Measuring the Economic Costs of Antimicrobial Resistance in Hospital Settings: Summary of the Centers for Disease Control and Prevention–Emory Workshop

David Howard,1 Ralph Cordell,2 John E. McGowan Jr.,1 Randall M. Packard,1 R. Douglas Scott II,2 and Steven L. Solomon,2 for the Workshop Group

1Rollins School of Public Health of Emory University and 2Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta

Health systems administrators and clinicians need refined calculations of the attributable cost of infections due to drug-resistant microorganisms to develop and assess cost-effective prevention strategies that deal with these infections. To date, however, efforts to provide this information have yielded widely variable and often conflicting estimates. This lack of reproducibility is largely attributable to problems in study design and in the methods used to identify and measure costs. Addressing these methodological issues was the focus of a workshop that included participants from a broad range of backgrounds, including economics, epidemiology, health care management, health care outcomes research, and clinical care. This workshop summary presents the advantages and disadvantages of various research designs as well as particular methodological issues related to the measurement of the economic cost of resistance in health care settings. Suggestions are made for needed common definitions and approaches, study areas for future research are considered, and priority investigations are identified.

In 1998, the Institute of Medicine’s report, Antimicrobial Resistance: Issues and Options, indicated that treating nosocomial infections caused by antimicrobial-resistant bacteria has an extensive economic impact [1]. Yet health systems administrators and clinicians need more refined calculations of the attributable cost of infection due to drug-resistant organisms (IDRO) to assess interventions related to specific infections, settings, and antimicrobial agents [2].

Efforts to provide this information have yielded variable and often conflicting estimates. This lack of reproducibility is in part attributable to problems in study design and in the methods used to identify and measure costs. The process of measuring the costs of antimicrobial resistance is also difficult, because it requires the linking of clinical and economic data in an epidemiologic framework.

Addressing these methodological issues was the focus of a 2-day workshop organized by the Center for the Study of Health, Culture, and Society at Emory University (Atlanta) in collaboration with the Division of Health Quality Promotion of the Centers for Disease Control and Prevention (CDC; Atlanta) and the Rollins School of Public Health (Atlanta). The workshop, Measuring the Economic Costs of Antimicrobial Resistance in Health Care Settings, was held on 29 and 30 November 2000 at the Emory Conference Center and was funded by an unrestricted educational grant to the Center for the Study of Health, Culture, and Society from IntraBiotics Pharmaceuticals, Inc. Because of the interdisciplinary nature of the problem, this workshop included participants from a broad range of backgrounds, including economics, epidemiology,
health care management, health care outcomes research, and clinical care.

The workshop began with the presentation of preliminary findings from 2 multidisciplinary teams that are investigating the costs of antimicrobial resistance in hospital settings. The first of these studies was part of the Chicago Antimicrobial Resistance Project at Cook County Hospital in Chicago. Researchers from the University of Maryland (Baltimore) and Johns Hopkins University (Baltimore) conducted the second study. Both studies were being supported by cooperative agreements from the CDC's Division of Healthcare Quality Promotion, formerly known as the Hospital Infections Program.

During the second day of the workshop, participants divided into 2 working groups. Each was charged with identifying the costs of antimicrobial resistance in health care settings and with discussing the advantages and disadvantages of various study designs as well as particular methodological issues related to the use of these designs. Discussion focused on 2 organisms of current concern in the health care setting: methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE; Intrabiotics Pharmaceuticals, Inc., unpublished data). The conclusions and recommendations of both groups were discussed by all of the workshop participants and are included in this summary report.

WHAT ARE RESISTANCE-RELATED COSTS AND HOW ARE THEY DEFINED?

We focus here mainly on the attributable cost of resistance, which we define as the incremental costs of care for an infection due to a resistant isolate minus the care costs of infection with a susceptible strain of the same organism, holding other patient characteristics constant. It is important to recognize that studies that have measured attributable costs may underestimate the total cost of resistance to society. If resistance induces physicians to prescribe expensive antimicrobial agents as empiric therapy or hospitals to undertake more intensive infection control programs, then resistance will increase costs for all patients, not just those infected with IDRO [3]. Along the same lines, patients whose infections last longer because of the failure of initial therapy are more likely to spread the infection to other patients. In some cases, then, the cost of infection in one patient should be attributed to another patient with IDRO [4]. Ultimately, policy-makers must consider the possibility that bacteria will become resistant to currently available antimicrobials, in which case the cost of resistance will be less than the cost of developing new antimicrobials, which will be passed on to consumers in the form of higher drug prices, or the cost of treating patients with bacterial infections without the benefit of antimicrobial agent therapy.

