Cost-of-Illness Studies—A Primer

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INTRODUCTION

Cost-of-illness studies measure the economic burden of a disease or diseases and estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated. Numerous cost-of-illness studies have been conducted over the past 30 years. Many of these studies have been instrumental in public health policy debates because they highlight the magnitude of the impact of an illness on society or a part of society.[1,2] Knowledge of the costs of an illness can help policy makers to decide which diseases need to be addressed first by health care and prevention policy. Additionally, these studies can indicate for which diseases cures would be valuable in reducing the burden of disease. For specific stakeholders, such as the federal government, cost-of-illness studies can show the financial impact a disease has on public programs, such as Medicare and Medicaid.[3,4,5] For employers, they can show which diseases have an especially large effect on their costs.[6,7] Moreover, cost-of-illness studies provide important information for cost-effectiveness and cost-benefit analyses. Although only one part of cost analysis, cost-of-illness studies can provide a framework for the cost estimation in these analyses.[1,8]

The value of cost-of-illness studies can be seen in their frequent use by policy makers. For example, in response to a request from Congress, the National Institutes of Health (NIH) released a 2000 report on the updated costs of illness for numerous diseases.[9] State smoking cost-of-illness estimates by Miller et al.[10] were used in state lawsuits against the tobacco industry to recover Medicaid losses.[11] A study of the cost of injuries by Rice et al.[12] was used to motivate Centers for Disease Control and Prevention (CDC) requests for proposals for injury centers.[1] A recent pilot study by the Bureau of Labor Statistics (BLS) used a cost-of-illness method to estimate the costs of fatal occupational injuries by state. The study "found such estimates would

benefit safety and health professionals and aid the overall education and prevention efforts aimed at eliminating workplace fatalities."[13]

In addition to their use by government organizations, cost-of-illness studies are often cited in disease studies that attempt to highlight the importance of studying a particular disease, as well as in cost-effectiveness and cost-benefit studies. For example, a study of how obesity causes diabetes,[14] a study about mitochondrial dysfunction and diabetes,[15] and numerous other studies cited a 2002 American Diabetes Association cost-of-illness study[16] to illustrate the magnitude of the burden associated with diabetes. On perhaps a more practical level, cost figures from cost-of-illness studies are also used in cost-effectiveness and cost-benefit analyses. For instance, a cost-effectiveness study[17] of treating Alzheimer's disease with Donepezil uses the cost figures from an earlier Alzheimer's disease cost-of-illness study by Rice et al.[18] Similarly, a cost-benefit analysis of physicians providing brief advice to problem drinkers[19] used the cost figures for health care utilization from a study by French and Martin[20] and the highway crash costs from a study by Miller et al.[21]

There are, however, limitations to the use of cost-of-illness studies. Cost-effectiveness and cost-benefit analyses provide additional information not included in cost-of-illness studies that can be used to determine the best course of action with respect to the disease studied.[22,23,24,25,26] Cost-of-illness studies can demonstrate which diseases may require increased allocation of prevention or treatment resources, but they are limited in determining how resources are to be allocated because they do not measure benefits. In addition, these studies employ varying methods, which can limit the comparability of findings.[23] Studies can vary by perspective, sources of data, inclusion of indirect costs, and the time frame of costs.[27] A clear

statement of the study methods can improve cost comparability.[1] When performed with a clear explanation, cost-of-illness studies represent an important analytic tool in public health policy.

COSTS

A comprehensive cost-of-illness study includes both direct and indirect costs, although the specific focus of a study may make one or the other unnecessary. Direct costs measure the opportunity cost of resources used for treating a particular illness, whereas indirect costs measure the value of resources lost due to a particular illness.[9] Opportunity cost, in this case, is defined by Hodgson and Meiners as "the value of the forgone opportunity to use in a different way those resources that are used or lost due to illness."[27] Although some studies also include intangible costs of pain and suffering, usually in the form of quality of life measures, this category of costs is often omitted because of the difficulty in accurately quantifying it in monetary terms. In such a case, the study should note that intangible costs have been omitted.[2,27,28]

Direct Costs

When measuring direct costs, studies often measure total direct costs (i.e., the costs of resources used) rather than net direct costs, which subtracts future medical costs avoided because of the death of a patient, from total costs.[27] Direct medical costs include hospital inpatient, physician inpatient, physician outpatient, emergency department outpatient, nursing home care, hospice care, rehabilitation care, specialists' and other health professionals' care, diagnostic tests, prescription drugs and drug sundries, and medical supplies.[2,9,27]

