities. Additionally, acquisition of foreign DNA begets acquisition of even more foreign DNA, possibly accelerating the evolution of multi-drug resistance.

The environment is an immense reservoir of resistance genes, and even many point mutations that result in resistance are part of existing natural variation (that is, variation that evolved in the absence of antibiotic pressure). The ecological impacts and roles of these genes and mutations are not well understood, nor are the mechanisms and frequency of resistance emergence and transfer. Recent observations that new resistance genes can supplant old ones (CTX-M for TEM, for example) highlight the lack of a detailed understanding of selection, spread, and maintenance of resistance.

The transfer of antibiotic resistance genes is evident between bacteria or fungi of the same species, but transfer between organisms that bear limited phylogenetic relatedness, including transfer between gram-negative and gram-positive species, is also possible. Transfer is more frequent for some genes than others. The amount of horizontal transfer should be proportional to the level of stress endured by the organisms of interest. Transduction (gene transfer mediated by viruses) is a more powerful player in the spread of antibiotic resistance than was formerly thought.

The environment plays an important role in gene transfer. *Vibrio* species, for example, are known to enhance their rates of gene transfer when they are growing on chitin cuticle (e.g., shrimp).

Genes for resistance are found on both plasmids and chromosomes. Conjugative plasmids can tolerate numerous resistance genes, so the acquisition of one plasmid under pressure from one antibiotic can result in resistance to many classes of antibiotics. Integrons can also tolerate a huge number of resistance genes, sometimes even multiple copies of the same gene (e.g., numerous copies of *sulA* in response to exposure to Sulfa drugs).

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SILENT OR CRYPTIC RESISTANCE GENES

Silent or “cryptic” resistance genes, which can be detected by molecular methods but do not apparently confer resistance on the cell, are known to occur. Many *Streptococcus pneumoniae* strains, for example, carry *Tet* and *sul* genes (for tetracycline resistance) but do not express them. It is thought that cryptic genes may play a role in the development of antibiotic resistance. Any of a number of scenarios could explain the phenomenon of cryptic resistance genes, including:

- The gene in question could be defective due to deletions not detected in the molecular assay,
- The gene may be present in cells screened by molecular means, but deleted in cells grown for phenotype testing,
- The gene may not be expressed in the cell, or
- The cell carries the gene on multiple plasmids that are not compatible.

Molecular screening is an important element in discerning the significance of cryptic resistance genes. Care must be taken to avoid contamination of the test, and the results must be interpreted in light of the possibility that resistance genes may contain deletions. Real-time PCR to assay gene expression could help discern between genes that are present, but silent, and those that are actively expressed.

BROAD SPECTRUM VS. NARROW SPECTRUM ANTIBIOTICS

The relative contributions of broad spectrum and narrow spectrum antibiotics to the problem of resistance are difficult to discriminate. On one hand, “narrow spectrum” selects for the species which being “naturally resistant” are not in the spectrum of the product; on the other hand, “broad spectrum” selects various resistant bacteria already present in the setting. Clinicians often continue prescribing broad-spectrum antibiotics to their patients even once the identity of the pathogen and its susceptibility to more targeted antibiotics is known. Intuitively, this would seem to lead to more widespread resistance, since the argument can be made that broad spectrum drugs, theoretically, can induce resistance in more species than narrow spectrum drugs. However, there is no clear evidence that broad spectrum antibiotics select for resistance any more than narrow spectrum drugs.

Moreover, the distinction between the two classes of drugs may be illusory. Since most commensal bacteria cannot be cultured in the laboratory, it is difficult to claim conclusively whether a given drug has a broader effect on the bacterial world than another. Also, the linkage of different resistance genes on a plasmid or the presence of efflux pumps, which can bestow certain levels of non-specific resistance on a bacterium, hides the expected effect of an antibiotic.

ANTI-INFECTIVE STRATEGIES AND ANTIMICROBIALS

Anti-infective measures, including the use of vaccines and biocides, can have distinct impacts on patterns of antibiotic resistance, but these effects are not well studied and scientists do not understand their ecological underpinnings. In one controversial example, an increase in the use of a vaccine for *S. pneumoniae* has been correlated with an increase in the incidence of Staphylococcal infections. The vaccine, which includes a serotype that is resistant to fluoroquinolones, also appeared to reduce the

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occurrence of fluoroquinolone-resistant strains. Any vaccine has to be adapted continuously to compensate for the evolution of new resistance.

Because they are ubiquitous and can induce broad resistance capabilities like efflux pump resistance, biocides, such as triclosan or quaternary ammonium compounds, may represent a more important threat to the future of antibiotics than antibiotics themselves. It is entirely possible that biocides have contributed to the rise of some of the very serious problems in resistance that we face today with bacteria like *P. aeruginosa*, *Acinetobacter*, and MRSA. Biocides are often included in consumer products like hand soap and household cleaners at sub-lethal concentrations that promote the evolution of bacterial resistance. This could have significant impacts in nursing homes and day care centers, where resistant bacterial populations are high. Biocides also eventually wash down the drain to water treatment facilities, where they may not be readily degraded and are ultimately discharged to surface waters, where they could impact biodiversity in natural areas and trigger significant environmental problems. None of these potential problems with biocide use are well studied.

Aside from vaccines and biocides, there are many chemical stressors that are not specifically designed to target pathogens that can, nonetheless, contribute to the selective pressure to develop antibiotic resistance. Some of these stressors include mercury and silver in dental fillings (which, by inducing metals resistance, may cause other resistance genes to be induced), phenothiazines, quinine, antiviral drugs, micronutrients like zinc, and arsenic and copper used in animal feed. Some of these compounds may stimulate survival mechanisms that result in mutagenesis—a quick, if unreliable, route to resistance. Overuse of many types of non-antibiotic drugs can have an antimicrobial effect. These drugs should be tested for their ability to induce antibiotic resistance.

ENVIRONMENTAL FATE

Selection for antibiotic resistance is not confined to the human body or even to hospitals, clinics, and farms. Selection takes place anywhere an antibiotic is present, especially in natural environments, most notably sewage and surface water sediments, where antibiotics are likely to be coupled with high densities of various microorganisms. The fate of antibiotics and their stability over time after they are used is a global issue, poorly explored and not addressed by any current laws or guidelines.

Large amounts of antibiotics and biocides wind up in sewage sludge, making it a hotbed for the development of antibiotic resistance. When dewatered sludge is applied as fertilizer to agricultural land there is a risk of introducing both antibiotics and resistant strains into the food supply. Different regions of the world bear different burdens of resistance in these environments. Antibiotic residues have been found even in the sediments of large bodies of water, like Long Island Sound, Chesapeake Bay, and the river Seine, where dilution might be expected to diminish their concentrations.

The stability of an antibiotic is one key to how it will impact resistance development in the environment; stable antibiotics are more likely to persist long enough to select for resistance. The fate of antibiotic molecules in environmental matrices is poorly studied and represents a high priority for research.

Increasing amounts of antibiotics and biocides in waste water, sediment, and sludge originate from agricultural applications (see Box A, below).

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BOX A: ANTIBIOTICS IN AGRICULTURE

Many antibiotics are used in agricultural settings, including therapeutic purposes and growth promotion in food animal species and treatment of a wide variety of diseases in other animals; aquaculture species; bees; horses; companion animals, etc. Antibiotics are also used in veterinary hospitals. On the crop production side, streptomycin, tetracycline, and gentamicin may be sprayed on fruit trees. Many antibiotics used in animals are members of the same classes of antibiotics used in humans, thus cross resistance is of concern with respect to foodborne pathogens. However, some classes of antibiotics are used only in animals, such as the polyether ionophores, bambamycins, and orthosomycins.