Perspective. The issue of perspective is crucial in deciding which costs to measure. The difference in perspective between providers, plans, society, and other parties has been discussed extensively by McGowan [5]. Optimal decisions regarding antimicrobial use and infection control must take into account all costs, as was recommended by The Panel on Cost-Effectiveness in Medicine [6]. However, we focus here mainly on the excess medical costs incurred by patients with resistant infections, measured from the point of view of a capitated health system. These are the easiest to measure with available data, are the focus of previous efforts to measure the cost of antimicrobial resistance, and are of interest to key decision makers in hospitals, who have direct influence on prevention strategies (e.g., the adoption of infection control measures and judicious antimicrobial-use policies) [7].

Direct medical costs of resistance include but are not limited to the cost of more expensive antimicrobial agents, labor costs, laboratory costs, the cost of extra hospital days because of failure of initial therapies, and the cost of isolation, and other infection-control measures (table 1). One study estimated that per diem costs accounted for 77% of the total costs of care for patients with serious S. aureus infections, whereas laboratory costs and antimicrobial agent costs were 2% and 21% of the total, respectively [8].

In studies of attributable cost, we recommend that per diem costs be specified as cost per day per bed by specialty (medicine, surgery, pediatrics, etc.) and cost per day per bed by intensity of the level of service (critical care units, stepdown units, etc.). Other patient level costs involve the costs of patient isolation, which include supplies (gowns and gloves), private room, housekeeping, waste disposal, additional portable services, additional infection control staff and nurse time, increased labor,

<table>
<thead>
<tr>
<th>Table 1. Examples of the direct costs of antimicrobial resistance among inpatients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost</strong></td>
</tr>
<tr>
<td>Hospital costs (general)</td>
</tr>
<tr>
<td>Cost per day per bed, by specialty</td>
</tr>
<tr>
<td>Cost per day per bed, by intensive care unit vs. general vs. others</td>
</tr>
<tr>
<td>Cost of patient isolation (supplies, housekeeping, waste disposal, increased portable testing services, and increased staffing)</td>
</tr>
<tr>
<td>Antimicrobial acquisition costs (and other drug costs)</td>
</tr>
<tr>
<td>Antimicrobial administration costs</td>
</tr>
<tr>
<td>Nursing staff time for specialized nurses</td>
</tr>
<tr>
<td>Occurrence of other infections and complications</td>
</tr>
<tr>
<td>Occurrence of other procedures</td>
</tr>
<tr>
<td>Laboratory costs for screening procedures (active surveillance)</td>
</tr>
<tr>
<td>Physicians staff time</td>
</tr>
<tr>
<td>Infection control staff</td>
</tr>
<tr>
<td>Lab testing for diagnosis</td>
</tr>
</tbody>
</table>
oratory tests, increased pharmacy costs, and the cost of complications (table 1). Hospitals also need to consider the cost of loss of good will in the community that may result from unfavorable publicity about presence of resistant organisms in the institution’s patients.

**Valuation.** Assigning dollar values to these costs, especially length of stay, is complicated by the fact that some resources used to produce these services are “fixed.” An example of a fixed cost of a hospital stay is the bed, which is a capital asset. The food consumed by a patient is an example of a “marginal” cost of a hospital stay. Typically, antimicrobial resistance studies value extra hospital days at the average cost (fixed costs plus total marginal costs divided by total number of bed days). However, the average cost of a particular hospital stay exceeds the marginal cost; one study found that eliminating the final day of hospital care for patients with a length of stay of ≥4 days reduced total costs by only 3% [9].

Ideally, studies should measure long-term marginal or incremental costs [6]. These are the appropriate costs to use for the assessment of interventions that reduce length of stay, which, in the long run, will lead to other uses of hospital resources. Because many decisions about appropriate antimicrobial use are made with short time horizons, investigators should also measure short-term marginal costs of the hospital stay. In either case, measurement is complicated by the fact that marginal costs, unlike average costs, are not readily observable. One option is to use econometric techniques to estimate marginal costs [10]; another is to use results from other studies to deflate average costs.

