The Global Impact of Drug Resistance

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Measuring the impact of drug resistance is an important step in understanding the scope of the problem and formulating policies to limit the emergence and spread of resistant organisms. Studies have focused on measuring the increased costs, morbidity, and mortality in patients with infections due to resistant versus susceptible organisms. These have generally found that resistance worsens outcomes. By focusing only on infected patients, however, they may understate the impact of resistance. It is important to recognize that resistance also affects the treatment of individuals with nonresistant organisms. In areas with high rates of resistance, physicians and governments have changed empiric therapy for malaria, tuberculosis, acute respiratory infections, and other diseases, increasing overall treatment costs. In some instances, these costs may exceed those attributable to treatment failure.

Estimates of the impact of antimicrobial resistance can help policy makers formulate policies that encourage appropriate use of antimicrobial drugs and prevent the emergence and spread of resistant organisms. In this article, we describe a framework for measuring the impact of resistance, and we review previous research on this topic. The term “impact” here refers to the increased treatment costs, prevention costs, and morbidity and mortality that result from resistance.

Many microorganisms have displayed antimicrobial resistance, but we focus mainly on the pathogens responsible for malaria, tuberculosis (TB), diarrheal diseases, and lower respiratory tract infections. According to the World Health Organization (WHO), these are 4 of the top 5 infectious diseases in terms of years of life lost (the fifth being AIDS) [1]. To date, most studies on the impact of antimicrobial resistance have focused narrowly on resistance to antibacterials and, more specifically, resistance among enterococcal and Staphylococcus aureus strains causing infections in hospitalized patients [2]. Emergence of resistance in these organisms is a worrisome trend in developed countries, but developing nations face a much greater threat from the growth of resistance in pathogens causing community-acquired diseases such as malaria.

FRAMEWORK FOR MEASURING THE BURDEN OF RESISTANCE

For most diseases, the burden of the illness consists entirely of treatment costs, morbidity and mortality among the ill, and the costs of public prevention efforts. Infectious diseases are different. Because they often are communicable, fear of contagion may induce even uninfected individuals (and their physicians) to alter their behavior [3]. The financial and psychological costs associated with these behavioral changes add to the burden of infectious diseases. Philipson and Posner [4] argue that in the case of AIDS, for example, some individuals living in areas with a high prevalence of infection will avoid risky sexual activities. They contend that the forgone welfare from these activities is a component of the burden of disease. These costs are excluded from standard measures of the cost of AIDS.

Most studies of the impact of antimicrobial resistance measure costs, morbidity, and mortality in patients...
identified as having an infection due to a resistant organism. For the reasons stated above, however, simply adding up the incremental costs of persons with infections due to resistant organisms understates the burden of resistance. Just as the number of individuals infected with HIV in a given area may affect individuals’ sexual behavior [3], local susceptibility patterns may influence even physicians’ empirical treatment of patients with infections due to susceptible organisms [5–7]. Before the identification of the infecting agent and its resistance pattern, patients often are given empiric therapy. In areas where resistant organisms are prevalent, physicians use alternative drugs rather than the medication that, in the absence of resistance, would be preferred on the basis of cost, dosing schedule, or side effect profile [5–7]. This substitution occurs for most newly diagnosed patients, not just those with infections due to resistant organisms. The excess drug costs, inconvenience, and side effects experienced by patients in areas where physicians have switched empiric therapies is a seldom-measured component of the burden of resistance. Other components of the burden of resistance include the cost of expanded prevention and drug-administration efforts (e.g., directly observed therapy [DOT] for TB) that result from concerns about resistance, and the cost of the increase in disease incidence that results from the transmission of infection from individuals whose infections due to resistant organisms are not treated in a timely manner. In some instances, use of antimicrobials will reduce disease prevalence [8]. Because effective treatment for susceptible pathogens reduces their transmission, drug-resistant strains will be responsible for a larger proportion of total cases [9]. Ultimately, the impact of treatment on transmission will be negated, and prevalence may return to pretreatment levels [10].

For reasons outlined above, studies that examine only the costs of treatment failure in patients with infections due to resistant organisms may underestimate the impact of resistance. The degree to which the cost of treatment differs from the actual burden will depend on how heavily physicians weigh individual versus community characteristics when choosing initial therapy. Practices such as susceptibility testing, which provides more information about patients’ infections, will diminish the impact of community characteristics on physicians’ choice of therapy. In the absence of susceptibility testing, however, physicians have few clues to help them predict whether or not a patient is infected with a resistant pathogen, and therapy will be selected on the basis of the prevailing levels of resistance in the community. In such instances, the costs of substitution of empiric therapies may account for a large portion of the total burden of resistance [5].