One challenge with calculating direct medical costs, particularly hospital costs, is that charges are often the only data available. Because of the nature of determining hospital charges, they often do not accurately reflect the underlying costs. Charges are often higher than costs to cover losses from patients who are unable to fully pay their expenses, such as procedures not

covered by insurance companies, and to cover the rising costs of replacing and updating medical equipment.[29] In addition, most insurers negotiate reimbursement rates and receive substantial discounts off listed charges. This practice causes surveys that provide charge data—such as the National Inpatient Sample, the American Hospital Association Annual Survey, and other surveys specific to certain diseases—to overestimate the costs of an illness. To obtain more accurate estimates, studies must use a cost-to-charge ratio, which can be obtained for specific hospitals from Centers & Medicare and Medicaid Services (CMS) data[30,31] or from the Agency for Healthcare Research and Quality (AHRQ) for Healthcare Cost and Utilization Project (HCUP) data.

Nonmedical direct costs include transportation costs to health care providers; relocation expenses; and costs of making changes to one's diet, house, car, or related items. However, some nonmedical direct costs are generally not included in cost-of-illness studies, such as research, training, and capital costs (e.g., construction). It can be difficult to attribute these costs to a particular disease. Additionally, training health care providers for a particular illness or capital costs, such as a new wing or equipment to treat an illness, are often reflected in the charges of care. To include them separately would lead to the double-counting of costs.[27] The specific purpose of the study or the data available may preclude the calculation of nonmedical direct costs. When calculated, the focus is often on direct financial costs because nonmonetary costs can be difficult to capture.[2,9,27]

Indirect Costs

Indirect costs represent the other portion of estimated costs. These include mortality costs; morbidity costs due to absenteeism and presenteeism; informal care costs (in terms of the opportunity cost of hiring outside care); and, for the few relevant cases such as substance use or

violence, losses due to crime (e.g., incarceration, policing, legal, and costs to victims of crime).[9,32] Several issues exist with the estimation of indirect cost, which are discussed in the Indirect Costs section.[27,28]

PERSPECTIVE

A cost-of-illness study may be conducted from several different perspectives, each of which includes slightly different costs. These perspectives may measure costs to society, the health care system, third-party payers, businesses, the government, and participants and their families.[1,8,33] Each perspective provides useful information about the costs to the particular group. Table 1 presents the costs included in each perspective.

Table 1. Costs Included in Cost-of-Illness Studies, by Perspective

Perspective	Medical Costs	Morbidity Costs	Mortality Costs	Transportation/ Nonmedical Costs	Transfer Payments
Societal	All costs	All costs	All costs	All costs	—
Health care system	All costs	—	—	—	—
Third-party payer	Covered costs	—	Covered costs	—	—
Businesses	Covered costs (self-insured)	Lost productivity (presenteeism/ absenteeism)	Lost productivity	—	—
Government	Covered (Medicare, Medicaid)	—	—	Criminal justice costs	Attributable to illness
Participants and families	Out-of-pocket costs	Lost wages/ Household production	Lost wages/ Household production	Out-of-pocket costs	Amount received

Note: Adapted from Luce et al.[8,27,34]

The purpose of the study ultimately determines the necessary perspective. A study concerned with the medical care costs of an illness would require the health care system perspective, while a study concerned with how much an illness costs the government would require the government perspective. A study is also not limited to only one perspective.

Researchers might estimate the more general societal costs but also include the more specific costs to the government.

Although other purposes may require different perspectives, the societal perspective is the most comprehensive because it includes all direct medical costs and indirect costs for all members of the society. It does not include transfer payments, such as Medicare, Medicaid, or Social Security benefits paid to individuals because they only represent a shift in resources, not a use of them.[8,27,34] The societal perspective is often favored because it allows a complete analysis of all of the opportunity costs attributable to a disease and is recommended for cost-effectiveness analysis by Gold et al.[35] The societal approach, however, requires the most data, making it difficult to use in certain cases. This is especially true with less common diseases, where data are more limited. In these situations, data from a third-party payer may be the only reliable data available, in which case the societal approach is clearly not feasible.