In the interest of food security, livestock suffering from infectious diseases must be treated. The issue of antibiotic use in food animals has been discussed for 40 years since the Swann report from the United Kingdom. In the 1990s, as vancomycin-resistant Enterococci emerged, an awareness of the potential contribution to human pathogen resistance from the use of antibiotics in animals led to a number of consultations called by the World Health Organization, the OIE (World Organization for Animal Health), and the Food and Agricultural Organization of the United Nations. Several recommendations were produced, including guidelines for the responsible use of antibiotics in animals; guidelines for bacterial resistance surveillance; monitoring programs for antibiotics use; and models for risk assessment of microbial food safety. Europe mandated the removal of growth promoter antibiotics use, which is currently being reviewed in other countries and should trigger more research on the results of the European experience. Guidelines from the Codex Alimentarius Commission are in progress to measure the risk of resistant pathogens in food as related to antibiotic use in animals.

Answers to the problem of using antibiotics as growth promoters are far from clear. Banning the use of antibiotics for growth promotion has been shown to increase the use of antibiotics later in an animal's life for treating infection, and assigning some antibiotics to human use and others to growth promotion does not account for the possibility of cross- and co-resistance, which would confer resistance of pathogens to multiple drugs. For reasons unknown, despite decades of using certain drugs as growth promoters in livestock, resistance to these antibiotics is still not completely pervasive. Hence, a total ban might not be the solution, but there is some evidence that shortening animal exposure to antibiotics, and thereby decreasing the quantity of antibiotics used, can still elicit the desired positive effects on animal health. More studies are urgently needed.

Streptomycin, used to treat bacterial infections in humans, is also applied to apple and pear crops in the United States and other countries to fend off fire blight. The impacts of this use, which totals 50,000 pounds of antibiotic in the U.S. alone, are not known.

Large quantities of antibiotics, like tetracycline, florphenicol, and flumequine, are used in aquaculture, an application that, considering the continuity between farmed waters, recreational waters, beaches, and possibly even drinking water sources, has undoubtedly had an impact on human health. The opportunity for rampant lateral gene transfer in aquatic environments is undeniable. There is no question but that research on the impacts of antibiotic use in agriculture on resistance in the clinic is scant and deserves more attention.

SUB-INHIBITORY CONCENTRATION OF ANTIBIOTICS

The use of sub-inhibitory (or sub-MIC) concentrations of antibiotics plays several important roles in the development of resistance. Like low concentrations of biocides (see *Anti-Infective Strategies and Antimicrobials*, above), low concentrations of antibiotics could enrich for resistance genes in a population while having little effect on overall mortality. The tendency to mutate also increases upon exposure to sub-inhibitory concentrations of antibiotics. Pathogens can initiate an SOS response (a DNA repair pathway) when subjected to low concentrations of antibiotics like quinolones, which affect DNA synthesis. This may make them more prone to develop resistance in the future. Low concentrations of antibiotics can also select for strains that increase expression of their existing resistance genes, further enhancing their resistance.

Different strains of microorganisms exhibit different sensitivities to antibiotics; hence, the bar of “sub-inhibitory concentration” is set differently for each strain—an important aspect of their ecologies. Moreover, despite decades of antibiotic use, no strain of sensitive pathogen has been completely displaced by a resistant form. *Staphylococcus aureus* infections, for example, have long been treated with penicillin, but 10 to 30% (according to different geographical location) of these infections are still sensitive to penicillin treatment. This phenomenon, in which the prevalence of a resistant strain climbs and eventually reaches a plateau, may have significance for understanding the epidemiology of resistant infections.

The range of possible sub-inhibitory concentrations and their effects is pleiotropic—they are potent modulators of transcription in bacterial cells—and there are a host of metabolic responses and mutations with different levels of antibiotics.

TRAVEL AND TRADE

International travel and global trade are more widespread than ever before, and these activities undoubtedly accelerate the movement of antibiotic resistance genes and strains around the world, but these influences are difficult to quantify. Health policies at the community or national level have minimal effect on regional and global movement of antibiotic resistance. Worldwide policies that are tailored to local conditions must be implemented.

Civilians and military personnel alike can contract resistant strains abroad, whether as active infections or as unaffected carriers. Any number of scenarios can result in an international traveler entering a hospital, for example, only to bring home an unwanted souvenir. In one memorable instance, carbapenem-resistant *Klebsiella pneumoniae* moved from New York City, to Israel, to Florida, all thanks to the travel of individuals.

Cases of antibiotic resistant infection imported by travelers should be monitored. Pockets of new resistance should be noted as they arise via a global alert system. ProMed mail, a list serve that monitors human and animal outbreaks and has professional medical moderators to filter information, could be used to help monitor the spread of these strains. Antibiotic-resistant pathogens move around the world as quickly as people do, threatening the health of travelers and homebodies alike. Surveillance of this movement, which may well include a GIS (geographical information system) component, is needed in order to understand it and, if possible, stanch it.

International trade of food and livestock is problematic for efforts to suppress the movement of antibiotic resistance. Food is distributed on a global scale today, and

produce, meat, processed foods, and other food types can all carry antibiotic resistant microorganisms and genes. In Finland, for example, a widespread outbreak of *Campylobacter* was recently linked to imported chicken. Antibiotic-resistant organisms have been detected in supermarket meat in many investigations. Surveillance of foods, particularly foods crossing international borders, is critical. Biological hazard controls should also be implemented. It may be necessary to resort to gamma irradiation of imported foods to head off further outbreaks. For livestock, a certification program that qualifies only animals not colonized by certain resistant strains for export may be an effective measure, but it is doubtful that such a program would be possible given the economic and logistic realities.

Aside from travel and trade, antibiotic resistance can move across borders via animal vectors (wild animals, rodents, birds, insects) and by the movement of water in rivers and oceans. There is also the potential for resistant bacteria to move long distances in dust clouds.

THE ROLES OF ANIMALS AND INSECTS

Antibiotic-resistant pathogens and genes can be found among the flora of insects (*Acinetobacter* have been detected in cockroaches, for example) and in wild animals (extended-spectrum beta-lactamases were detected in pigeon guano in numerous cities in Europe, for example). Rodents and wild animals, including migratory birds, are particularly difficult reservoirs to control, as well as companion animals, which live in intimate contact with their owners.

Clearly, non-humans can bear and transmit antibiotic resistant pathogens, but the burden this places on human health is not known. Cases in which humans have transmitted resistant strains to animals have also been documented. The cycle of transmission between humans and animals, as well as plants, operates in all directions.

MODELING TRANSMISSION

Although a model cannot represent all the complexity of real life or capture all the factors that contribute to the transmission of antibiotic resistance, we can develop valid general predictive models of particular situations like intensive care units. Precise models to predict spread from person to person and quantitative prediction of the impact of antibiotics on resistance spread, for example, can also be developed for particular scenarios (e.g., pandemic influenza, prediction of Tamiflu resistance and efficacy, and use of antibiotics to suppress secondary infection). The fitness costs of particular resistance genes have also been modeled (and shown to be neutral in some cases).

It is important to note that, as with any model, the data acquired from applying a transmission model are only as good as the parameters and controls that are used. Also, models of antibiotic resistance transmission cannot be extrapolated beyond their basic parameters to incorporate the possibility of random events. Generic models can be problematic, since they cannot always account for differences between various pathogen species, transmission rates, and persistence rates. Models that rely on laboratory strains to estimate the transferability of conjugative plasmids might be misleading, because laboratory strains do not possess the virulence factors, restriction enzymes, and other elements that contribute to the spread of resistance.

ASIDE FROM
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AND TRADE,
ANTIBIOTIC
RESISTANCE
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ACROSS
BORDERS
VIA ANIMAL
VECTORS (WILD
ANIMALS,
RODENTS,
BIRDS, INSECTS)
AND BY THE
MOVEMENT
OF WATER IN
RIVERS AND
OCEANS.

Communication of the models is vital. Often modelers write papers for other modelers, not for other audiences. Empirical journals should be tolerant and, if possible, encouraging of papers that are based on hypotheses and not on experimental data. Modelers need to be much better at communication and place less emphasis on equations and more emphasis on easy to understand graphics, for example.