Another factor to consider in measuring resistance-induced drug substitution is the income and wealth of patients and countries. Physicians in developed countries may be quicker to switch empiric therapies in response to increasing resistance levels, whereas patients in developing countries may have to make do with older drugs and the high rate of treatment failure with which they are associated. Consequently, for the same underlying rate of resistance, the burden will be larger in developing countries.

Table 1 characterizes the costs of resistance according to whether or not susceptibility testing is performed at diagnosis and whether or not empiric therapy is effective against resistant organisms (where resistance is defined relative to older drugs). When empiric therapy is ineffective against resistant organisms and physicians do not perform susceptibility testing, only patients with infections due to resistant organisms will incur costs due to resistance. The magnitude of these costs will depend on the length of time that patients with infections due to susceptible organisms receive ineffective therapy. If physicians perform susceptibility testing immediately, then the cost of resistance will consist only of the incremental cost of second-line therapy and the costs of susceptibility testing. If the prevalence of resistance is high, then physicians will begin using second-line drugs as empiric therapy [5, 7]. As stated above, the incremental cost of these drugs comprises the burden of resistance because patients with infections due to resistant organisms are treated with effective therapy initially. Obviously, there are

### Table 1. Categorizing the impact of drug resistance.

<table>
<thead>
<tr>
<th>Category</th>
<th>Initial susceptibility testing</th>
<th>No initial susceptibility testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1: Empiric therapy ineffective against resistant organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with IDSO</td>
<td>No costs</td>
<td>No costs</td>
</tr>
<tr>
<td>Patients with IDRO</td>
<td>Incremental cost of second-line therapy</td>
<td>Increased hospital length of stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incremental morbidity and mortality</td>
</tr>
<tr>
<td>Case 2: Empiric therapy effective against resistant organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with IDSO</td>
<td>Not applicable</td>
<td>Incremental cost of empiric therapy</td>
</tr>
<tr>
<td>Patients with IDRO</td>
<td>Not applicable</td>
<td>Incremental cost of empiric therapy</td>
</tr>
</tbody>
</table>

**NOTE.** IDRO, infections due to resistant organisms; IDSO, infections due to susceptible organisms.
RESISTANCE AND EMPIRIC THERAPY CHOICE

Few data exist on the impact of resistance on physicians’ choice of empiric therapy. One study (1980–1998) that used data on physicians’ drug choices for patients with otitis media attempted to link changing patterns of antibiotic use to increasing levels of resistance among Streptococcus pneumoniae [5]. The study found that in the late 1990s, rising levels of resistance increased antibiotic expenditures for otitis media by 20%. Treatment patterns for other infectious diseases have not been subject to formal analysis, although clinical guidelines and trends in use of various agents suggest a link between resistance and use of newer, more expensive agents. In this section, we review treatment guidelines, WHO reports, and other published literature on treatment patterns. In the next section of this article, we will examine efforts to measure the costs of therapeutic responses to resistance.

Chloroquine was the main antimalarial agent used for first-line treatment of malaria for decades. During the past 10 years, Plasmodium falciparum and Plasmodium vivax have grown increasingly resistant to chloroquine in many areas of the world [11]. Health care providers in Malawi and Kenya have discontinued the use of chloroquine as first-line therapy and have begun using sulfadoxine-pyrimethamine in its place. Resistance to sulfadoxine-pyrimethamine has been documented in East Africa, and it may not be long before it too has to be replaced [11]. In parts of Southeast Asia, only multidrug therapies are effective against Plasmodium strains that have developed resistance to all 4 leading antimalarial drugs [12].

The WHO recommends a change in first-line treatment when 25% of patients treated experience recrudescence of infection [6]. This is an arbitrary figure; an optimal switching policy would balance the cost of the second-line drugs against the benefit of prompt treatment [7]. Nevertheless, at some point, whether it is above or below the 25% threshold, physicians must switch first-line therapies. Phillips and Phillips-Howard [7] calculated that the use of quinine versus chloroquine as first-line therapy in 150 million patients with malaria would increase spending by as much as $100 million (1990 US dollars), a relatively large amount for the countries in which malaria is endemic. Besides costing more, drugs such as quinine that replace chloroquine often are associated with higher rates of side effects, the financial and psychological costs of which should be attributed to resistance.

