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The Economic and Clinical Implications of Antibiotic Resistance

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There is no doubt that antibiotic resistance is a growing phenomenon. As Nobel Prize Winner and famed molecular biologist Joshua Lederberg put it, "We are running out of bullets for dealing with a number of bacterial infections. Patients are dying because we no longer in many cases have antibiotics that work (2007)." This issue can be attributed to over-prescription of available antibiotics, their currently limited diversity, as well as lack of incentives to encourage investment in development of new classes of antibiotics. Antibiotic resistance is a problem that afflicts both affluent and impoverished countries, and the outlook it generates appears to be bleak due to rapidly rising costs of treatment, the threat of cross-resistance, as well as increased morbidity.

The Problem

The dilemma of antibiotic resistance has evolved to become a multifaceted issue exacerbated by a series of molecular, operational, psychological, and economic factors.

On the molecular level, antibiotic resistance is the result of bacteria changing in ways that lead to the reduced effectiveness of antibiotics to cure or prevent infections. There are three main mechanisms through which resistance is acquired in bacteria: 1) Natural selection, or the gradual scientific process by which biological traits such as resistance to antibiotics become common in a population (i.e. bacteria); 2) plasmids, or independent circular pieces of DNA that may carry genes for antibiotic resistance that can be conferred between bacteria; and 3) mutations, or permanent changes in the DNA sequence of a gene that can lead to the formation of new traits such as resistance (Ramanan, 2012). Furthermore, cross-resistance, or the possession of a resistance mechanism by a bacterial strain that enables it to survive the effects of several antibacterial molecules, may continue even after halting or reducing antibiotic use. As such, antimicrobial resistant bacteria may emerge under the selective pressure of antibiotics and become the dominant flora.

There are a series of operational factors, such as the role of setting, modes of transmission, and lack of regulation enforcement, that appear to be rather simple to remediate, but in practice this has not been the case. An increasing number of cases of antibiotic resistance occur within hospital and institutional settings; in these situations, antibiotic resistant flora may live within the institution and be transferred to the patient (Sipahi, 2008). Transmission may occur when coming into contact with soiled hands of staff as well as contaminated surfaces and equipment, in addition to passing from patient to patient, which is why effective infection control and hygiene are essential to inhibit their spread. The severity of the disease being treated, length of current hospital duration, exposure to other ill patients, invasive surgical procedures, intensity of clinical therapy, and advanced age further increase the odds of susceptibility to antibiotic resistant bacterial strains.

Over-prescription of antibiotics by physicians further increases the likelihood that particular strains will develop resistance and can be simplified into two main causes: 1) consumer insistence that antibiotics are a magic cure-all for flu, infections, and unrecognizable conditions and 2) doctors' fear of malpractice lawsuits that impels them to err on the side of over-prescription. For example, contracting the flu comes from a virus, rather than a particular bacterial strain; therefore there is no reason to take an antibiotic as treatment for the flu. Taking antibiotics more frequntly than necessary results in natural selection in the body for the most resistant bacteria and contributes to higher levels of resistance; consumers incorrectly believe "better safe than sorry" and thus err on the side of overconsumption of antibiotics when in reality, by doing so, they are increasing their odds of susceptibility to antibiotic resistant bacteria. For this reason, associations have provided and implemented regulations that restrict the supply of antibiotics created in the first place. However, these appear to be mainly ignored by antibiotic manufacturers in order to promote antibiotic sales and resulting profits.

The role psychological factors play in contributing to growing antibiotic resistance should not be underestimated. For instance, in many cases, patients fail to take antibiotics according to specifications, stopping treatment early when symptoms cease to appear or ignoring time specifications. Ingesting, for example, only three of five doses for a particular condition generates problems for the following reasons. 1) The three doses clear the body of the least-resistant bacteria, making it easier for more resistant, powerful bacteria that remain to proliferate faster than they would have been otherwise able in the presence of competitors. 2) By default, patients possess leftover doses they may choose to take at a later date for a condition that antibiotics are not designed for treating. 3) It increases consumer complacency, making it likely