LESSONS FROM NON-ACQUISITION OF RESISTANCE BY SOME MICROORGANISMS

Despite repeated and prolonged exposure to antibiotics or biocides, some microorganisms do not acquire or retain resistance. There is often a correlation with genome size; organisms with small genomes, such as Group A *Streptococci*, apparently cannot tolerate the extra baggage of resistance genes, whereas organisms with large genomes, like *P. aeruginosa*, can retain many extraneous genes and readily acquire resistance. Organisms with efflux pumps may be able to survive in the presence of low concentrations of antibiotics, “buying them some time” to acquire specific resistance genes. Conversely, it is logical to reason that organisms without efflux pumps do not have such a grace period, and are wiped out even by low concentrations of antibiotics. We can learn about the genetics of organisms that fail to acquire resistance by comparing them with organisms that are more amenable to acquiring resistance. We may learn also from organisms where resistance markers were abortive; for example, what happened to producers of beta-lactamase in *Enterococcus faecalis*?

THE NEED FOR MORE RAPID DIAGNOSTICS

Physicians usually resort to prescribing antibiotics empirically due to a lack of rapid, easy diagnostics. Access to more rapid diagnostic tests that could determine the causative agent and antibiotic susceptibility of infections would inform better decision making with respect to antibiotic use and help slow the selection of resistant strains in clinical settings. With the right tools, physicians would be able to prescribe targeted therapies in a time frame that protects patient health without sacrificing accuracy. Moreover, clinicians in hospitals could rapidly determine whether new patients carry resistant strains, enabling them to isolate colonized patients within hours instead of days. This type of testing is especially relevant for patients with a history of care in other clinical settings, where they may have picked up any of a number of resistant organisms.

Polymicrobial diseases may not be easily dealt with using rapid diagnostics, however, which may fail to correctly identify the causative agent in these more complex circumstances. Quantitative detection of expressed virulence factors or strain-specific genes could present a solution, so long as the results are easy to translate into treatment strategies. However, the number of possible resistance genes for screening can be overwhelming, and epidemiological studies are needed in order to establish which are the major players. Also, the presence of a resistance gene does not necessarily predict expression (see *Silent or Cryptic Resistance Genes*, above), and these technologies would miss the emergence of novel virulence factors and resistance genes (but once recognized, they can eventually be incorporated into the technology). The high cost of assays for virulence factors or strain-specific genetic markers would, for the time being, place these methods out of reach for developing nations and for routine screening.

Proteomics may also play a role in the future of antibiotic resistance diagnostics, perhaps as second tier testing. By identifying the end products of resistance genes, proteomics could more accurately discriminate between cryptic resistance and active

resistance. These techniques must be enhanced to improve their speed, ease of use, and robustness. Diagnostic companies should be involved in making these improvements.

It should be noted that although speed is of great importance in detecting resistance, accuracy is paramount and must not be sacrificed. Falsely labeling an organism as susceptible to a given antibiotic can have disastrous consequences for patients. An error that overstates resistance is more acceptable than an error that calls an organism falsely susceptible. That said, the condition of the patient is also a factor in the conflicting priorities of speed and accuracy. For a severely ill patient, time is of the essence, and a fast, less accurate test is acceptable. There is less time pressure in treating less ill patients, and the relative importance of accuracy is greater. The sensitivity and specificity of resistance assays must be balanced as well.

ANTIMICROBIAL SUSCEPTIBILITY TESTING: WORTH DOING RIGHT

Although prescribing antibiotics according to established formulas for treating known pathogens with certain compound families is correlated with positive clinical outcomes, for the sake of achieving the best possible outcomes and preventing the development of resistance, it remains critical to obtain microbiological data to guide treatment. Prescribing antibiotics empirically surely contributes to the problem of resistance, and the costs of prescribing an inappropriate antibiotic can be tragic since the patients keep shedding resistant bacteria. When prescribing empirically, it is acceptable to use the most appropriate drug, given the type of infection and the resistance problems faced in that particular hospital or region. Ideally, after 48 hours, the patient's condition should be reevaluated and testing results should be reviewed to determine whether a more targeted drug may be used. However, clinicians are often reluctant to de-escalate treatment and "step down" to older, more targeted drugs. A primary goal of this approach is to avoid maintaining empiric, ineffective therapy for resistant infections. Any guideline for empiric therapy must be reviewed regularly and judged according to the patient's response to therapy.

Inadequacies exist in antimicrobial susceptibility testing that can compromise both patient care and the ability to manage antibiotic resistance. Testing is not well standardized in many countries outside the U.S. and Western Europe. For example, differences in breakpoints between the U.S. and Europe are confusing and may lead to differences in interpretation and therapy. Also, the panel of drugs tested in a given hospital does not always reflect the specific resistance patterns that hospital or region is coping with. Disk tests are not suitable for some drugs (e.g., Colistin, Vancomycin, Daptomycin), so resource-limited laboratories cannot test for susceptibility to these compounds. Finally, there is a need for more data linking minimum inhibitory concentration (MIC) testing with clinical outcomes.

Although MIC testing is necessary and sufficient in many ways, clinicians need faster, more reliable, and more quantitative measures of antibiotic susceptibility that link *in vitro* activity with pharmacology and clinical outcomes. Moreover, metabolic variants in chronic infections, intracellular pathogens, and biofilms present special problems that MIC testing on cultures or on a petri plate cannot address, such as the term of the infection, the growth stage of the pathogen, the inoculum, and other factors not captured in standard MIC measurements. Expanding and validating robust, broadly acceptable assays for screening and evaluating drug candidates would be particularly useful.

INADEQUACIES
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RESISTANCE.

In developing new measures of susceptibility and standards for conducting these tests, a number of improvements and new features are needed, including:

- Methods that incorporate a standard set of antibiotics adapted to the species, showing the resistance pattern, and allowing comparisons;
- Enforcement of validation, quality control, and standardization;
- Testing to account for the differences between susceptibility of planktonic bacteria and biofilm bacteria;
- Flow cytometry to detect subpopulations of pathogens;
- Gene chips to enable faster, more accurate results;
- Automated systems;
- Optimized computer programs (WHONET system is a useful example); and
- Training for staff and reducing test costs.

RESISTANCE SURVEILLANCE

In the U.S. and many other countries, resistance surveillance takes the form of pharmaceutical company-sponsored studies undertaken to support the release of new products. Widespread, independent surveillance efforts are rarely undertaken. However, a surveillance requirement for newly-approved antibiotics will be instituted in the U.S. under the Food and Drug Administration Amendments Act of 2007. These changes mirror the rules already in effect in the European Union.

The magnitude of the resistance problem on a global scale cannot be measured. A rigorous, coordinated surveillance network is needed to provide quantitative data that can be used to assess the current and future impacts of drug resistance; the financial, morbidity, and mortality costs; and determine whether increases in costs follow from increases in resistance, among other things. The relationship to the benefits of antibiotics treatment is even more difficult to assess.

Ideally, surveillance should begin at the local level and collected and compared at the national level. Data are currently lacking at the community level; continuous community sampling would be ideal. Better stratification of surveillance is also needed. We need to know the rates of resistance in relation to a number of risk factors.

Sampling strategies are critical to an effective surveillance program. Sampling bias is important to consider. Structured surveillance is critical, as is sampling of consecutive patients. Careful consideration must be given to the species that should be monitored, and strains and sampling conditions must be targeted very precisely to avoid confusion. It will be vital to delineate the full context for sampling so that the meaning of the surveillance results can be interpreted.

A study similar to the model created by the Framingham Heart Study Cohort would be valuable. The study could follow groups of people for decades, recording the antibiotics used, health outcomes, and morbidity and mortality.