Multidrug-resistant TB (MDR-TB), which is caused by strains resistant to ≥2 antituberculous drugs, has been increasing in a number of regions around the world. The WHO has promoted DOT, which helps to ensure that all patients receive a full course of the standardized drug therapy for the treatment of TB. Depending on Mycobacterium tuberculosis resistance patterns, patients are given a 3- to 4-drug regimen for a total of 6 months. In the United States, hospitals and physicians use M. tuberculosis drug-susceptibility testing to individualize treatment. As a result of a lack of financial resources, susceptibility testing is not the standard of care in most developing countries that have a high prevalence of MDR-TB. In these countries, treatment is selected on the basis of regional susceptibility patterns. Local prevalence rates of resistance to isoniazid ≥4% require treatment with 4 first-line drugs, including isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin [13]. Although the additional drugs increase the probability of successful treatment, they also increase the chance of unwanted side effects and augment the financial burden of the disease. DOTS-Plus regimens, used in areas with high rates of resistance, may include fluoroquinolones or additional drugs as empiric therapy, further increasing treatment costs.

Diarrheal diseases are one of the leading causes of morbidity and mortality worldwide, with the greatest burden of severe illness involving infants and young children in developing countries. Irrespective of future improvements in economic development and progress in health care delivery, diarrheal diseases are predicted to remain a leading health problem during the next 30 years [14]. Adding to this dilemma is the large increase in antimicrobial resistance that has emerged among many of the major bacterial pathogens, including Shigella dysenteriae, Campylobacter, and Salmonella [15–18]. In sub-Saharan Africa, S. dysenteriae has become resistant to multiple drugs, with strains that are resistant to all common antimicrobial agents except fluoroquinolones [19]. The WHO recommends that physicians use drugs that are active against at least 80% of the local Shigella isolates [20]. Drug price data in the developing world are difficult to obtain, but in the United States, the price of some of the newer fluoroquinolones may exceed that of trimethoprim-sulfamethoxazole by 400% [1]. Given these price differentials, it is unlikely that developing countries will strictly adhere to the WHO’s 80% switching criteria. Nevertheless, even a small amount of switching can increase costs substantially.

Acute respiratory infections comprise the fourth leading cause of mortality worldwide, killing ≥3 million people each year [1]. The majority of deaths result from lower respiratory tract infections that occur in developing countries with high poverty rates and inadequate medical care. The primary bacterial agents that cause lower respiratory infections include S. pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. The rise in antimicrobial resistance among these pathogens has been documented in many regions and now poses a major challenge worldwide [21].
Clinical guidelines for respiratory diseases commonly advise physicians to tailor empiric therapy to local susceptibility patterns. The Infectious Diseases Society of America (IDSA) guidelines for community-acquired pneumonia in adults, for example, advise physicians to consider "regional antibiotic susceptibility patterns for *S. pneumoniae*" when selecting antibiotics for outpatients [22]. Unlike similar guidelines for malaria, TB, or diarrheal diseases [6, 13, 19], the IDSA guidelines do not state a specific level of resistance after which standard empiric therapy should be removed. The guidelines recommend that physicians use penicillin or amoxicillin to treat penicillin-susceptible *S. pneumoniae* and cefotaxime, ceftriaxone, a fluoroquinolone, or vancomycin to treat penicillin-resistant *S. pneumoniae*. The cost of an amoxicillin treatment is about $6 (1999 US dollars), and the cost for levofloxacin, one of the recommended fluoroquinolones, is $69 [20]. Suppose that, initially, all newly diagnosed pneumonia patients in a given region receive amoxicillin. If resistance caused the market share of levofloxacin to increase from 0% to 10%, then total empiric-therapy spending in this population would increase by >100%. Thus, small changes in prescribing habits brought about by antimicrobial resistance can have a large impact on drug costs.

We used drug use data from the National Ambulatory Medical Care Survey [23] for the years 1980–1996 and drug price data from the 1996 Medical Expenditure Panel Survey [24] to calculate the average cost of a new prescription for patients diagnosed with otitis media (figure 1). Many factors contributed this increase, but it is interesting to note that it occurred concurrently with a large increase in the level of penicillin-resistant *S. pneumoniae*.

**RESISTANCE AND TREATMENT FAILURE**

As mentioned above, previous research on the impact of resistance has focused on measuring costs, morbidity, and mortality in patients with infections due to resistant organisms. The incremental effects of resistance will be inversely related to the effectiveness of empiric therapy. When physicians use ineffective drugs as empiric therapy, resistance will manifest itself clinically as treatment failure, and costs, morbidity, and mortality will be greater for patients with infections due to resistant organisms than for patients with infections due to susceptible organisms.