Because of the relatively larger range of costs included, the societal and health care system perspectives inevitably tend to result in higher cost estimates than the other approaches. A 2001 study by Szucs et al.[36] illustrates the effect of choosing different perspectives. The study estimates the costs of genital herpes using both a health care system and a health maintenance organization (HMO), or third-party payer, perspective. The health care system perspective uses an expert panel to estimate the direct medical costs to be $984 million, whereas the third-party payer perspective uses an HMO claims database to estimate direct medical costs to be $283 million. The difference in approach explains most of the difference in costs, although the study notes two additional possible explanations for some of the difference in costs. Because of the stigma attached to sexually transmitted diseases, patients may not comply with physicians' prescriptions or they may seek treatment anonymously at community health clinics, both of

which would lead to fewer claims being filed than estimated by the expert panel. Although the explanation helps to clarify the reasons for the differences in cost estimates, the choice of perspective can have a large effect on the actual cost estimates.

The perspective of the cost-of-illness study should be made clear because each includes slightly different costs. While the societal perspective is the most comprehensive, the purpose of the study drives which perspective should be chosen. More comprehensive studies may also divide the costs by stakeholder to allow analysis from multiple perspectives, which may be especially relevant for public policy.

DISCOUNTING

Discounting is an economic method that captures an individual's preference for income today rather than income in the future. This time preference is often explained by the opportunity cost of interest. Income earned today can earn interest through investment. For example, given an interest rate of 3 percent, a payment of $100 today is worth more than the same payment in one year because $3 of interest can be earned if the payment is received today. Discounting allows us to calculate the present value of payments (or costs) that occur in the future. The present value of $100 received n years in the future when the discount rate (which is closely related to the real interest rate) is r is given by the formula $PV = payment/ (1+r)^n$.

Discounting is relevant for direct and indirect costs that accrue past the first year. Numerous possible discount rates can be used to discount future costs, with each representing a slightly different approach. The discount rates range from zero percent to 10 percent. Gold et al.[35] suggested a cost-effectiveness analysis discount rate of 3 percent. Given that cost-of-illness studies can provide a basis for cost-effectiveness studies, the 3 percent discount rate represents a

good starting point. Other discount rates can be applied to determine their effect on the cost estimates.[27,37,38]

INCIDENCE-BASED VERSUS PREVALENCE-BASED STUDIES

Incidence-based studies, which estimate lifetime costs, measure the costs of an illness from onset to conclusion for cases beginning within the period of the study, usually a year. Incidence costs include the discounted, lifetime medical, morbidity, and mortality costs for the incident cohort. Prevalence-based studies, which estimate annual costs, measure the costs of an illness in one period, usually a year, regardless of the date of onset. Prevalence-based studies include all medical care costs and morbidity costs for a disease within the study year. However, the mortality and permanent disability costs of prevalence-based studies are calculated differently from the other costs. Discounted mortality and permanent disability costs are calculated for all patients who die or become permanently disabled in the study year for that year and each year until the expected age of death.[37,39]

Prevalence-based studies are far more common because they require less data and fewer assumptions than incidence-based studies. Data only need to be collected from one year, and nothing has to be known or assumed about the survival rate or course of the illness. Lifetime costs can be calculated from annual costs, assuming a steady state of disease incidence, progression, survival rate, and treatment; but the estimates may not be as accurate as using actual longitudinal data on the full course of the illness because of potential future changes in medical care technology and other assumptions.[39] Despite this limitation, numerous methods provide useful approximations of lifetime costs using annual data, all of which involve the assumption that the structure of future costs is the same as the structure of current costs and then discounting future costs.[1,23,27,37,39]

While the specific methods for calculating lifetime costs using annual cost data differ, the basic approach of each method is to use annual data as a cross-section of how costs are distributed by age. The assumption is that the cross-sectional view of the costs at different ages represents the progression of the disease. One method is to estimate the difference in costs incurred by those with the disease and those without the disease by age group. This provides an "incremental" per person cost by age for those with the disease, which can be combined with data on the number of people with the disease who are expected to survive to each age to obtain lifetime cost estimates.[40] Another method is to combine annual unit cost data with expert opinions about the course of the disease to obtain lifetime cost estimates.[41] A third method is to use data on the percentage of costs incurred in the first year for a related condition to determine the total lifetime costs.[12] Additional related methods also exist, which are similar in the basic approach of the aforementioned examples. Hodgson provided a description of the relationship between annual and lifetime costs and how lifetime costs can be calculated using annual costs.[39]