A system of easy-to-access global surveillance and molecular epidemiological data could help track critical organisms and phenotypes. Existing regional systems, such as the European Antimicrobial Resistance Surveillance System (EARSS) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), are good starting points for a system. Sentinel sites could provide a reasonable coverage of the steady state and emerging strains. Funding for these sites would have to be provided by regional authorities; however, a resistance monitoring network will probably result in a net savings for

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health care. Surveillance programs should be designed as Alert Systems. As in the WHO-NET system, the follow up and comparison of bacterial resistance patterns to a standard set of antibiotics may be good indicators for the detection of emerging resistance traits.

Data should be accessible both electronically and in real time. Reliance on written reports that can be months or years out of date by the time they are published is not acceptable. An electronic surveillance system should feed into a reference laboratory that can collect the unusual resistant isolates and integrate information from multiple sources to identify trends and outbreaks. In a system like this, if a Penicillin-resistant *Streptococcus pyogenes* is isolated, for example, the reference laboratory would contact the local laboratory and ask them to repeat the test. If the result is confirmed by the local laboratory, then the isolate must be sent overnight to the reference laboratory for further confirmation and investigation of the resistance mechanism. In addition to invasive pathogens, surveillance should include some monitoring for commensal organisms, since detection of resistance in commensals can be an early warning of the development of resistance in pathogens.

The phenotype of an antibiotic-resistant pathogen is important for the responsible clinician to know, but in surveillance the phenotype is not sufficient. It is critical to identify resistant genotypes in order to control spread of infective strains. The capacity to identify resistance genes should be available to major institutions. It is also important for hospitals to know the resistance patterns at nearby institutions because patients may be transferred from location to location for specialty procedures and tests. It is not clear what kind of communication about antibiotic resistance currently occurs or how this information can best be transmitted.

There is currently a mass of surveillance data generated by a large number of programs in many countries. There is no agreement on how to use them best to improve in "real time" the use of antibiotics and the control of resistant strains. There are currently no global regulations targeting the usage of antibiotics, but all antibiotics should be available only by prescription, in all countries. A global tracking system should be instituted for the use of antibiotics in humans, agriculture, and aquaculture.

ECO-SOCIOLOGICAL FACTORS

Many social factors play critical roles in the development and spread of antibiotic resistance. Certain types of environments (for example, long-term care facilities and daycare centers) are hotbeds of antibiotic resistance, presumably because of crowding and the chronic or repeated use of antibiotics by both patients who need long-term care and small children, respectively. In hospitals, the prevalence of resistant infections is also related to the structure of the facility and the frequency with which patients are moved from facility to facility, since movement assists dissemination of pathogens.

The non-regulated use of antibiotics is also very problematic for managing resistance. In many developing countries, antibiotics are available without a prescription, a situation that gives rise to widespread misuse and resistance. But the problem of over-the-counter antibiotics is not limited to developing countries; some shops in New York City neighborhoods often carry antibiotics for sale without prescription. This conceivably could result in a higher burden of resistance.

On an individual basis, there is a correlation between increased wealth, increased willingness to seek health care, and a concomitant willingness, on the part of clinicians, to prescribe antibiotics without direct evidence of a bacterial infection. Those

are anecdotal studies. The problem is to avoid needless prescription and treatment prolongation and to reserve antibiotics for the treatment of bacterial diseases.

Changing behavior can have dramatic impacts on the spread of antibiotic resistant pathogens. Hand hygiene, in particular, has been shown to decrease the spread of diarrhea and respiratory illnesses and limit the spread of pathogens in multiple settings—from the kitchen to the hospital.

THE DEVELOPING WORLD: UNIQUE PROBLEMS AND CHALLENGES

When it comes to antibiotics and resistance, developing countries are confronted with a number of different problems and challenges than developed countries. The results of these distinctions are mixed, according to the few studies that have examined them. For example, the rates of resistance in *Escherichia coli* in the developing world are apparently higher than they were in Boston over 20 years ago, and surveillance of beta-lactamases in enteric bacteria in South America shows higher resistance in those countries than in the U.S. However, another study shows that rates of resistance in *S. pneumoniae* in Latin America may be similar to or lower than rates in the U.S. The countries with the worst resistance problems may well be those stuck between “developed” and “developing,” such as China and Argentina, where medical practice is advanced, but effective infection control in hospitals and public health measures are not yet in place.

The most obvious difference between antibiotic use in developed and developing nations may be the fact that, in developing countries, many of these important drugs are available without prescription. Without the benefit of guidance from a clinician or even a pharmacist, antibiotics are usually used indiscriminately, without regard for specific symptoms and without any information about the organism at the root of the problem. Antibiotics are sold at pharmacies on a per-dose basis; customers usually buy whatever they can afford and take them until their symptoms are alleviated or the antibiotics run out.

Moreover, generic drugs are frequently approved for sale in developing countries with little scrutiny, and controls on quality and potency are often absent or deficient. It is not known whether a lack of quality control, which could lead to low potency and sub-inhibitory doses, contributes to resistance, but logic would say that it does. In some clinics and hospitals, Trimethoprim/Sulfa is administered to all AIDS patients as a prophylaxis to prevent pulmonary infection with *Pneumocystis jirovecii*. Eighty percent (80%) of *S. pneumoniae* isolated in these hospitals are now resistant to these drugs.

Epidemics involving large numbers of individuals are not uncommon in developing countries because of delayed diagnosis and lack of medical assistance. Due to a lack of potable water and flawed waste management, waterborne diseases—hence, resistant waterborne infections—are common in the developing world. Hygiene and sanitation are critical controls on infection spread in developing countries, management tactics that are controlled in a strictly top-down manner, handed down from the government.

Humans live in much closer contact with animals in developing countries, and this provides greater opportunities for passing resistant pathogens back and forth. In developed countries, the distinction between infection spread in homes and spread in hospitals is quite clear. In the developing world, on the other hand, where hospital patients are often fed and cared for by family members, this division is less obvious, and pathogens are readily transmitted from home (where animals may well be present) to the clinic and

vice versa. Hospital overcrowding and a lack of isolation wards also contribute to the spread of resistant nosocomial infections, including tuberculosis and salmonellosis.

ECONOMIC DILEMMAS OF ANTIBIOTIC RESISTANCE

There is no doubt that antibiotics offer enormous benefits. They have prevented many, many deaths from infection, helped curtail the spread of nosocomial infections, and allowed the development of sophisticated surgical practice. However, the benefits of antibiotics come at a price; controlling resistance is extremely expensive. Antibiotic-resistant infections often incur longer hospital stays, more expensive drugs, and greater losses of productivity than non-resistant infections. Also, hospitals are often forced to maintain precise systems for detecting and treating resistant infections. Research is needed to determine what percentage of infections would benefit from developing a new antibiotic and how that antibiotic should best be handled. Using antibiotics prudently is an obligation (clinical good practice). These resources, and the money to control resistance, must not be squandered.

For pharmaceutical companies, there is little financial incentive for developing new antibiotics and in managing resistance once the antibiotic is off-patent. With the current patent system in place, the costs of antibiotic discovery and development, coupled with the requirement for long-term clinical trials, outweigh profits; therefore, many pharmaceutical companies have abandoned antibiotics as therapeutic portfolios.

In the U.S., the regulatory approval process for new antibiotics is unduly time-consuming and expensive. The hurdle of drug approval is a major factor influencing the exit of drug companies from the antibiotic field. To make matters worse, drug companies pay significant fees to guarantee a 10-month review time for antibiotics by the Food and Drug Administration (FDA), but the FDA fails to meet these deadlines. There are many new drugs currently under review at the FDA, including drugs active against MRSA (telavancin, oritavancin, dalbavancin, tigecycline, and ceftobiprole to name a few), but it is not known when the review process for these antibiotics will be complete. Regulatory agencies must make it clear to pharmaceutical companies at the outset what, exactly, is needed to get a drug approved. Changing the rules during the approval process is not acceptable.

