Antibiotic resistance: The unfolding crisis

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The introduction of penicillin in 1941 is among the most significant technological advances in modern medicine. Although many improvements in public health and medicine and a decline in infectious disease mortality preceded the introduction of penicillin, antibiotics have made possible further reductions in deaths and disability from infectious disease (Figure 1.1). Perhaps equally important, they have facilitated the vast expansion of other medical interventions, such as kidney and heart transplants, by allowing clinicians to prevent surgical site infections and infections in immuno-suppressed patients, such as organ recipients. Now, growing levels of bacterial resistance to antibiotics threaten our ability not just to treat infectious diseases but also to perform other procedures and treatments that fundamentally depend on affordable and effective antibiotics.

The timeline of emergence of drug resistance is best illustrated by the case of Staphylococcus aureus (S. aureus), a common pathogen that causes life-threatening infections and is transmitted in both health care and community settings. The mortality rate from a S. aureus infection was as high as 82 percent in the preantibiotics era (Skinner and Keefer 1941) but fell dramatically after the introduction of penicillin. Resistance to penicillin emerged soon after its introduction and was linked to patient deaths in the early 1950s (Abboud and Waisbren 1959). In 1960, penicillin was replaced with a beta-lactam compound, methicillin, which was effective against penicillin-resistant S. aureus, but methicillin-resistant S. aureus (MRSA) emerged in the 1970s in Europe and soon after in the United States. MRSA prevalence in U.S. hospitals, which was 2.4 percent in 1975, increased to 29 percent in 1991 (Archer 1998) (Figure 1.2), and 59.5 percent in 2003...
(CDC 2004), growing at an average rate of more than 12 percent per year. Vancomycin is the main and potentially last available drug that can reliably treat MRSA infections, and the massive use of vancomycin for treating MRSA is believed to be an important reason for the emergence and spread of vancomycin-resistant enterococci (VRE) (Weinstein 2003). Meanwhile, strains of MRSA resistant to vancomycin have been detected, providing the first glimpse of medical outcomes in a post-antibiotics era (Chang, Sievert et al. 2003).

The fast evolution of S. aureus from a bacterium that was easily treatable at pennies a dose to a pathogen that now requires powerful, expensive antibiotics is paralleled by other predominantly hospital-acquired infections, like those caused by VRE, Enterobacter and Pseudomonas aeruginosa. In each case, the ability to treat bacterial infections has been rolled back by the evolution of resistance. In this chapter, we describe the medical and economic impacts of resistance and explore why drug resistance is a compelling problem that, if left unaddressed, has the potential to derail the health care system by returning us to a world where children, the elderly, and other vulnerable populations routinely die from simple bacterial infections.

**Trends in resistance**

The pathogens that are transmitted in hospitals and communities are different in their ecology and epidemiology, as explained in Chapter 2. Drug resistance is growing in both types of pathogens. Common hospital-acquired, or nosocomial, infections include Gram-positive infections, such as those caused by S. aureus and enterococci, whose resistance
has been increasing at a rapid pace. In 1998, MRSA was detected among patients without recent health care exposure or other predisposing risk factors (Herold, Immergluck et al. 1998), and it has since become an important threat to community health.

Resistance has become a serious problem among hospital-acquired Gram-negative pathogens, such as Escherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae, and Pseudomonas aeruginosa, as shown in Figure 1.3 (Gaynes and Edwards 2005). Gram-negative pathogens are even more challenging than MRSA because there are fewer antibiotics available to treat infections caused by them.

**Comparison with other countries**

Hospitals in the United States have among the highest rates of MRSA in the world: on average 60 percent of patients infected with S. aureus in intensive care units of U.S. hospitals cannot be treated with methicillin or older antibiotics (CDC 2004). Surveillance for drug-resistant hospital-acquired infections has been less successful than in Europe, where a concerted effort has been made to identify antimicrobial rates in both hospital and community settings. Figure 1.4 shows MRSA rates for the United States and other high- and middle-income countries for 2004. In Europe, only Romania and Malta had higher rates of MRSA than the United States in that year. MRSA levels were high in East Asia, specifically South Korea, Japan, and Taiwan, probably because of high levels of antibiotic use, but not much higher than for the United States. In the Americas, only Argentina, Brazil, and Colombia had a higher MRSA prevalence than the United States.