Cost-of-illness studies are particularly useful for measuring the potential savings of averting a case of an illness. To this end, they can aid in cost-effectiveness analysis, cost-benefit analysis, or illness prevention analysis by providing the baseline costs of maintaining the status quo. For an acute illness that only has costs within one year, a prevalence-based or incidence-based study would be the same because future costs would not exist. For chronic illnesses with costs that extend past the first year, incidence-based studies provide more information about the costs of averting a case. A prevalence-based study can be performed with a chronic illness, but it needs to be interpreted as a snapshot of the costs in one year, rather than the costs that could be saved if all cases of the illness were averted.[1,23,27,37,39]

Although both methods use the same costs (i.e., medical costs, morbidity costs, mortality costs, and other nonhealth costs), the discounting of future costs in the incidence-based studies results in different actual cost estimates. As Hodgson noted, incidence costs tend to be lower than prevalence costs because of the use of discounting.[37] Table 2 illustrates a hypothetical example. For a given illness, there is one new case every year, with the illness lasting 3 years; the annual cost of the illness is $100. Suppose the year of the study is Year 3. The prevalence-based study would add the column of Year 3 costs for patients A, B, and C to obtain a cost-of-illness estimate of $300. The incidence-based study only measures the row of costs for patient C, who is the only patient to become ill in Year 3. With an annual discount rate of 3 percent, the incidence-based study would obtain an estimate of $291.35, equal to ($100 + $100/(1.03) + $100/$(1.03)^2$), which is slightly lower than the prevalence-based study's estimate. Additionally, the greater the length of the illness, the greater the difference between the cost estimates of the two approaches.

Table 2. Hypothetical Example of Discounting

Patient	Year 1	Year 2	Year 3	Year 4	Year 5
A	$100	$100	**$100**		
B		$100	**$100**	$100	
C			**$100**	**$100**	**$100**

Incidence-based studies also lead to lower cost estimates, even if costs are front-loaded or back-loaded. Front-loaded costs occur when an illness has high costs when the illness first occurs, but then lower costs in subsequent years. Pneumonia, an acute illness with limited future complications, is an example. Back-loaded costs occur when initial costs are low but future costs are high; for example, smoking or obesity among youth.

The difference is more pronounced in the estimates generated by the incidence-based and prevalence-based approaches for back-loaded costs than for front-loaded costs. In the case of back-loaded costs, shown in Table 3, a prevalence-based study would obtain a cost estimate of $700, while an incidence-based study would obtain a cost estimate of $668.39, equal to ($100 + $100/(1.03) + $500/$(1.03)^2$). An example of front-loaded costs is shown in Table 4. A prevalence-based study would estimate the costs of illness to be $700, while an incidence-based study would estimate the costs to be $691.35, equal to ($500 + $100/(1.03) + $100/$(1.03)^2$). This example demonstrates that the difference between the approaches is greater for the back-loaded costs than for the front-loaded costs, which is due to later costs being discounted more and therefore contributing less to total cost estimates than earlier costs.

Table 3. Back-Loaded Costs

Patient	Year 1	Year 2	Year 3	Year 4	Year 5
A	$100	$100	**$500**		
B		$100	**$100**	$500	
C			**$100**	**$100**	**$500**

Table 4. Front-Loaded Costs

Patient	Year 1	Year 2	Year 3	Year 4	Year 5
A	$500	$100	**$100**		
B		$500	**$100**	$100	
C			**$500**	**$100**	**$100**

A study by Begley et al.[42] in 2000 of both the annual and lifetime costs of epilepsy showed that prevalence- and incidence-based studies tend to have similar cost estimates, with

prevalence-based studies often having slightly higher estimates. In the Begley study, the total prevalence-based estimates are $12.5 billion, whereas the total incidence-based estimates are $11.1 billion. It should be noted, however, that the direct costs using the prevalence-based approach are $1.7 billion compared with $1.8 billion using the incidence-based approach. The relatively similar results can be explained by the calculation of the lifetime costs using the annual cost estimates and survival rates. As mentioned earlier, these types of shortcuts to estimate lifetime costs are often necessary because of the prohibitive difficulty of gathering cost data on the full course of an illness.