Many pharmaceutical companies have found that developing drugs for chronic diseases, which patients take daily for the rest of their lives, is much more lucrative than developing antibiotics, which are, at most, needed for a week or a month. Pharmaceutical companies take on some responsibility for managing resistance to antibiotics for which they still hold a patent because it is in their financial interest to follow and update resistance to their products. Once a patent expires, lower-cost generic products capture a large part of the market share; since any number of manufacturers can produce the generic drug, the financial incentive to manage resistance is diminished, and the original patent owner discharges their responsibility in this regard.

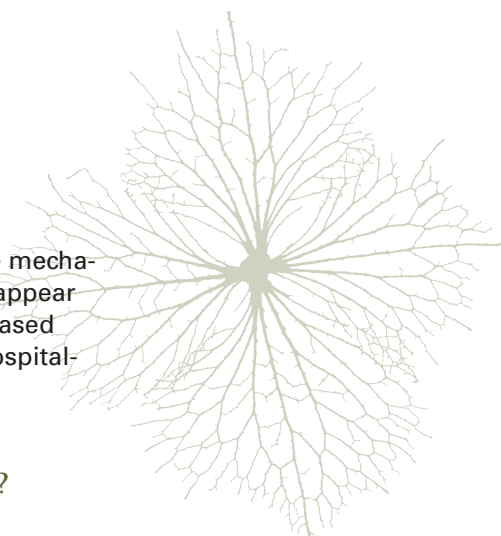
Quality control of imported generics is important, but it can be improved, and must be rigorously established in countries where counterfeit, low potency, and substandard products are legion and are underreported. This can impact the value of an entire class of antibiotics, since substandard products can result in low doses and, hence, enhanced opportunities for pathogens to develop resistance.

Responsibility for quality control testing of generics should be taken on by the countries importing the drugs. Unfortunately, government dysfunction often makes this impossible.

THE BENEFITS
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RESISTANCE
IS EXTREMELY
EXPENSIVE.

ADAPT OR OVERCOME? COEXISTING WITH ANTIBIOTIC RESISTANCE

Antibiotic-resistant pathogens and the potential to evolve novel resistance mechanisms can never be prevented. On the surface, this forced coexistence would appear to be a dismal prospect, but careful management of antibiotic use, evidence-based methods for containing resistance, and reductions in the overall burdens of hospital-acquired infections offer promise for preserving public health in the future.



CAN WE PREVENT SELECTION OF ANTIBIOTIC RESISTANCE?

Antibiotic resistance prevention needs to find a middle ground between individual health and the greater public good. Before prescribing antibiotics to patients, physicians must be aware of the impact on community resistance and determine if the needs of the patient are acute or not. Antibiotics are a limited resource, and there are few antibiotics in the development pipeline.

There are no known methods for preventing development of antibiotic resistance, and any proposed method for doing so should be viewed with a skeptical eye. Decreasing the amount of antibiotic prescribed might limit the development of resistance, but the extent of the reduction is not known or predictable. The smarter approach to resistance prevalence, an approach that positions less immediate risk on the shoulders of individual patients, would be to identify and target effective ways to control antibiotic use. Guidelines that spell out when not to use antibiotics are as important as those that specify when and how to use them (see *Communication Issues*, below). For example, the UK National Health Service has guidelines that clearly state which antibiotics should be prescribed by primary care physicians and which are reserved for prescription by infectious disease specialists, but there is no evidence that this program has been effective in limiting resistance development.

The roles of dosage regimens, routes of administration, and duration of treatment in selecting for resistance depend on the drug and the mechanism involved in resistance. For most drugs, increasing doses and shortening the treatment period apparently are less effective in selecting for resistance than the usual dose and regimen. Pharmacokinetics and excretion of intravenous antibiotics into the gut may also play a role in how effective changing antibiotic use would be at curbing the development of resistance.

Combination therapy, an approach in which more than one antibiotic is administered simultaneously for a given infection, does not appear to reduce the probability of developing resistance. Oftentimes, combinational treatment is tantamount to monotherapy because a pathogen is not susceptible to one or more of the drugs, or one of the drugs does not penetrate the site of infection. However, combination therapy is indicated in certain diseases, like Enterococcal endocarditis where a synergistic bactericidal effect is needed to cure the patient. In tuberculosis the aim of combination treatment is to decrease the risk of resistance mutation.

The duration of treatment is an important part of the selection of resistant bacteria; on one side, needless prolongation increases the amount of antibiotic used, and on the other side, more prolonged antibiotic treatment provokes more changes in the indigenous flora of the patient, thereby increasing colonization and resistance.

Researchers and clinicians should carry out a systematic review of the evidence-based guidelines concerning optimal duration of therapy for each infection type.

To prevent overuse of antibiotics, it may be advisable to place the burden of accountability on clinicians.

On the farm, the use of antibiotics should be improved and more extensively controlled. Europe has banned the use of growth promoters, but this is only a part of needed improvements in veterinary medicine, including promotion and implementation of prudent use of antibiotics, quality of animal housing, biosecurity, and vaccinations. A global effort is essential. Every country should revise animal production practices with responsible use of antibiotics; the amounts used currently must be decreased or eliminated.

It is entirely likely that managing antibiotic usage should be a necessary part of any program to contain resistance, but there is still not a great deal of data to support the possible actions. More research is needed. Tracking the emergence of problematic strains is key to figuring out the effects of antibiotic use policies. At the very least, swifter, more precise diagnostic techniques would enable clinicians and veterinarians to use antibiotics prudently and limit their use.

EFFECTIVE TECHNIQUES FOR CONTAINING RESISTANCE

Controlling the spread of disease is familiar territory in medicine and veterinary science, and any approach that limits the spread of microorganisms and infections will also, providentially, limit the spread of resistance.

The single most effective technique for limiting the spread of disease in clinical settings like hospitals and nursing homes is instituting good hand hygiene practices. The positive impacts of hand washing and hand sanitizer use among health care workers are well established, and these practices have a broad effect on all infectious organisms, not just antibiotic resistant strains. On the down side, alcohol-based hand sanitizers might strip away beneficial lipids from the surface of the skin, thus opening up niches for pathogens and the potential for subsequent spread. Environment cleaning is another important technique for limiting the spread of pathogens, particularly spores.

Rapid resistance testing is another weapon in the arsenal against resistance. More and better screening techniques are needed (see *Need for More Rapid Diagnostics*, above). If the results of patient screening could be known within hours of arrival at a hospital, it would be possible to decolonize a patient who carries a resistant strain before he or she has exposed others. A rapid screen for MRSA would be particularly useful, since isolation precautions for MRSA-infected patients can reduce the occurrence of secondary complications. Unfortunately, rapid resistance testing is somewhat expensive, and specialized training is required to conduct the test, so it is often necessary to target testing only to certain high risk populations. Sensitivity and specificity are also of concern. These tests need to be made simpler and less expensive; in the meantime, clinicians must continue to use them in order to spur further investment and development by the companies that make them.

Nursing homes represent important control points for preventing the spread of antibiotic resistance. As such, surveillance of background levels of resistance in these locations is critical to help establish the effectiveness of controls on the movement of resistant organisms to hospitals. Scientists need better access to nursing homes for the purposes of surveillance. It is also important to screen nursing home workers for carriage of resistant pathogens.

Judging from the few studies of farms and veterinary hospitals, the spread of antibiotic resistance in these settings should not be neglected. One study found that farmers are host to more resistant bacteria than other members of the population, and another study showed that multidrug resistant *E. coli* can spread from dogs to human hospital patients with no known direct connection between them. A recent report documented the transmission of multidrug resistant *Staphylococcus aureus* (MRSA) from a veterinary nurse to horses in her care. We are not aware of all the possible routes resistant strains may take in passing from humans to animals and vice versa, but it is important to remember that these transmissions can work both ways. Unfortunately, studies on the transfer of antibiotic resistant strains from pets to humans are seriously lacking. One easy means of control in industrial livestock production is to clean facilities between each introduction of new animals. Some European countries, including Denmark, for one, present effective models for improving farming practices. Surveillance data from farms should be integrated with clinical data and food monitoring.