Prevalence of vancomycin-resistant enterococci (VRE) in U.S. hospitals is estimated to be roughly 12 percent on average across all hospital patients (McDonald 2006) and according to the CDC is more than 28 percent in intensive care units (CDC 2004). VRE rates in the United States and other countries are shown in Figure 1.5. In Europe, only Portugal had a higher prevalence of VRE than did the United States. Data on VRE prevalence outside Europe are less reliable but show lower rates than the United States, with the exception of South Korea. Reliable studies from Japan have found isolated outbreaks but no evidence of VRE transmission (Arakawa, Ike et al. 2000; Matsumoto, Muratani et al. 2004).

One reason for the higher prevalence of resistance in the United States may be the higher levels of antibiotic

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**FIGURE 1.3**

The proportion of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococcal (VRE) infections is increasing (1987–2003)

Note: Data refer to infections in intensive care unit (ICU) patients only.

Antibiotic prescribing in this country (see Box 2.5, Chapter 2). Although antibiotic prescribing has fallen in the United States since 1994, it remains among the highest in the world (Steinman, Gonzales et al. 2003). Data from the European Surveillance of Antibiotic Consumption (Goossens, Ferech et al. 2003) show prescribing rates for most countries from 1997 to 2002 (Figure 1.6). The prescribing rate in the United States was 24 defined daily doses per 1,000 population per year. Only five countries—France, Luxembourg, Italy, Greece, and Portugal—had higher rates, but some of these countries had lower rates of resistance than the United States, indicating that there may be other casual factors.

Health impact of drug resistance

Patients who have a hospital infection have a lower probability of survival (Osmon, Warren et al. 2003), as shown in Figure 1.7. This survival disadvantage is worse if the infection is due to a drug-resistant pathogen. Studies have shown that patients infected with resistant strains of bacteria are more likely to require longer hospitalization (Holmberg, Solomon et al. 1987; The Genesis Report 1994) and are more likely to die. For instance, the mortality rate for patients infected with MRSA has been found to be significantly higher than for patients infected with a methicillin-sensitive strain (Rubin, Harrington et al. 1999; Blot et al. 2002; Cosgrove et al. 2005).

Estimating the number of people who die from drug-resistant infections is challenging, for a number of reasons. First, patients who get resistant infections tend to be older and sicker, and therefore it is difficult to separate the impact of having a resistant infection from other complications they may have, such as HIV or TB co-infection (in community settings). Second, drug-resistant infections are not coded differently from sensitive infections. Therefore, most estimates

![Figure 1.3](source: Adapted from Gaynes and Edwards (2005).)
**Box 1.1**

**WHY MULTIPLE ANTIBIOTICS USED IN COMBINATION MINIMIZE RISK OF TREATMENT FAILURE**

Let us assume that with probability $q$, a doctor finds acceptable as a threshold probability that at least one of the antibiotics used to treat the patient will work. Suppose there are $n$ antibiotics. The probability that the infection is treated by any single antibiotic is $p$, the probability that the drug will not work is $(1 - p)$, and the probability that none of the drugs will work is $(1 - p)^n$. Consequently, the rule to choose $n$, the number of antibiotics so that the patient will recover without needing a second course of medications, is

$$1 - (1 - p)^n > q$$

If $q = .95$ and $p = 0.7$, then we can easily calculate that $n$ must be at least 3. Even if each drug is 70 percent effective, the patient must be prescribed three antibiotics in combination to ensure that there is a less than 5 percent chance of treatment failure.

**Figure 1.4**

**Methicillin-resistant *Staphylococcus aureus* infection rates in the United States and other countries**

*Sources:* Canada and United States, 2000–2002 (Jones, Draghi et al. 2004); Latin America, 1998 (Diekema, Pfaller et al. 2000); Brazil, 1998 (Melo, Silva-Carvalho et al. 2004); Colombia, 2001–2002 (Arias, Reyes et al. 2003); Argentina, 2002 (Bantar, Famiglietti et al. 2004); European countries, 2004 (RIVM 2005).
of the burden of drug resistance are based on the number of infections multiplied by resistance percentages. One such study that used data from the National Hospital Discharge Survey (NHDS) found 125,969 hospitalizations for MRSA between 1999 and 2000. These accounted for 3.95 of more than 1,000 hospitalizations (compared with a diagnosis of S. aureus infection in 9.13 of every 1,000 hospitalizations) (Kuehnert, Hill et al. 2005). Estimates of methicillin resistance in this study indicated that older patients were most likely to have an MRSA infection (6.36 per 1,000 hospitalizations for those above age 65, compared with 1.31 per 1,000 hospitalizations for those aged 14 and under). A 1995 CDC study, unpublished but cited in Kuehnert, Hill et al. (2005) and based on data from NHDS and the National Nosocomial Infections Surveillance System (NNIS), found that S. aureus infections accounted for 0.58 percent of hospitalizations and MRSA accounted for 0.2 percent of hospitalizations.