INDIRECT COSTS

For many diseases, indirect costs are substantial and can be significantly greater than the direct medical costs.[2,42,43,44] Indirect costs include the loss of resources due to morbidity and mortality, which inherently places a monetary value on the value of life. While the inclusion of indirect costs in cost-of-illness studies is common and widely accepted, it is not without controversy.[28,37,38] The idea of placing a value on life raises ethical questions, especially with the wide range of estimates that exist over disagreement on the correct method of estimation. Because indirect costs inevitably place a lower value on the elderly, and often those who do not work, there are some questions as to whether such costs should be included.[23] Even when indirect costs are included, debate exists about the correct approach.[45,46,47,48] There are three primary approaches to estimate indirect costs: the human capital method, the friction cost method, and the willingness to pay method.

Human Capital Method

The human capital method measures the lost production, in terms of lost earnings, of a patient or caregiver.[27,38,49] For mortality or permanent disability costs, the approach multiplies

the earnings lost at each age by the probability of living to that age. The earnings in future years are discounted and often a one percent real annual growth rate in earnings is assumed.[2,12] The human capital approach often includes the value of household work, usually valued as the opportunity cost of hiring a replacement from the labor market.[27,28,38]

Friction Cost Method

A related method, the friction cost method, measures only the production losses during the time it takes to replace a worker.[50,51,52] This approach assumes that short-term work losses can be made up by an employee and the loss of an employee only results in costs in the time it takes a new employee to be hired and trained, known as the friction period.

Willingness to Pay Method

The willingness to pay approach measures the amount an individual would pay to reduce the probability of illness or mortality.[27,38] There are various methods of determining an individual's willingness to pay, including surveys, examining the additional wages for jobs with high risks, examining the demand for products that lead to greater health or safety (e.g., seatbelts), and other related methods.[12,53]

Advantages and Limitations of the Three Methods

The human capital method is the most common approach used to calculate the indirect costs of an illness. A criticism of this approach is that certain groups are assigned a higher value than others. Because the human capital approach uses wage rates and employment rates (often by age, sex, or race), certain groups that earn less are consequently assigned a lower value.[2723,27,37] The willingness to pay approach, usually with higher estimates of the value of life than the human capital approach,[53] attempts to ameliorate these problems. However, this approach is often difficult to implement in cost-of-illness studies. For specific diseases, extensive surveys of

people's preferences are needed, although the results rely heavily on people's responses to very specific hypothetical questions about their willingness to avoid certain illnesses.[27,38] For communicable diseases, surveys may not fully capture the cost of the disease because of externalities. People only take into account the cost to themselves, without taking into account the societal benefit that having fewer people with a communicable disease benefits everybody because the disease is less likely to spread. Thus, the willingness to pay method is often not feasible for a cost-of-illness study.

Proponents of the friction cost method criticize the human capital method for overvaluing the indirect costs, claiming that the productivity losses are often eliminated after a new employee is trained and can replace the former employee. However, the friction cost method is rarely used because it requires extensive data to attempt to estimate only the losses in the friction period. Valuation of the productivity losses is complicated further by firms' use of internal reserves of labor during the friction period, which lowers the estimates of losses even more but can be difficult to calculate.[52,54,55]

The choice of method, however, can have a dramatic effect on the estimates of indirect costs. A review by Hirth et al.[53] shows the wide range of estimated values of life that exist and how the method of estimation can affect these values. The study reviews estimated values of a quality adjusted life year (QALY), which measures both the quantity and quality of life. It takes a value of 1 for each year of perfect health and 0 at death, with values in between for various states of illness. Hirth et al. categorized the estimates by the method used and then provided the median value of a QALY by method. Hirth et al. found that the median value using the human capital method is $24,777. Three willingness to pay methods are examined, all with higher median values than the human capital method. An approach that uses revealed preferences, such

as seat belt use, smoke detector use, and similar non-job-related safety measures, has a median QALY value of $93,402. Studies using contingent valuation, a method involving answers to direct questions about a person's willingness to pay, have a median QALY value of $161,305. The highest median QALY value, $428,286, is for a method using revealed preferences from higher wages for higher risk occupations.[53] A study by Goeree et al. of the productivity costs of schizophrenia found the productivity costs using the human capital method to be nearly 70 times those using the friction cost method.[56] Because of the potential for such wide variation, it should be clear which method is used to estimate indirect costs, especially with the impact indirect costs can have on the total costs of illness.