In veterinary hospitals, as in human hospitals, early monitoring of colonization by resistant pathogens can allow efficient treatment and resistance management. Veterinary laboratories need improved capacity for testing.

In some cases, when a hospital stops using a particular antibiotic, a reduction in the prevalence of resistant organisms can be measured. Modeling of resistance management tactics shows that if resistance carriage in the community is low, controlling resistance can be effective in the hospital. Conversely, according to the models, higher levels of carriage in the community can reduce the chance of success in the hospital.

In hospital settings, resistance management often takes the form of combining the prudent use of antibiotics with hand hygiene and infection control measures, and though the control of resistance development is not perfect with this approach, the results are almost always positive. But we should expect better.

There is a need for more reference centers that can offer services for identifying new modes of resistance. More training and funds for identifying novel resistance are also needed.

The movement of organisms from community to hospital and vice versa also makes it difficult to evaluate the impacts of resistance management. The communities outside hospitals are not free of antibiotic-resistant strains; we know that resistance exists in the community and may move from the community into the hospital. The boundary between the hospital setting and the community is a gray area. This potential for movement from the community to the hospital setting is especially problematic in developing countries, where animals live in close proximity to humans, and caretaker roles in hospitals are often taken on by family members (see *The Developing World: Unique Problems and Challenges*, above).

Another confounding factor for evaluating resistance control efforts is the decreasing length of the average hospital stay. Between multiple, short hospital stays, a

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patient could conceivably acquire an infection outside the hospital that can be mistaken for a hospital-acquired infection and vice versa.

Preventing a particular type of resistant infection from taking on pandemic proportions requires knowledge of the resistance genes involved. Currently, rooting out new mechanisms of resistance is a disordered matter. If someone in academia takes an interest in investigating a particular resistance problem, work gets done; if there is no interest, nothing gets done. Few major funding agencies recognize research on antibiotic resistance to be important. To address this inefficiency, the availability of expertise for identifying resistance genes should be more clearly structured and characterized resistant strains should be made freely available to serve as controls and aids for recognizing local resistance.

Any measures to prevent antibiotic resistance run the risk of changing the ecology of the organisms in question. Efforts to stop one strain can have unforeseen impacts on other strains, particularly in the hospital setting.

BOX B: REDUCING AND CONTROLLING NOSOCOMIAL INFECTIONS

In hospitals and other healthcare environments, reducing the incidence of nosocomial infections will concomitantly reduce the spread of antibiotic resistance. Tactics for preventing nosocomial infections include:

- **Hand hygiene measures,**
- **Isolation of infectious patients,**
- **Requiring hospitals to report infection rates (with the goal of motivating hospitals to take steps), and link those rates to resistance mechanisms and to antibiotics used,**
- **Withholding reimbursement for treating nosocomial infections—a step Medicare has already taken,**
- **Mandating the use of checklists for specific procedures to target transmission of pathogens from one patient to another, and**
- **In developing countries, access to basic healthcare equipment and resources (including clean running water and ordinary sanitation) would help.**

WHAT OTHER ACTIONS MAY CONTRIBUTE TO THE CONTAINMENT OF RESISTANCE? AVENUES TO INVESTIGATE

There are several promising avenues of exploration open for pursuing new and enhanced controls on the selection and spread of antibiotic resistance, including vaccines, anti-clone therapy, public health initiatives, and others. Vaccines can be designed to fight resistant and non-resistant pathogens alike. Merck, for example, is developing a vaccine against *Staphylococcus aureus* that may protect against MRSA infection. On the other hand, by specifically targeting the mechanisms of resistance, it may be possible to develop vaccines against antibiotic resistant bacterial pathogens, thereby supplanting populations of resistant bacteria with susceptible, treatable bacteria.

Developing vaccines for resistant pathogens is an alternative approach to antibiotics and would require massive research efforts. Careful consideration needs to be given to:

- Which organisms to target,
- Target groups for the intended vaccine (e.g., age groups, pre-surgical patients, patients with chronic lung disease),
- The number of people in those groups, and
- The possibility of vaccination in animals.

Public health initiatives that address the ecological aspects of resistance, the environmental milieu, and patients' prior exposure to antibiotics might be another key to preventing the selection and spread of resistance. These topics are not well understood and require a great deal of research.

Different programs that establish real time control of antibiotic prescription and to give trained infection control doctors or pharmacists the sole power to prescribe antibiotics in hospitals might be effective in cutting back on antibiotic use. Such an "antibiotic manager" would work in liaison with the laboratory, the infection control team, and the infectious diseases specialists. These programs can be expensive, however, and computer programs have been the source of some difficulties. Examples of these programs can be found in hospitals in the U.S. and some countries in Europe.

Other approaches that might produce results in the struggle to cope with resistance include:

- Treating all effluent—from hospitals and farms—before it is released to municipal wastewater facilities,
- Researching the possibility of inhibiting plasmid replication in resistant strains,
- Assigning novel compounds to research microbiologists to determine the potential mechanisms of resistance so if resistance does develop in the community or the environment we will have a handle on the means of preventing its spread,
- Developing drugs to co-administer with antibiotics that prevent the development of resistance,
- Administering drugs that prevent interactions between pathogens and commensal organisms (which can bestow resistance on the pathogen by lateral transfer),
- Developing natural peptide toxins as antibiotics (although low potency and manufacturing problems present difficulties on this path, peptide mimetics could help overcome some challenges),
- Developing bacteriophages and their lytic enzymes as antibiotics, and

- Antibiotics contained in nanoparticles are being investigated as methods of localized drug delivery (e.g., inhaled).

ACCELERATING AND IMPROVING CLINICAL TRIALS

Clinical trials would benefit from using new technologies and refinements that clearly define outcomes and the mechanisms of resistance that may arise. Clinical trials should make use of geographic information systems (GIS) technology to examine shifts in populations and track the movement of antibiotic resistance. This has been done for the recent influenza epidemics and for malaria.

The outcomes of clinical trials should be more clearly defined than they are currently; the dichotomous “cured” and “not cured” categories do not meaningfully depict the range of outcomes of a trial. Other factors to consider are rapidity, image analysis results, and the results of continuous blood testing. Quantification of the bacteria in samples is also critical.

Molecular screening of the resistance mechanisms in specific populations, such as ICU patients, nosocomially-infected and nursing home patients, and UTI patients, could be incorporated into clinical trials at select medical centers.

GETTING MORE ANTIBIOTICS TO MARKET

As resistance relegates many antibiotics to the dust heap, medicine requires other drugs to take their place. Healthcare systems in developing countries, in particular, need these drugs to be inexpensive. Regulators should ensure that the pipeline of generic drugs is supported by rigorous quality control. It is also important that the availability of generic drugs does not impede development of new antibiotics; a portion of the funds from the sale of generic antibiotics should be directed to research and development of new drugs.

Reintroducing old, abandoned antibiotics may help meet antibiotic resistance challenges. In the U.S., many effective antibiotics have been limited by the FDA on the basis of their toxicity, but it may be advisable to consider these drugs as last lines of defense in struggling with antibiotic-resistant infections. Daptomycin is a prime example of a drug that was neglected because of its toxicity in high doses, but then rediscovered and used as treatment for severe cases of resistant infection. Capreomycin, a drug with some toxicity that is now used to treat tuberculosis, is another example.

In the U.S., the intellectual property policies in place play some role in preventing the introduction of new antibiotics. A paradigm shift in these policies is needed to meet the needs for new drugs. Given this problem and the fact that pharmaceutical companies are exiting the field of antibiotic development, stewardship of existing antibiotics is extremely important.

Ultimately, effective incentives for industry to actively engage in antibiotic discovery and development will be driven by the profit motive. Numerous economic incentives have been suggested over the years, including tax breaks and patent extensions, but none of these have been accepted.