There is a growing body of literature on the cost and health impacts of resistance and treatment failure in hospital settings. In 1992, the US Office of Technology Assessment (OTA) developed a summary estimate of the hospital cost of antibiotic resistance resulting from 6 different organisms (methicillin-resistant *S. aureus* [MRSA], vancomycin-resistant enterococci [VRE], imipenem-resistant *Pseudomonas aeruginosa*, methicillin-resistant coagulase-negative staphylococci, ampicillin-resistant *Escherichia coli*, and resistant *Enterobacter*) causing infections at 5 different sites [25]. The types of health care–acquired infections (HAI) included surgical site infections, pneumonias,

![Figure 1. Average prescription prices, 1980–1996](image-url)
bacteremias, urinary tract infections, and a fifth category containing other miscellaneous infections. The OTA estimated that the cost of extra hospitalizations resulting from infections with the resistant organisms listed above was ~$1.3 billion (1992 US dollars).

Recent studies examining the attributable morbidity, mortality, and costs associated with sensitive and resistant S. aureus and enterococci in hospitals (for a review of studies before 1987, see Holmberg et al. [2]) now offer contradictory conclusions about the impact of these organisms. A key factor underlying these differing results is patient severity of illness and how it is used to evaluate HAI on patient outcomes. Matched cohort studies that do not adequately adjust for patient severity produced overestimates of the attributable mortality due to HAI.

An example of a study that did not control for severity of underlying disease of studies comes from Rubin et al. [26]. This study examined the economic and health impacts of both community-acquired and health care–acquired MRSA infections (pneumonia, bacteremia, and endocarditis for mortality and costs; and surgical site infection, osteomyelitis, and septic arthritis for costs only) within all New York metropolitan hospitals in 1995. They used an administrative database on hospital discharges to estimate the attributable mortality rate for MRSA (based on unmatched group comparisons between infected and uninfected patients) to be 21% (vs. 8% for methicillin-resistant S. aureus [MSSA]). The attributable per-patient hospital costs associated with treatment of all MRSA infections was $2500 higher than cost for patient treatment for all MSSA infections (a total attributable costs of $34,000 for MRSA and $31,500 for MSSA). The extra attributable cost of treating just nosocomial MRSA compared with MSSA was $3700 (total attributable costs of $31,400 for nosocomial MRSA and $31,500 for nosocomial MSSA).

Other comparative studies that did not explicitly control for severity of illness also observed attributable cost impacts of MRSA and VRE. Abramson and Sexton [27] used what they called a prospective pairwise-matched nested case-control study design in an intensive care unit (ICU) population; they estimated the attributable total patient costs due to MRSA primary nosocomial bloodstream infections to be ~$27,000 (although there was no observed mortality effect). Other studies have found a patient mortality rate attributable to nosocomial VRE bacteremia of 31% (as opposed to non-VRE patient controls, 37%) and an attributable per-patient cost of $98,367 over non-VRE patient controls [28, 29].

Other studies have used severity of illness at admission to a specific ward or ICU as a matching criterion. Chaix and co-workers [30] conducted a retrospective case-control study that matched patient severity of illness at admission to ICU. Their results showed a significant difference in mortality between ICU patients with health care–acquired MRSA infections (bacteremia, lower respiratory tract, urinary tract, or catheter-related infections) when compared with ICU patients without MRSA infections (67% vs. 30%). The attributable cost per MRSA infection was estimated at $9300.

Montecalvo et al. [31] used severity of illness at admission to an oncology ward as part of their matching criteria in conducting a historical analysis to measure the cost savings associated with an intervention to reduce VRE infections in an adult oncology ward. The estimated excess hospitalization cost due to VRE was $15,385. The annual net hospital cost savings due to the enhanced infection control program was $189,318 (due to 8 fewer VRE infections, fewer VRE colonizations, and reductions in antimicrobial use).

Studies that use severity of illness measured either just before or at the onset of infection report differing results, possibility as a result of varying matching algorithms. After matching patients for severity of illness at the onset of bacteremia, Stosor et al. [32] found a significant difference in the mortality rate for bacteremic patients with VRE versus bacteremic patients with vancomycin-susceptible enterococci (VSE) (76% vs. 41%) and significantly greater average per-patient total hospital costs of $27,000 for VRE patients over VSE patients ($83,897 for VRE and $56,707 for VSE). However, other studies have found that after controlling either for severity of illness at onset of bacteremia or for changes in patient severity of illness up to the onset of infection, acquiring MRSA and VRE do not significantly increase the risk of mortality [33–35].