TOP-DOWN, BOTTOM-UP, AND ECONOMETRIC APPROACHES

Direct costs can be estimated using one of three approaches: the top-down approach, the bottom-up approach, or the econometric approach.

Top-Down Approach

The top-down approach, also known as the epidemiological or attributable risk approach, measures the proportion of a disease that is due to exposure to the disease or risk factor.[57,58] The approach uses aggregated data along with a population-attributable fraction (PAF) to calculate the attributable costs.

Studies often use an epidemiological measure known as the population-attributable fraction,[16,59,60] which was developed by Morganstern et al.[61] In this approach, the proportion of medical care for disease B attributable to disease A is measured as follows:

$$PAF = p(RR-1)/ [p(RR-1)+1],$$

where p is the prevalence rate of disease A and RR is the unadjusted relative risk of disease B for people with disease A, compared with those without disease A.[16,59,62] However, this equation

applies only in limited cases where other factors do not affect the association between diseases A and B.[63]

Commonly, confounding variables (e.g., age, sex, and other similar variables) may be related to both disease A and disease B. If not controlled for, the confounding variable causes a bias (usually upward) in the relative risk and consequently the PAF. For example, there is an association between diabetes and heart disease, yet those with diabetes and heart disease tend to be older. Failing to account for age when calculating the PAF in this case would lead to a bias. A couple of adjustment methods exist to account for confounding variables when calculating the PAF, namely the Mantel-Haenszel approach and the weighted-sum approach. Both methods are discussed in more detail by Benichou.[62,63,64]

A common error when using the top-down approach, which can significantly impact the estimates, is to use a partially-adjusted method rather than one of the two methods suggested by Benichou.[64] The error consists of using the PAF equation (shown above), which can only be used with unadjusted relative risks, with adjusted relative risks. The error occurs when the study accounts for the confounding variables when calculating the relative risks and plugs these adjusted relative risks into the PAF equation. This error is exacerbated if effect modification is also present but not accounted for.

Similar to confounding, effect modification exists when a third factor affects the association between disease A and B through interaction. For example, as mentioned earlier, age is correlated with diabetes and heart disease, but as one gets older the effect of diabetes on heart disease gets stronger. Not only are older people more likely to have diabetes and heart disease (confounding), but as one gets older diabetes is more likely to lead to heart disease (effect

modification). As this example shows, it can sometimes be difficult to tease apart how the additional variable affects the association between the two illnesses.[63,64]

Bottom-Up Approach

While the top-down approach is a valid approach to avoid the need to calculate PAFs and the potentially more cumbersome methods needed to prevent a bias in the estimate, the bottom-up or econometric approach can be used. The bottom-up approach estimates costs by calculating the average cost of treatment of the illness and multiplying it by the prevalence of the illness.[57,58] Because the average cost of treatment for an illness is seldom readily available, the bottom-up approach often calculates the average cost of treatment by adding together the various pieces of the treatment. The bottom-up approach often multiplies the unit cost of a particular treatment by the average amount of utilization of the treatment to get an average cost estimate of the treatment. For example, the average cost of an outpatient physician visit is multiplied by the number of visits to get an average cost of outpatient physician care for the particular illness. The method is repeated for each type of care to obtain a total average cost per case, which is then multiplied by the prevalence of the illness to get an estimate of the total direct costs.[2,43]

Econometric Approach

The econometric or incremental approach estimates the difference in costs between a cohort of the population with the disease and a cohort of the population without the disease. The two cohorts are matched, usually via regression analysis, by various demographic characteristics (e.g., sex, age, race, geographic location) and the presence of other chronic conditions. Within the econometric approach, there are again two methods of estimating costs: a mean differences approach and a multistage regression approach. The mean differences approach compares the mean costs incurred by each of the two cohorts to determine the incremental difference

attributable to the disease of interest.[65,66,67] Studies using the mean differences approach sometimes only provide the cost per case of the disease of interest, rather than a total cost estimate.[66,67]

A multiple-stage regression is typically run if there are a large number of cases with zero costs and a few cases of very high costs. The incremental cost of the disease is measured by comparing the regression estimate with the disease dummy variable turned on to the regression estimate with the disease dummy variable turned off. The multiple-stage regression often uses a two-stage regression in the cost estimation, although there are many other possible variants of the multiple-stage regression.[3,68,69,70] The approach involves estimating the likelihood of an individual receiving any care and then the excess cost of care if care is received.