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BOX C: PRESERVING THE INTEGRITY OF A “SUPER ANTIBIOTIC”

To control the use and preserve the efficacy of a novel, effective antibiotic, the usual practice is to make that drug available only in hospital settings. However, these limits necessarily curb use of the drug and, therefore, curtail profits for the manufacturer. This represents a significant deterrent for pharmaceutical companies that want to undertake expensive research and development for new antibiotics, an endeavor that averages \$800 million. If there is a policy to hold new antibiotics in reserve, there must also be incentives like tax breaks, patent extensions, or possibly reimbursements for companies that place their drug under this restricted use. Also, hospitals without good systems for infection control are, effectively, breeding grounds for re-

sistance. Restricting the use of a “super antibiotic” to hospital settings like these is a perfect recipe for resistance development. Finally, since antibiotic resistance genes are often linked, flagrantly overusing most antibiotics while singling out one or more drugs for prudent use will ultimately fail. In promoting the prudent use of antibiotics, the goal should be to preserve the efficacy of all antibiotics.

Medicine is in need of antibiotics for use in critical patients—those for whom death is a possibility. The bar of acceptable risk is raised in these cases, and some toxicity may be acceptable in an effective antibiotic.

THE DEVELOPING WORLD: UNIQUE MANAGEMENT TACTICS

With respect to antibiotic resistance, the developing world faces unique challenges that require unique solutions, but every country is different, so even among the various developing countries there are diverse needs and strengths. In general, the most acute problems with resistance are found not in the least developed parts of the world, but in countries like China and Argentina, which are developing rapidly and have access to many and diverse antibiotics but few controls on their import, manufacture, use, and disposal. Broad recommendations for addressing the problems in the developing world include proposals for training and infrastructure; surveillance; susceptibility testing; controls on import, manufacture and use; vaccines; and incentives for pharmaceutical companies to supply drugs to these countries.

Managing bacterial resistance in the developing world is a crucial but largely unacknowledged issue. A conference to address the issues surrounding resistance, evaluate the situation, and sum up the needs for low cost medicines and training is absolutely necessary.

INFRASTRUCTURE, TRAINING, AND EDUCATION

For developing countries coping with problems of public health and antibiotic resistance, the need for better infrastructure, training, and education trumps the need for money. Facilities, hardware, and training schools are more effective tools for improving health than donations of cash. Increasing the capacity for laboratory testing is of fundamental importance. Existing research laboratories in developing countries should establish better connections and share resources with community hospitals. Every country, and if possible, every region, in the developing world should maintain at least one reference laboratory to provide feedback to local laboratories and identify pathogens of global importance. These reference laboratories should be arranged

in partnership with a major academic center or reference laboratory in a developed country. To accomplish this, global health authorities like the WHO and the World Organization for Animal Health need to identify institutions that can train local citizens. There is a need for more microbiologists at every level of training, but technicians are in particularly short supply.

Reference laboratories and hospitals in developing countries should be strongly encouraged and offered financial support to perform microbiological cultures—a task that is often neglected because of the high costs involved. Adequate quality control and regulation for running and managing laboratories is also often overlooked, but they are key to efforts aimed at improving public health.

It is possible to provide charitable foundations, private donors, and other interested organizations with proposals and a cost breakdown for the minimum set of features for building an effective, functioning microbiology laboratory in a developing country. Good quality supplies are essential, but it is not necessary to purchase dedicated apparatuses for every purpose; a laboratory on a tight budget could be equipped with handmade or hand constructed equipment. Mobile military laboratories might be good examples of the type of simple set-up and equipment necessary to provide an adequate number of services and good quality control.

SURVEILLANCE

To manage antibiotic resistance in developing countries, health officials need local profiles of resistance to the antibiotics that are available. Antibiotic resistance can be a local phenomenon, and in the absence of any reliable data from developing nations, we cannot begin to address the problem. It may also be advisable to classify antibiotics used in different locations.

ANTIBIOTIC SUSCEPTIBILITY TESTING

One of the biggest obstacles to the judicious use of antibiotics in the developing world is identifying infectious organisms, since empiric therapy naturally results from the failure to pinpoint a pathogen and carry out susceptibility testing on it. Hospitals, pharmacies, and clinics in these countries need access to cheap and reliable antibiotic susceptibility testing that is easy to use and requires little specialized training. The Etest is easiest to use, and its patent has expired so prices should decrease. Rapid and cheap methods that identify surrogate markers of bacterial and viral infections would be extremely helpful in prescribing antibiotics.

Sentinel sites for susceptibility studies should be established to monitor drug activity and resistance in key pathogens. Susceptibility studies are not needed at every site, but if each region could have access to information on the prevalence of resistance, it would be possible to tailor antibiotic use. In this case, one of the most complex problems would be to organize the sampling system to make it representative of the local situation. This undertaking should be a high priority.

CONTROLS ON IMPORT AND USE OF ANTIBIOTICS

Although regulatory authorities should ensure that the antibiotics that are needed in developing countries are supplied, there also should be tighter restrictions on the over-the-counter distribution of antibiotics. In particular, second or third generation drugs that, in developed countries, are used only in hospitals should not be available in the community without a prescription. It may be necessary to train community health workers to prescribe antibiotics in order to cut back on inappropriate use.

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Antibiotic use outside the health sector in developing countries, and use in animals in particular, needs to be regulated. Controls on antibiotic use need to be accompanied by public and professional education to better ensure compliance. Expert boards should be established in each country to oversee antibiotic usage, prevent the distribution of counterfeit drugs, and assure the quality of generics.

Developed countries need to lead by example. Decreasing antibiotic use in the developed world may lead to a decrease in the developing world. The WHO should play a lead role in this.

VACCINES

Vaccines that target the right resistant serotypes could be very important for reducing antibiotic resistance in the developing world, but surveillance is needed to ensure that the right organisms are targeted. In developing countries, the cost of vaccines is a big issue, and it will probably be impossible to produce vaccines for resistant strains inexpensively or generically, given the complicated formulations (and correspondingly large investments in development) that would be needed.

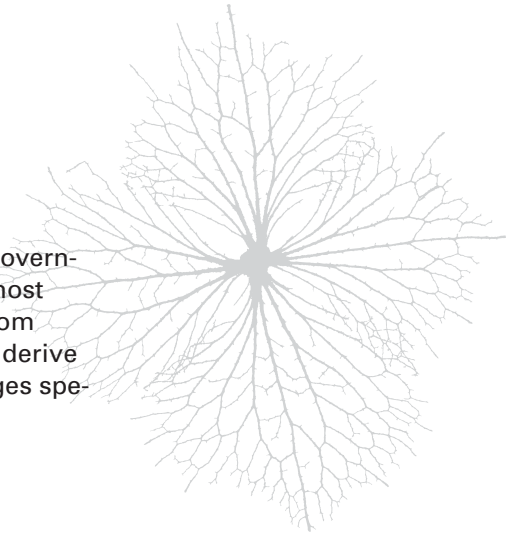
INCENTIVES FOR PHARMACEUTICAL COMPANIES TO SUPPLY DRUGS TO THE DEVELOPING WORLD

Extending the lengths of patents on drugs supplied to the developing world could help get more quality drugs into the hands of the people who need them. In several instances, pharmaceutical companies provided free anti-infectives for the developing world or maintain research programs that focus on drugs or diseases that are important in these countries (ivermectin for filariasis or capreomycin for tuberculosis, for example). These are laudable efforts, and it is not clear how to incentivize this to encourage other companies to follow suit.

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COMMUNICATION ISSUES

Antibiotic resistance is a serious public health threat, but physicians and government officials still know little about the problem, and the public remains in almost complete ignorance. Clearly, the important messages are not getting across from scientists and doctors who study the problem to the stakeholders. We need to derive innovative and effective techniques for communication, then tailor the messages specifically for each of the stakeholder groups.