Estimates based on more recent data are presented in Table 1.1 of this report.

**Economic impact of resistance**

Drug resistance places a burden on patients, hospitals, and the health care system. The annual figures quoted most often for the economic impact of resistance in the United States range from $350 million to $35 billion (in 1989 dollars). These estimates assume that 150 million prescriptions are generated each year and vary with, among other factors, the rate at which resistance grows with respect to increasing antibiotic use, and the probability that a patient will die following infection with a resistant pathogen (Phelps 1989). A recent study that measures the deadweight loss from antibiotic resistance associated with outpatient prescriptions in the

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**Figure 1.5**

Vancomycin-resistant enterococci rates in the United States and other countries

Sources: Brazil, 2002 (Titze-de-Almeida, Filho et al. 2004); Egypt, Lebanon, Saudi Arabia, South Africa, and Turkey, 2001–2002 (Bouchillon, Johnson et al. 2004); Hong Kong, 2000 (Ho 2003); Japan, 2000 (Arakawa, Ike et al. 2000); New Zealand, 2000 (Briggs, Upton et al. 2002); Taiwan and United States, 2000 (McDonald, Lauderdale et al. 2004); Kuwait, 1999–2001 (Udo, Al-Sweih et al. 2003); Australia, 1999 (Nimmo, Bell et al. 2003); Colombia, 2001–2002 (Arias, Reyes et al. 2003); China (Liu, Xu et al. 2003); South Korea, 2002 (Lee, Kim et al. 2004); European countries, 2004 (RIVM 2005).
Antibiotic prescribing rates for the United States and other countries

**Figure 1.6**

Antibiotic prescribing rates for the United States and other countries

<table>
<thead>
<tr>
<th>Country</th>
<th>DDD/1,000 inhabitants</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>35%</td>
</tr>
<tr>
<td>Greece</td>
<td>30%</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>25%</td>
</tr>
<tr>
<td>United States</td>
<td>24%</td>
</tr>
<tr>
<td>Portugal</td>
<td>20%</td>
</tr>
<tr>
<td>Italy</td>
<td>15%</td>
</tr>
<tr>
<td>Belgium</td>
<td>10%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>5%</td>
</tr>
<tr>
<td>United States</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Sources:** Canada, Australia, and United States, 1994 (McManus, Hammond et al. 1997); Russia, 1998 (Cizman, Beovic et al. 2004); Australia, 2002 (National Prescribing Service 2005); European countries, 2004 (Goossens, Ferech et al. 2003).

**Note:** DDD=defined daily doses, a standardized measure of antibiotic consumption.

**Figure 1.7**

Probability of survival in patients with and without a microbiologically confirmed infection

**Source:** Adapted from Osmon, Warren et al. (2003).
United States puts the cost at a minimum of $378 million and as high as $18.6 billion (Elbasha 2003). A report by the Office of Technology Assessment to the U.S. Congress estimated the annual cost associated with antibiotic resistance in hospitals, attributable to five classes of hospital-acquired infections from six species of antibiotic-resistant bacteria, to be at least $1.3 billion (in 1992 dollars) (OTA 1995). The CDC estimated that the cost of all hospital-acquired infections, including both antibiotic-resistant and antibiotic-susceptible strains, was $4.5 billion. The lack of time-series data on both antimicrobial use and bacterial resistance has made it difficult to estimate the dose-response relationship between antimicrobial use and resistance. As a result, assessing resistance-related economic costs becomes more complicated. Although burden estimates can convey an idea of the overall size of the problem, they are usefully complemented by assessments of the economic benefit of lowering resistance—by, say, 10 percent—to evaluate the benefit-cost ratio of any particular policy.

Infections caused by antimicrobial-resistant bacteria result in increased morbidity and mortality for those affected and...
drive up health care costs as well. The costs and consequences associated with failing to address antimicrobial resistance arise on many levels. There is lost time at work and school, plus longer and repeated hospital stays. Given the variety of ways in which antibiotic resistance can impose direct and indirect costs, it should be no surprise that its financial burden is staggering. In fact, the Institute of Medicine estimates that the price tag may be as high as $30 billion a year (Palumbi 2001).

An analysis of U.S. inpatient hospital days in 2000 and 2001 found that 1 percent of all admissions acquire *S. aureus* infections, for a total of 300,000 cases and 2.7 million excess patient days per year (Noskin, Rubin et al. 2005). The study also found that length of stay for infected patients increased from 4.5 days to 14.3 days, there were 12,000 deaths, a 4 percent increase in in-hospital mortality, and the cost was estimated to be $9.5 billion a year. Another study that examined the economic impact of *S. aureus* in Canadian hospitals showed that MRSA infections resulted in, on average, 14 additional hospital days. In the same study, the total attributable cost to treat MRSA infections was $14,360 per patient, and the cost for isolation and management of colonized patients was $1,363 per admission (Kim, Oh et al. 2001). A more complete description of the higher economic costs imposed by hospital-acquired drug-resistant infections is presented in Chapter 4.