Because the econometric approach measures the incremental difference between persons who have the disease and those who do not, it often only requires one dataset.[65,69] The top-down approach usually requires data on the costs as well as on the relative risks, which are needed to calculate the PAFs. The bottom-up approach often requires data from multiple sources for the unit cost and utilization rate of the different types of care. While each method is valid, the econometric approach has the advantage of requiring less data.

DEFINITION OF ILLNESS

Diagnostic Definition

The costs attributable to an illness depend largely on how the illness is defined diagnostically. Studies typically use the International Classification of Diseases, 9th/10th Revision codes as a basis of defining the illness of interest.[9,28,49] Yet the actual choice of which codes to include can vary significantly for a disease. For example, heart disease can be defined in different ways, by including or excluding conditions ranging from angina to ischemic heart

disease to hypertension. Which condition to include is an important issue and can have a dramatic effect on the levels of costs estimated.

A study by Javitz et al.[71] of the costs of angina demonstrates the extent of the issue. This study defined angina specifically and then more generally as all coronary heart disease. The cost estimates ranged dramatically from $1.9 billion to $74.8 billion, emphasizing the need for a study to clearly state how the disease is defined.

Secondary Diagnoses

A second issue in defining a disease is whether to include secondary diagnoses. With multiple diagnoses for a medical treatment, a study must decide how to attribute the costs among the diagnoses. To accurately include the costs of secondary diagnoses, the causal pathway of the various diagnoses must be understood. The secondary diagnosis may be listed because it is the underlying cause, because it is a complication, or possibly just as a note to inform the health care provider. For instance, diabetes may be listed as a secondary diagnosis for a foot amputation because it is the underlying cause, for a heart-related procedure because diabetes is a complicating factor, or for pneumonia just as a note to warn the provider that the patient has diabetes. In this example, the costs attributable to diabetes should be highest when it is the cause, slightly lower when it is a complicating factor, and minimal if not zero when it is unrelated to the primary diagnosis.

In addition, knowledge of the causal pathway is needed to determine how the costs are to be attributed to a secondary diagnosis. The simplest method is to include only primary diagnoses, but this may ignore a large contribution of the secondary diagnoses to the attributable costs. Another method is to include secondary diagnoses with relative weights. For instance, a disease with a primary and a secondary diagnosis might have 80 percent of its costs attributed to the

primary diagnosis and 20 percent to the secondary diagnosis. The costs of a disease may also be estimated as the incremental increase in cost attributable to the secondary diagnosis.[72]

A study by Ward et al.[72] examined the effect that the different approaches can have on the cost-of-illness estimates. This study used data from the National Hospital Discharge Survey to estimate the costs of chronic obstructive pulmonary disease (COPD) with three different approaches. The costs are estimated with COPD as the primary diagnosis, with a weighted approach, and with an incremental approach. The weighted approach assigns various weights to the secondary and tertiary COPD diagnoses depending on whether the diagnosis is related to the primary diagnosis. The more related the diagnoses, the higher the weight. The study estimates the costs of COPD, when listed only as the primary diagnosis, to be $710 million. Using the weighted approach, the costs are estimated to be $2.2 billion. Using the incremental approach, the costs are estimated to be $1.6 billion. There is a threefold difference in cost between the approaches, highlighting the importance of choosing an appropriate approach.

Ward et al. also provided recommendations for when to use each approach. They recommended only including primary diagnoses if there are not any particular comorbidities associated with the disease. Illnesses with no appreciable secondary diagnoses on the causal pathway are rare, although examples include rhinitis and some types of skin disease. If significant comorbidities exist, the costs could be underestimated. The study suggests the weighted approach is most appropriate for diseases where treatment is clearly attributable to the condition, even with the presence of comorbidities, such as psychiatric disorders. The drawback to the approach is the subjective nature of the weights assigned and the possibility of double-counting. Because the weights are selected for each individual disease, the total costs of all diseases if added together could exceed 100 percent of the total amount spent on health care. The

difficulty in selecting appropriate weights limits the use of this approach. Although it requires illness prevalence data by age and gender, the authors recommended the incremental approach for diseases that have significant comorbidities.