METHODS OF COMMUNICATION

Health authorities and the scientific community need to completely re-vamp the means and methods of communicating messages about antibiotic resistance. Communicating with different stakeholders will require different approaches, and given the importance of the topics, communication needs to be ongoing and some up-to-the-minute techniques are called for.

COMMUNICATING WITH THE PUBLIC

In the past, certain public health campaigns to inform the community have proven to be very effective. The push to educate the public about oral rehydration therapy in Egypt, for example, targeted specific audiences with appropriate messages. A few important messages were fed to the media, and simple advice was dispensed to parents to avoid doctors who do not prescribe oral rehydration salts to dehydrated children. This is a good model to follow for educating the public about the importance of using antibiotics wisely.

A number of avenues are open for delivering messages about antibiotics and resistance to consumers and farmers. The mass media could be used as a bullhorn for two simple but important facts: (1) the incidence of antibiotic resistant infections is rising and (2) there is a lack of new antibiotics for treating these infections. Media in all tiers of the market should carry messages like these, from tabloids on up to nationally-read newspapers, for example. A list of answers to frequently asked questions could be included in drug packaging, both on paper or via new media, including the internet. Of course, patients should also be directed to ask their family doctors, and farmers should be directed to ask a veterinarian with their questions about resistance.

In Europe, November 18, 2008, was designated as “Antibiotic Day,” a day when key opinion leaders spoke out on the issues to raise public awareness of the consequences of antibiotic resistance. A similar initiative in the U.S. could be very effective at raising awareness.

Another approach might be to dispense trading cards depicting diseases to pre-teens. Communication through blogs can also be effective. In France, a handy shorthand term—“antibiotics aren’t automatic”—employed as part of a campaign by

the French National Health Insurance Fund for Salaried Workers, proved effective in conveying a message about antibiotics to consumers. Direct to consumer advertising of antibiotics encourages misuse and should be banned.

COMMUNICATING WITH PHYSICIANS AND OTHER HEALTH CARE WORKERS

Aside from guidelines to avoid use of antibiotics in pediatric cases of otitis media, there are currently no guidelines for physicians about when not to use antibiotics. Some consensus between countries should be established. Moving forward with efforts to manage antimicrobial resistance, the most important information to provide to physicians is evidence-based practice guidelines. These guidelines need to be readable and available to physicians and offer disease-specific guidance particular to the resistance profile of the disease. For the sake of consistency, guidelines are also needed to clearly define what comprises successful treatment of a given type of infection to identify clearly the time to change therapy or to stop it. Guidelines should be revised on an ongoing basis as new data become available. Training for other health care workers should also include evidence-based guidelines.

It is important to communicate to physicians that antibiotics, as with any therapeutic agents, should be used according to their strict indications.

Drug companies exert a great deal of influence over prescribers. National regulations, as well as local guidelines, have been enacted to limit this influence, but considering that industry is the sole source of antibiotic therapies, and is capable of providing information that can assist in the optimal use of these agents, it is not clear how much to discourage interactions between industry and doctors.

It may be possible to take the idea of “Antibiotic Day” to medical schools and encourage them to focus on antibiotics for a day.

MESSAGES FOR STAKEHOLDERS

Messages about antibiotic resistance to the various stakeholders need to be consistent, but the details of the messages should be tailored. In general, messages to the public need to include more science and less “noise” than they do now. Messages that patients and the public should hear about antibiotic resistance include:

- **The risks to individuals.** Without denying the benefits of antibiotic treatment in the right contexts, people should be made aware, for example, what the risks are from taking antibiotics or staying in a hospital. Anti-smoking and second-hand smoke campaigns have communicated risk messages to the public effectively in the past. Comparable figures about the risks from contracting a resistant infection should be calculated.
- **Global mortality statistics.** The fact that antibiotic resistance is a global issue must be communicated. Two or three illustrative examples relayed to the public and to politicians would help convey the scope of the problem. The global impact of resistance and the reasons industrialized countries should take notice about what is happening in developing countries should also be spelled out. The public needs to know that these conditions are not limited to any single country or segment of the population.
- **Economic costs.** In addition to the toll it takes on human life and productivity, antibiotic resistance creates longer hospital stays and often requires expensive treatments. Moreover, gains made through massive global spending on malaria, tuberculosis, and HIV prevention are in jeopardy because of resistance.

ASIDE FROM GUIDELINES TO AVOID USE OF ANTIBIOTICS IN PEDIATRIC CASES OF OTITIS MEDIA, THERE ARE CURRENTLY NO GUIDELINES FOR PHYSICIANS ABOUT WHEN NOT TO USE ANTIBIOTICS.

- **Many respiratory diseases do not call for antibiotic therapy.** Posters in doctor's offices could convey this message to patients with mild respiratory disease.
- **Resistance is not a new phenomenon and it cannot be reversed.** Antibiotic resistance has existed for a very long time, and we need to strike a balance between resistance and susceptibility. The media should not convey the idea that resistance is reversible.

Generally speaking, education for physicians on infectious diseases and antibiotics is lacking. Specific messages for physicians should include:

- **Molecular diagnostics** are important and require close cooperation with the clinical microbiology laboratory.
- **In the hospital, antibiotic use needs to be revised after 48 hours.** Infection control programs are essential.
- **Resistance is more widespread than doctors think it is** and often not perceived as responsible for treatment failure in individual patients.

Governments need to know other facts about resistance:

- **Surveillance is key and should be a national imperative.**
- **Investment in rapid diagnostics is vital for maintaining the utility of antibiotics.** Considering that new drugs are not coming on the market in significant quantities, conserving the limited number of antibiotics left is crucial.
- **Regulatory agencies**, including the U.S. Food and Drug Administration, need to be part of the solution and not introduce unrealistic barriers to new drugs and indications. Superiority trials are actively blocking new drug development.

COMMUNICATIONS NEEDS

In order to relate the above messages to the public, doctors, governments, and others, researchers need to derive reliable data on the risks of antibiotic resistance. This goes back to the need for surveillance. We cannot convey the importance of the resistance problem without first conducting surveillance to at least find out the prevalence of resistant organisms and the incidence of resistant infections.

Public health authorities and the scientific and medical communities need resistance figures that regulators and health departments can use, like the numbers of childhood deaths or deaths in burn units due to resistant organisms.

CONCLUSIONS

Antibiotic resistance is an international pandemic that compromises the treatment of all infectious diseases. At the present time, resistance essentially is uncontrollable. The enormity of the situation is such that it is virtually impossible to conceive of any solution, or combination of solutions, that will have a significant global impact. The reasons behind the establishment and spread of resistance are complex, mostly multi-factorial, and mostly unknown. More research bridging medical, chemical, and environmental disciplines is needed now.

There are no scapegoats. Responsibility is partly due to medical practice, including patient demand; veterinary practice; industrial practices; politics; and antibiotics

themselves. Ultimately, resistance development is founded in the inevitability of microbial evolution.

Nonetheless, as outlined in this report, we believe that deliberate efforts at containment and minimizing transmission of resistant organisms can have positive effects within localized human populations and in particular settings.

Responsible actions taken to ensure appropriate use where necessary and disposal of antibiotics, in concert with containment policies, will impact on human health benefits. Such actions to be taken at the local, national, and international levels imply considerable efforts on both the human and the financial sides. Examples of actions include:

- Improvement and speed of diagnostic tools;
- Enhancement of capacity building in most laboratories, particularly in developing countries;
- Development of infection control and containment of bacterial transmission;
- Development of antibiotic stewardship;
- Agreement and implementation on “judicious and prudent use” of antibiotics;
- Guidance to physicians and to veterinarians;
- Building and coordinating surveillance programs;
- Development of communication initiatives; and
- Control of generic antibiotics.

The continuation of antibiotic use for human and animal diseases is at stake unless worldwide efforts are taken. Research for new antibiotics under new paradigms must consider what the functions of these molecules are in nature, how resistant populations relate to them, and where and how to find them.

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