If the provider’s perspective is used, cost data ought to be taken from hospital accounting systems when available. This approach is commonly referred to as “microcosting.” Although these data may not reflect the real resources used in producing various hospital services, they are often the best data available. If possible, investigators then should adjust accounting data to reflect true economic costs, as in the case of the cost of extra hospital days. For studies that measure infection costs by use of large administrative data sets, charges deflated with an appropriate “cost-to-charge ratio” may serve as a substitute for accounting system cost data, although adjusted charges are often a poor approximation of actual costs [11]. Typically, cost-to-charge ratios, which can be obtained from Medicare Cost Report data, are in the range of 0.6–0.8 [7].

Reimbursement data, although useful for evaluating providers’ incentives to prevent and treat infections, do not contain much information about the attributable costs of nosocomial IDRO. Most of the costs are incurred in the course of a single inpatient episode, and nosocomial infection is a secondary diagnosis and is thus not assigned to its own diagnosis-related group.

**PROBLEMS IN MEASUREMENT**

Investigators need to consider a number of issues to produce an unbiased and functional measure of the economic impact of antimicrobial resistance, including (1) study designs and case definitions, (2) units of analysis, (3) variables and their measurement, and (4) generalizability, sample sizes, and power. Conference attendees offer the following suggestions.

**Study design.** Potentially useful study designs include case-control studies, decision modeling on case data, cohort studies, and, in the case of evaluations of interventions to reduce resistance, randomized clinical trials. Case-control studies have traditionally been used to identify risk factors for a condition. With cost used as an ordinal outcome variable, case-control studies can identify the attributable cost if case patients and control patients are selected without bias. Cohort studies that compare the cost of illness in patients with IDRO with both the cost of illness in patients with infection due to susceptible strains of the same organism as well as the cost of illness in patients without infection may provide the best current estimates of attributable cost. The biggest drawback to this design is the difficulty of controlling for potential confounders. Although prospective studies are ideal, retrospective cohort studies can provide cost estimates when needed data elements are available.

**Severity of underlying illness.** Prior treatment with antimicrobial agents and a long length of stay in an intensive care unit are risk factors for acquiring an infection due to a resistant, rather than a susceptible, organism. These relationships imply that patients with IDRO will be sicker, on average, than are patients with infections due to susceptible organisms. A major difficulty faced by researchers, then, is separating the costs associated with treating IDRO from the costs of treating the underlying disease.

A recent study that used inpatient records for patients with *Pseudomonas aeruginosa* illustrates the importance of controlling for severity of illness [12]. Unmatched data indicated that patients with IDRO had hospital charges that were $11,981 higher than those for patients with infections due to susceptible organisms. Matching reduced this figure to $7340—still a large difference, but only 60% of the unadjusted estimate.

Standard techniques for controlling for severity of illness entail matching case patients to control patients on the basis of observable characteristics and the use of multivariate regression to adjust for observed patient characteristics. Another method is to summarize information about patients’ severity of illness by use of a severity score. Current indices for severity of illness include those suitable for examination of administrative databases, such as the Charlson scoring system [13], and those more suited to chart review or studies where clinical details are available, such as the Acute Physiology and Chronic Health Evaluations (APACHE II and APACHE III) [14, 15] and
the Simplified Acute Physiology Score (SAPS II) [16]. However, it is not known whether these or any other indices can be used for adjusting for the risk of acquiring infection with an IDRO. Most were developed for predicting mortality upon admission to critical-care units and have not been validated for other uses. The development and validation of indices for specific types of infection, such as that used in the Pittsburgh Patient Outcomes Research Teams study of community-acquired pneumonia, is an area in which further work is needed [17].