The varying treatment and prescribing practices across hospitals also can influence study results. Infection control practices can vary depending on the type of hospital (privately owned hospitals, teaching/academic hospitals, or public hospitals) and the case mix of the hospital population [36]. Given these problems, inferences about the economic burden of resistance in HAIs on the basis of single-center studies are limited. Most studies do not attempt to measure the cost of resistance from a societal perspective (including all the economic impacts on patients, physicians, health care providers, third-party buyers, drug manufacturers, and overall societal welfare) [37]. Phelps [38] attempted to measure the external social cost of resistance, including the costs of prescribing more-expensive drugs (both inside and outside hospitals), the costs of additional hospital days, and the costs of premature death for the United States. The estimated costs (1989 US dollars) ranged from $100 million to $30 billion annually (depending on varying the rate of resistance, the rate of inappropriate use, and the incidence of premature death). The wide range of these estimates reflected the uncertainties associated with both the epidemiologic and economic information needed to measure the economic burden of resistance. Many of these uncertainties remain today.
Recent studies document the burden malaria and other diseases place on the developing world [39]. However, in contrast to the number of studies on the costs associated with VRE and MRSA, little research has been performed on the impact of resistance on treatment failure and its associated costs in malaria, TB, or similar diseases.

The DOT treatment failure rate for patients with MDR-TB can be as high as 95% [40]. Treatment failure in TB is associated with use of hospital services and more expensive drugs and increased mortality. In South Africa, treatment costs are $12,000 per patient with MDR-TB versus $500 per patient with susceptible TB [41]. The spread of *M. tuberculosis* resistance in Russia has corresponded to an increase from 9% to 30% in mortality rates among those treated [40]. Patients with strains resistant to ≥2 drugs can be especially difficult to treat. Farmer et al. [40] report that in Peru, it costs more than $8000 to treat a patient with a 5-drug–resistant strain compared with $277 to treat a patient with a 2-drug–resistant strain. Extrapolating these figures to the Russian Federation, Farmer et al. calculate that the spread of 5-drug–resistant strains could increase treatment costs by $100 million. One study estimated that care for patients with strains resistant to first-line therapy in the United States can be as high as $180,000 [42]. The resurgence of TB in New York City has been associated with increases in public expenditures of hundreds of millions of dollars over a 15-year period [43], although it is difficult to determine the costs attributable to resistance versus the costs attributable to increased incidence generally.

A few studies have attempted to link mortality and chloroquine resistance in patients with malaria. However, these have small sample sizes and lack internal validity when outcomes for individuals with infections due to resistant versus nonresistant organisms are compared. In the absence of comprehensive studies, information about the impact of resistance can be discerned from trends in mortality rates. In Senegal, for example, one study shows sharp increases in childhood mortality from malaria during a period corresponding to increases in the rate of chloroquine-resistant strains [44]. A disadvantage of these types of studies is that it is impossible to control for secular trends in factors other than resistance that affect outcomes. In the Senegal study, one must accept the authors’ assurances that the increase in mortality due to malaria was not the result of a decrease in the prevalence of other childhood diseases.

**CONCLUSION**

The preceding discussion has attempted to provide a framework for assessing the impact of antimicrobial resistance in terms of increased treatment costs, prevention costs, and morbidity and mortality that result from resistance. Efforts to describe the global impact of antimicrobial resistance are hampered by the lack of data on the impact of resistance outside of hospital settings. Estimates of the cost of treating a patient with MDR-TB in Russia or Peru, for example, are not subject to the kind of scrutiny and review devoted to estimates of the cost of medical procedures in the United States. Even efforts to measure the economic costs of resistance to MRSA or VRE in US hospitals have suffered from methodological problems and often are of questionable validity. Finally, there has been little, if any, effort to assess the larger societal and macroeconomic costs of resistance, especially in the developing world, related to lost wages, the costs of caring for orphaned children, and the impact of increased infant and child mortality on fertility patterns and demographic growth, or the costs for surveillance and other systemwide interventions of the type recommended by the WHO [45]. In short, although there is little doubt that antimicrobial resistance is increasing the global burden of disease, we are a long way from being able to quantify this burden.

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**References**