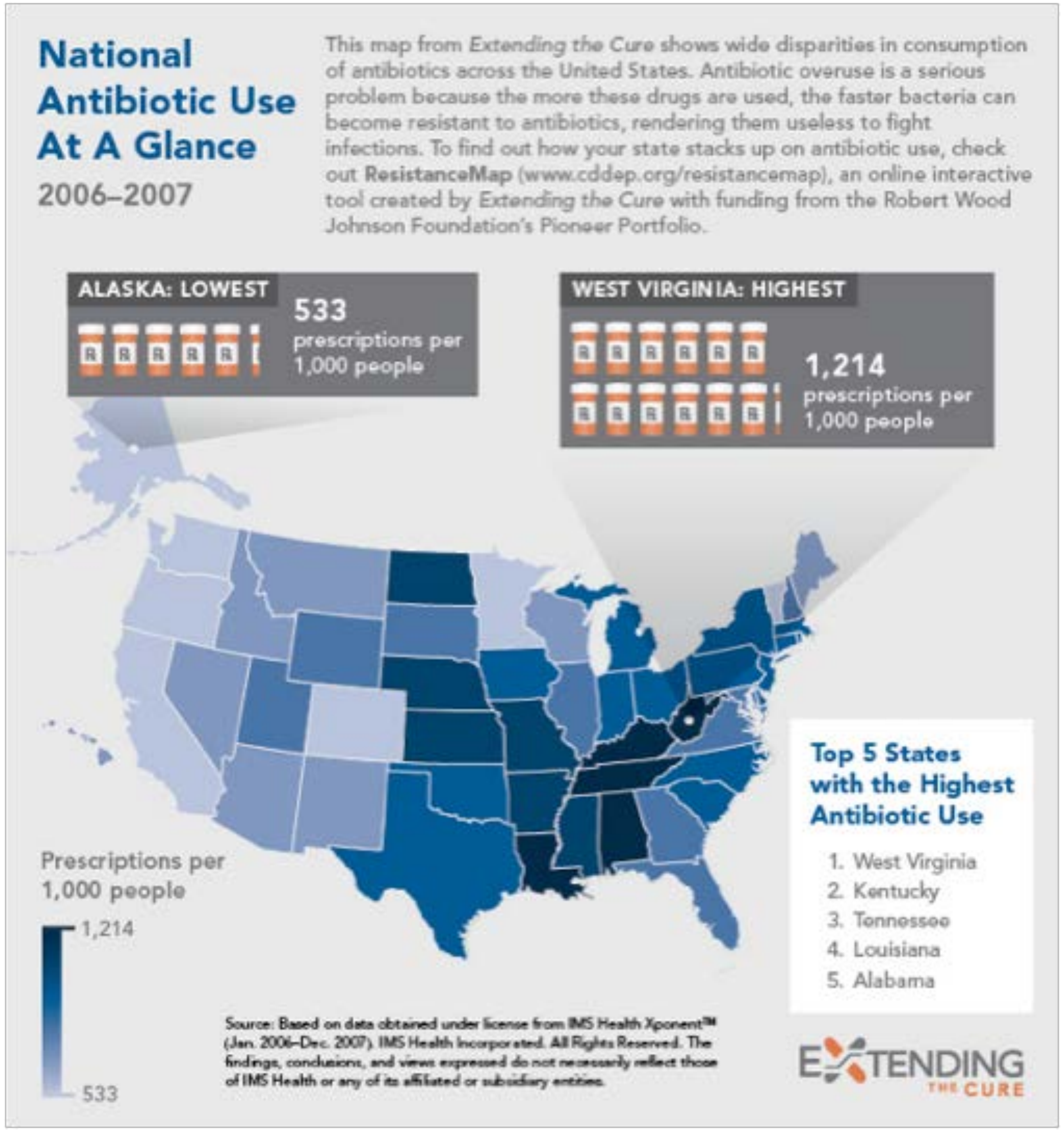

Figure 1: These five states with the greatest antibiotic use can be especially targeted to reduce excess and unecessary antibiotic prescriptions in order to limit the threat of growing antibiotic resistance.

they will repeat the behavior in the future, and put themselves at risk for contracting a similar infection again. Antibiotic self-treatment is especially common in countries where antibiotics may be gained without a doctor's prescription. This is one reason why U.S. hospitals are increasingly distributing antibiotics only in the exact dose required per infection, rather than in fixed packets (Sipahi, 2008).

"Direct-to-consumer"advertising represents the shift in targeting physicians directly rather than patients in the purchase or request of antibiotic prescriptions. This is evidenced by the fact that drug companies increasingly spending more on advertisements in newspapers and popular magazines than in medical journals (Woloshin, 2001). While the original purpose behind such a transformation involved enabling individuals to engage in more rational and informed healthcare decision-making, instead it led to inappropriate antibiotic usage through the proliferation of artificial demand (Sipahi, 2008). According to research published by the Center for the Evaluative Clinical Sciences at Dartmouth Medical School, pharmaceutical companies spent US $1.8 billion on direct-to-consumer advertising for prescription drugs in 1999, and this number is rapidly rising, with no signs of stagnation.