Recently, a number of techniques have been developed by econometricians and statisticians to obtain unbiased estimates in the presence of confounding variables. Of these, instrumental variable estimators are especially promising because they permit researchers to control for confounding variables that are unobserved or, like illness severity, are measured with a great deal of error. An instrumental variable estimate of attributable costs due to an IDRO would be based on a variable that is correlated with the probability that a patient has an IDRO but uncorrelated with costs. The intuition behind this approach is similar to that used to justify randomization in clinical trials: randomization affects patients’ treatment but does not directly affect the outcome of interest. A potential instrumental variable in this context could be patient location in the hospital. If different organisms are present in different sections of a hospital unit, location in the unit will affect the probability of acquiring an IDRO, but it will not have an independent effect on costs. Instrumental variable estimators have been used successfully in a number of medical outcomes studies [18, 19], although typically in conjunction with samples that were much larger than those found in studies of infection costs.

Length of stay. Patients with longer hospital stays have a greater risk of becoming infected, but length of stay is also an indicator of severity of illness. This confounding relationship has several implications for studies of attributable costs. First, comparative studies should match on length of stay so that the reference group has a length of stay at least as long as the time between admission and onset in cases [20]. Second, researchers should be careful about using length of stay as an outcome variable. Without proper matching, length of stay will reflect factors other than the resource use brought about by an IDRO.

Context. Many studies of the costs of antimicrobial resistance have focused on hospital critical-care units. However, it is important to recognize that attributable costs will depend critically on varying practices within and between hospitals. For example, outcome differences in patients with and without IDRO will be less pronounced in hospitals that treat patients initially with newer, more expensive antimicrobial agents. Besides antimicrobial regimens, other factors to consider are infection-control policies, criteria for defining resistance, compliance, and advanced directives about end-of-life treatment. Couple these differences with variations in hospitals (academic teaching hospitals, public hospitals, etc.) and the demographics of the patient populations they serve, and one must appreciate the diverse environment in which antimicrobial resistance is studied. Hospital practices related to use of formularies, treatment pathways, empiric therapy, and infection-control measures should be part of the study description, to facilitate comparisons.

Mortality. The impact of mortality on subjects in comparative studies can influence results. Some studies have excluded patients who do not survive (particularly those who die very soon after infection), because truncation of the cost data affects the results. However, omission of mortality leads to a distortion in costs, particularly from a societal perspective. The handling of mortality data could be improved by clearly defining the study context and analyzing data from patients who die separately from those who live. Providing estimates of the expected mortality rates of study patients would assist in the interpretation of study results. Researchers should also consider the use of statistical techniques to control for the truncation of patient records.

NEEDED STUDIES OR ACTIVITIES

Determining attributable impact requires that we define epidemiologically the “person, place, and time” under study and that we ensure, either in the study design or in the analysis, that we have the capacity to compare patients or populations of patients infected with susceptible or resistant organisms. At the present time, our ability to conduct such studies is hampered by the need for several critical elements, which are considered below.

Assessment of key cost drivers. Collecting detailed and precise data on the costs and resources used in health care is difficult and labor intensive. Some studies have been based on the premise that a smaller number of identifiable variables (e.g., number of days in the hospital, drug costs, laboratory tests, etc.) may consistently account for a sufficiently large proportion of total costs, in which case calculation of this more limited number of cost elements is a reasonable estimate of overall economic impact. Studies to assess the extent to which such estimates may be consistent enough (within specified populations or delivery sites) to allow for this type of research design have not been conducted. One approach would be to study the distribution of costs in various categories within different populations, including patients with and without IDROs.

Clear definition of the population to be studied. To facilitate measurement and minimize bias, many studies have looked at specific populations within a single institution, such as patients in the intensive care unit or patients with severe underlying illnesses. It is thus difficult to generalize the conclusions of these studies to broader populations, even within the same institution. Sampling strategies or studies of greater
scope will be needed to develop broadly applicable cost estimates.

Common definitions and data collection methods. For certain combinations of microorganisms, such as MRSA or VRE, there are well-established definitions of resistance. For other microorganisms, resistance is often defined as “deviation” from standard resistance profiles, and this definition may conceivably vary from country to country, region to region, or even facility to facility. Even where well-established definitions exist, the method of determining resistance may be phenotypic, genotypic, or may depend on isolation of specific microbial enzymes. In addition, their resistance profiles with regard to antimicrobial agents other than the defining agent (i.e., methicillin for MRSA and vancomycin for VRE) may vary. Researchers should strive to use standardized definitions of resistance, such as those from the National Nosocomial Infection Surveillance system. Studies are also needed to assess the reliability of infection data collected from chart review, billing records, and microbiology laboratory reports.