Another significant burden imposed by drug resistance comes in the cost of periodic switches to newer, more expensive antibiotics. As the risk of treatment failure increases with resistance, the entire system has to shift over to new drugs even if older drugs retain substantial effectiveness. The increase in cost with successive generations has been enormous. Penicillin costs pennies a dose; the most recent antibiotics can run as high as a few thousand dollars for a course of treatment. (Newer antibiotics are more expensive largely because they are still on patent, and these costs will go down as they come off patent.) From the perspective of the health care system, these periodic upgrades to the antibiotics used most often for treatment impose a significant burden. The cost of patented drugs reflects monopoly rents to some extent, but also the significant and

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TABLE 1.1

<table>
<thead>
<tr>
<th>RESISTANT BACTERIA</th>
<th>1995</th>
<th>2000</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>70,000$¹</td>
<td>125,969$⁰</td>
<td>250,438$⁰</td>
</tr>
<tr>
<td>Vancomycin-resistant enterococci</td>
<td>14,000$¹</td>
<td>20,710$¹</td>
<td>26,085$¹</td>
</tr>
</tbody>
</table>

real resource costs of investing in new antibiotics. Moreover, even with modest levels of resistance to antibiotics, patients have to be treated empirically with two or more drugs to ensure that treatment will be successful (Box 1.1). Sequential treatment with different antibiotics until the clinician hits upon one that works is not an option when patients are immuno-compromised and treatment failure could put their lives in jeopardy.

Figure 1.8 compares current (nominal) prices of different generations of antibiotics. There is a general increasing trend in prices, with newer antibiotics, such as oxazolidinones and quinolones, costing much more than penicillins, sulfonamides, and other older drugs. Since most antibiotics, with the exception of the most recent ones, are off patent, the higher cost of relatively newer drugs likely reflects the enormous regulatory costs of bringing a drug to market. To date, there has been only one analysis of the drug-related cost of bacterial resistance. Howard and Rask (2002) take 1980–1998 data on antibiotics used to treat ear infections from the National Ambulatory Medical Care Survey to estimate the increase in the cost of antibiotic treatment attributable to increases in bacterial resistance. Lacking data on resistance, they used time trends as a proxy for resistance to show that between 1997 and 1998, increases in drug resistance are estimated to have raised the cost of treating ear infections by about 20 percent ($216 million). This approach is not perfect, however, since time trends may capture costs unrelated to resistance, such as the costs of antibiotics with lower side-effect profiles or more convenient dosing.

Discussion

Drug-resistant infections impose a significant cost on patients, health care systems, and society by increasing the cost of treating infections and causing greater disability and death. However, their impact is not restricted to infectious diseases. Many aspects of modern medicine—whether organ transplants, chemotherapy, or surgery—require effective drugs that can ward off infection. In that sense, antibiotics can be considered a complement to other medical technologies, and thus the higher cost (or diminished effectiveness) of antibiotics lowers the value of other medical technologies. No one has yet estimated this indirect cost, but it could well dwarf the direct costs of antibiotic resistance.

Many studies have documented longer hospital stays and increased costs for medication and care associated with resistant pathogens. The situation where an infection does not respond to any known antibiotic is becoming increasingly common. Since death is the likely outcome, the costs of contracting such a multidrug-resistant strain are likely to be much greater than current estimates.

Quantifying the health and economic impacts of resistance has proven to be a significant though surmountable research challenge. In hospital settings, the challenge has been disentangling two effects: the longer the hospital stay, the greater the likelihood of being infected with a resistant pathogen, and in turn, a hospital-acquired infection with a resistant pathogen lengthens the hospital stay. In community settings, the challenge has been correctly estimating both the benefits and the costs of antibiotic use. Resistance-related costs alone are insufficient reason to recommend that fewer antibiotics be used, since antibiotics bring benefits as well as costs. To date, there has been no reliable benefit-cost estimate of antibiotic use in either setting.

The scale of the resistance problem may be self-evident to those in the medical and public health communities who deal with it on a daily basis. However, assessing the economic impact at a national scale is a necessary first step to bring the problem to the attention of policymakers and stakeholders, including purchasers of health insurance and government agencies like the Center for Medicare and Medicaid Services.
References