Economically speaking, the increase in antibiotic resistance is not solely dependent on whether physicians fail to take the negative externalities of increased cost and decreased effectiveness into account, but is also due to underinvestment in other means of infection control such as immunizations and good management practices (Ramanan, 2012). A negative externality is a common term used in economics to describe a behavior of an individual (or individuals) that leads to a negative result that impacts society and others not involved in the behavior or action. To "internalize the externality" is to require the individual perpetrating the behavior to take the additional costs he/she imposes on society into account. Generally, this occurs in the form of a tax or penalty imposed by the government, or in this case, by some higher regulatory medical, pharmacology, or epidemiological authority best suited to deal with antibiotic resistance.

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Upon expounding on the factors that lead to antibiotic resistance, it is important to delve into the epidemiological consequences of antibiotic resistance on death and dying. For one, ineffectiveness of current antibiotics leads to longer and increased hospitalizations that may result from a higher frequency of surgical interventions required to control infection. The most obvious and dangerous consequence is increased risk of infection; many surgical procedures such as transplants and bypass operations depend on effective antibiotics to keep patients free of infection at times when their vulnerability to them is particularly amplified. Increased morbidity typifies a common result with infections of nosocomial bacteria, or hospital acquired infections, attributing to a mortality rate of thirty-five percent and adding on average twenty-four additional days of hospitalization as well as an excess cost of $40,000 per survivor (Niederman, 2001). According to Sipahi, antibiotic acquisition costs and increased length of stay are well-described parameters that have been studied widely and thoroughly (2008). However, necessary control measures, impaired hospital activity, increased morbidity, and higher mortality rates are poorly researched and described in the medical literature. More information and research regarding the effects on the latter categories of antibiotic resistance is vital to thoroughly assess the penetration of resistance in the community.

Increased antibiotic resistance leads to elevated costs associated with using more expensive antibiotics in stronger potencies or even simply larger doses in order to combat the stronger, more resistant bacteria. For instance, the cost difference between amoxicillin and the combination of amoxicillin plus clavulanic acid is on the order of a factor of two (Sosa, 2010). Amoxicillin is a penicillin antibiotic that may be used to treat urinary tract infections, Lyme disease, bacterial skin disease, and ulcers, among others. However, due to bacterial resistance to amoxicillin, the combination of amoxicillin plus clavulanic acid may be necessary to more effectively combat the bacteria. Reported additional costs of MRSA (methicillin-resistant Staphylococcus aureus) versus MSSA (methicillin-susceptible Staphylococcus aureus), VRE (vancomycin-resistant Enterococcus) versus VSE (vancomycin-susceptible Enterococcus), and ESBL+ (positive extended-spectrum beta-lactamase) versus ESBL (extended-spectrum beta-lactamase), range between US $7,212 and $98,575, and additional length of a hospital stay ranges between 2 and 15.3 days (Sipahi, 2008). The aforementioned examples contrasting normal strains of bacteria with resistant strains exhibit the fatal consequences of the loss of an affordable antimicrobial and the need to supplant it with a more expensive replacement. On a larger scale, antimicrobial compounds account for more than thirty percent of hospital pharmacy budgets due to specialized equipment, longer hospital durations, utilization of stronger antibiotics, and isolation procedures that involve private patient rooms, dedicated personnel, as well as gowns and gloves, that inevitably increase the time and cost of treating infections (Siphai, 2008). The Forum on Emerging Infections of the U.S. Institute of Health discovered in 1998 that hospital cases associated with antibiotic-resistant bacteria generate a minimum of $4 to $5 billion in costs to U.S. society and individuals yearly (Horowitz, 2004).

The international outlook similarly portrays trends of increases in resistance and morbidity, but for vastly different reasons. In developed countries, adequate housing and support for personal hygiene minimize interpersonal exchange of resistant bacteria and clean water limits their ingestion. However, many developed countries also feed substantive amounts of resistance-selecting antimicrobials to food animals and the countries' residents ingest antibiotics found in both the food and water supply. Developed countries, primarily found in the North America, Eastern Asia, and Southern America, thus suffer from over-prescription of antibiotics.