Appropriate study power. Because many existing studies were conducted within a single institution, the number of patients studied has been relatively small. This has limited the ability of these studies to provide precise estimates and also makes difficult the application of statistical tools to control for severity of illness. Multicenter studies are needed to achieve adequate statistical power in addition to producing results that are generalizable. These require common definitions of resistance, infection, and colonization and uniform data collection methods. Investigators must also collect data regarding participating institutions’ treatment and infection control protocols.

Clear delineation of scope of treatment. As was indicated in the previous section, most existing studies have limited their assessment of impact of infections on cost and other outcomes to the duration of the patient’s hospital stay. Thus, costs incurred after discharge or transfer to other facilities (e.g., long-term care facilities) are often not calculated within the study. Alternatively, some studies have used fixed and arbitrary cutoffs (30 days after infection, 6 months, etc.), without data that demonstrate the validity of such cutoff points. Conversely, for some severely ill patients with unusually long admissions or series of readmissions, all costs incurred after the onset of an IDRO may be included as attributable costs. This may add costs unrelated to the infection and costs incurred after the infection has run its course. An important study to clarify this issue would be a longitudinal assessment of costs after an IDRO, which would track the attributable proportion of costs over time.

Integrating, funding, and reporting of studies. Studies of the economic costs of antimicrobial resistance require the integration of multiple perspectives and methods, including those of health economists, epidemiologists, clinicians, and health outcome researchers. Such integration presents challenges. Perhaps the most central problem is funding. Measuring the economic costs of antimicrobial resistance is not central to the disciplines of any of the researchers required for such studies. The sources of funding to which members of each discipline look often find such hybrid research initiatives problematic. Finding outlets for publishing is also difficult for much the same reason. Agencies and journals that provide grants need to support this kind of research if it is to be properly conducted.

COMMENTS

Resource limitations will restrict the degree to which investigators can adhere to all of the recommendations listed above. Yet we strongly urge investigators in this field to (1) adopt a microcosting approach, (2) value resources like hospital bed–days at the marginal cost, and (3) carefully match case patients and control patients or collect detailed measures of patient severity for adjustment of prospective data. In addition, we hope that researchers on larger projects will explore the use of instrumental variable analysis and innovative methods for modeling mortality in study participants.

WORKSHOP PARTICIPANTS

Centers for Disease Control and Prevention (Atlanta): Ralph L. Cordell, Ph.D., and Steven L. Solomon, M.D. (Healthcare Outcomes Branch); Elamin H. Elbasha, Ph.D. (Division of Prevention Research and Analytic Methods); Julie L. Gerberding, M.D., Ph.D. (Division of Healthcare Quality Promotion); Martin I. Meltzer, Ph.D., R. Douglas Scott II, Ph.D., and J. Todd Weber, M.D. (National Center for Infectious Diseases); and Sameer Rajbhandary, Ph.D. (Prevention Effectiveness). Emory University School of Medicine (Atlanta): James P. Steinberg, M.D., (Department of Medicine). Rollins School of Public Health of Emory University (Atlanta): W. Dana Flanders, M.D., and John E. McGowan, Jr., M.D. (Department of Epidemiology); Curtis S. Florence, Ph.D., and David H. Howard, Ph.D. (Department of Health Policy and Management); and Randall M. Packard, Ph.D. (Center for the Study of Health, Culture, and Society). Cook County Hospital (Chicago): Rebecca Roberts, M.D., (Department of Emergency Medicine); and Robert A. Weinstein, M.D. (Division of Infectious Diseases). Covance Health Economics and Outcomes Services, Inc. (Gaithersburg, Maryland): Thomas F. Goss, Pharm.D. Johns Hopkins Medical Institutions (Baltimore): Xiaoyan Song, M.D. (Hospital Epidemiology and Infection Control Programmer Analyst). University of Maryland Medical School/Veterans’ Affairs Maryland Health Care System (Baltimore): Mary-Claire Roghmann, M.D., Douglas D. Bradham, Dr.P.H., and Brett R.South, B.S. (Division of Healthcare Outcomes Research, Department of Epidemiology and Preventive Medicine). IntraBiotics Phar-
References