On the other end of the spectrum, developing countries face the opposite problem; individuals suffer from under-prescription of effective antibiotics coupled with lack of sanitation and hygiene, leading to increased morbidity from curable infections (Sosa, 2012). At the same time, in such underdeveloped countries, it is not uncommon for many communities to operate under the false notion that the drugs they utilize retain their full potency, when in reality many have lost their efficacy due to resistance. One notable example involves the usage of data from Africa which indicated that antimalarial drugs lose their effectiveness long before the population recognizes their failure. Accordingly, preventative measures would ensure that individuals become sick with lower frequency, and are thus less likely to pass on fewer resistant infections to others.

Response to antibiotic resistance greatly varies between the two environments as well. In prosperous nations, disposable items arrive in truckloads from warehouses and well-organized infection control teams stymie the spread of resistant bacteria. Impoverished nations lack these effective responses as afflicted individuals struggle with shortages of reusable items and one sink for an open ward.

Solutions

When determining potential solutions to alleviate the challenges associated with antibiotic resistance, the main purpose should be to consider both the rate of infection and the decreasing effectiveness of antibiotics with use. Accordingly, when two antibiotics are available, the optimal portion and timing of their usage depends on the "difference between the rates at which bacterial resistance to each antibiotic evolves and on the differences in their pharmaceutical costs" (Laxminarayan, 2011). Potential solutions need to harmonize epidemiological consequences as well as economic factors and cost-benefit analysis.

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To reduce the need for antimicrobial compounds to begin with, the healthcare community can increase immunity through vaccinations, improved nutrition, and minimizing the time for which the patient is immunocompromised. Improving the spacing between beds in hospitals can limit the spread of resistance as well since many of the cases are endemic to hospitals and institutions. On a larger scale, policymakers may consider employing economic instruments such as taxes, subsidies, and redesigned prescription drug insurance programs to ensure that incentives facing doctors and patients align with society's needs and interests. Further research and implementation of alternative treatment options such as antiseptics, probiotics, and cranberry juice (for urinary tract infections) can further reduce the U.S.'s current dependence on antibiotics (Sipahi, 2008).

With regards to assessing antibiotic effectiveness, tools called antibiograms provide information on the susceptibility of common bacteria to varying antibiotics, serving as a useful guide for physicians when prescribing antibiotics. Their use arose from the preparation of cumulative antimicrobial susceptibility data for trend analysis and clinical decision-making. However, there are challenges involved with the usage of antibiograms, including 1) maintaining accurate and current susceptibility ratings, 2) applying them to all facilities with only a minute number of bacterial isolates, 3) distributing them in accordance with access restrictions that limit the streamlined dissemination of information, and 4) analyzing susceptibilities to predict the best initial drug combination in the face of unpredictable cross-resistance across antibacterial classes. The final challenge can be mitigated to a degree by utilizing cross-table susceptibility analysis, which permits selection of dual regimens with greater odds of being effective (Fox, 2010).

To remediate over-prescription, the use of formularies can restrict the menu of antibiotics available to the physician to prescribe from, on the hospital level. While traditionally a formulary contained a collection of formulas for the compounding and testing of medication, today the main function involves specifying which medicines are approved to be prescribed under a specific contract and is based on evaluations of efficacy, safety, and cost-effectiveness of antibiotics. Setting and enforcing more stringent standards to the supply of antibiotics available can prevent leftovers when prescribing, remediate reliance on antibiotics as the go-to prescription, as well as limit exorbitant profits pharmaceutical companies reap from flooding the market with antibiotics. Also, educating physicians regarding tactics to employ when working with patients may potentially halt consumer insistence and physician complacency, if promoted on local, regional, and national levels. Moreover, since resistance patterns vary from country to country and hospital to hospital, physicians and pharmacists greatly benefit from being informed about resistance patterns in their geographic locations at various points in time (Rapp, 2011).

Consumer education embodies a more difficult and tedious process, but it must be addressed. For example, if patients understand that incorrect dosages of antibiotics increase the resistance of bacteria in their bodies and reduce effectiveness of antibiotics to be consumed in the future, they may be more concerned about knowing what the proper dosage is.

Usage of the same antibiotics for a multitude of conditions remains a key contributor to why antibiotic resistance is developing at an accelerated pace. As a result, it is increasingly important to advocate for diversity in antibiotic use in hospitals and pharmacies. However, as depicted in Figure 2, there are limited options to prescribe from, compared to the past. As such, from a long-term perspective, creating incentives for investing in research and development for the synthesis of new antibiotics is essential so that a larger range of antibiotics, in different classes, may become available for prescription.

Patents encourage investment in such efforts as they signify protection of intellectual property rights as well as the ability to sell one's innovation for use; accordingly they possess key advantages and disadvantages and should be weighed accordingly. On one hand, extending the duration of an effective patent life could increase incentives for a company to minimize resistance, as the company would potentially reap the benefits of a longer period of monopoly over the antibiotic's effectiveness. Pharmaceutical companies would then effectively exercise their market power, or ability to charge higher prices than

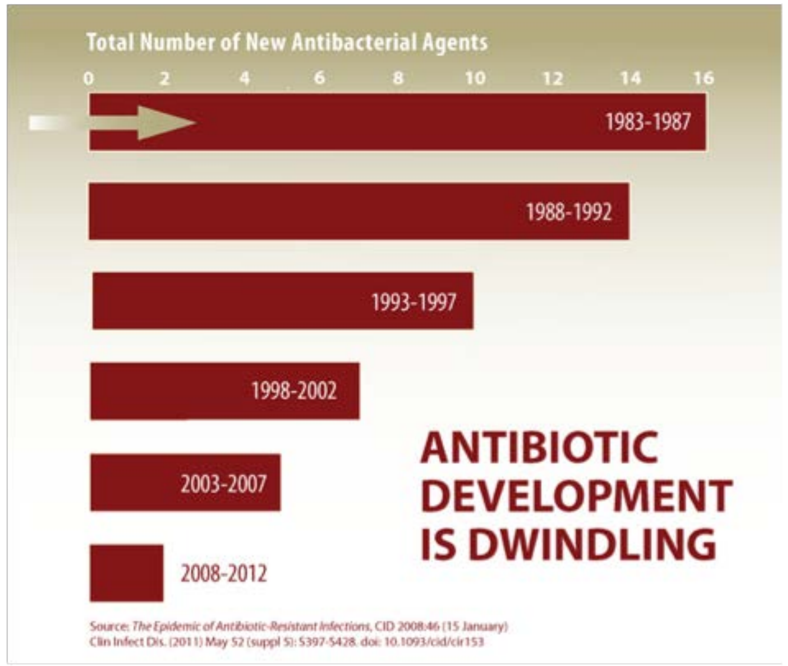

Figure 2: Greater diversity of antibiotics will decrease the development and spread of antibiotic resistance.

the competitive market, and reap greater profits as a result. Yet, a pharmaceutical company under the protection of a specified patent on a drug that is cross resistant may have little concern about future resistance because when different antibiotics are employed, the benefits of reducing current production transfer to other companies. Assigning broad patents that cover a class of antibiotics as opposed to a single one may prevent firms from competing inefficiently for the same range of effectiveness embodied in a class of antibiotics, as well as further drive the incentive for investment in development of new antibiotics. From the insurance perspective, a single buyer such as national or private health insurance may have an incentive to reduce antibiotic resistance since they will likely bear the costs of future resistance in the form of higher costs for more expensive prescription coverage.

Doctors, pharmacists, consumers, and regulatory agencies all possess roles to play in addressing increased antibiotic resistance. Of these actors, pharmacy's involvement and role in the hospital system makes it a viable candidate for engaging in opportunities for leadership in antimicrobial stewardship (Rapp, 2011). Core strategies for antimicrobial stewardship would involve identifying the optimal selection, dose, and duration of an antibiotic that results in the optimal clinical result with regards to the treatment of infection, with minimal toxicity to the patient and minimal impact on the development of resistance (Fox, 2010). To propagate global coordination, the World Health Organization already released "Global Strategy for Containment of Antimicrobial Resistance," a document designed to urge governments to take substantive action aimed towards containing antibiotic resistance. Along these lines, experts agree that a global system for tracking developments in antibiotic resistance trends would prove useful by serving as an indicator for recognizing "hot spots" and determining whether prevention programs contribute to positive results.

Prominent organizations such as the Alliance for Prudent Use of Antibiotics and programs like the Global Antibiotic Resistance Partnership further seek to identify weaknesses in how antibiotics are developed, regulated, and maintained, and the degree to which countries track antibiotic use and resistance globally. It is evident that in order to affect meaningful change, implementation of policy on the government level, cost effectiveness analysis on the business platform, analysis of impacts on morbidity and mortality from the epidemiological setting, as well as direct targeting of consumers in an attempt to alter their behavior are all required in tandem to make substantive progress forward and protect the future in which antibiotics still possess the ability to cure illness.

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