COMORBIDITY

The presence of comorbidities on the causal pathway, often defined via secondary diagnoses, can lead to significant increases in the cost of an illness. Ignoring the comorbidities of an illness can cause significant underestimation of the costs of an illness.[38,73,74] However, including all costs of multiple diagnoses can lead to the problem of double-counting,[54,74] which can occur because of the difficulty in accurately separating the costs of related diseases. When the costs of illness are estimated for related diseases, such as diabetes and heart disease, the overlap may be counted twice, once for each disease. The problem can potentially lead to the sum of the cost estimates exceeding the total expenditures for health care.[72]

Attributable costs of comorbidities can be calculated using either attributable risk analysis or econometric analysis. Attributable risk analysis, often known as the epidemiological approach, uses the same method as the top-down approach described earlier. Econometric analysis uses the same method as the econometric approach described earlier.

The use of one of the two methods of calculating comorbidity costs is especially important for estimating the costs of risk factors, such as smoking and obesity. Risk factors have few directly attributable costs because the majority of the costs reflect the costs of diseases for which they are causes. For example, obesity itself has few costs; rather, its high costs are due to the causal effect on heart disease, diabetes, musculoskeletal disorders, and other illnesses.

DATA

The appropriate data source to use for a cost-of-illness study varies by the illness, perspective, and approach of the study. The following are some possible data sources as a starting point for performing a cost-of-illness study using the societal or health care system perspective. This is not an exhaustive list of data sources.

Common Illnesses

National datasets are appropriate for more common illnesses, such as diabetes, cardiovascular disease, asthma, cancer, and others with relatively high prevalence rates. Table 5 presents possible data sources for calculating medical costs using a prevalence-based approach. The data sources for utilization rates and costs vary by type. While data of annual costs can be used for the calculation of lifetime cost estimates, as mentioned earlier, incidence-based studies may also require illness-specific data on the course of the illness. One example of this is the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, which provides incidence and survival data for various types of cancer.

Table 5. Data Sources for Calculating Medical Costs of Common Illnesses

Type of Care	Source
Sources of Health Utilization Data	
Inpatient Care	National Inpatient Sample (HCUP/NIS) National Hospital Discharge Survey (NHDS)
Outpatient Physician Care	National Ambulatory Care Survey (NAMCS)
ER and Hospital Outpatient Care	National Hospital Ambulatory Care Survey (NHAMCS)
Ambulatory Surgery	State Ambulatory Surgery Database (SASD)
Nursing Home Care	National Nursing Home Survey (NNHS)
Home and Hospice Care	National Home and Hospice Care Survey (NHHCS)
Mental Health Care	National Comorbidity Survey-Replication (NCS-R)
Prescription Drug Use	Physician Drug and Diagnosis Audit (Verispan's Vector One)
Multiple Types of Care	Medical Expenditure Panel Survey (MEPS) Medicare/Medicaid claims
Sources of Health Care Cost Data	
Care, Drugs, Other expenses	Medical Expenditure Panel Survey (MEPS) [linked to NHIS] Medicare Standard Analytic Files (SAF)
Wholesale Prescription Drug Prices	Red Book

The data sources in Table 5 are most useful when used with either the bottom-up approach or the econometric approach. The bottom-up approach combines utilization data with cost data by type of care. Using diabetes as an example, the utilization rate of outpatient physician care for people with diabetes from the National Ambulatory Medical Care Survey (NAMCS) can be combined with the unit cost of outpatient physician care for diabetes patients using either Medical Expenditure Panel Survey (MEPS) or Medicare claims data. The econometric approach can be used with either MEPS or Medicare claims data.

The more specific utilization datasets are less appropriate for the econometric approach because the econometric approach tends to use one large, national dataset rather than adding together pieces from many datasets. The data sources in Table 5 can be used with the top-down

approach, although additional data would be needed to calculate the population-attributable fractions.

Sources for calculating indirect costs are based on the use of the human capital method. Mortality costs are calculated as the lost earnings due to premature mortality. Mortality data, including age and cause of death, can be obtained from the National Center for Health Statistics' Division of Vital Statistics, including the Mortality Data, Multiple Cause-of-Death Public-Use Data Files or the Compressed Mortality File from CDC Wonder. The number of years of life lost, using life expectancy data from the National Center for Health Statistics, can be combined with wage data from the BLS—including its Current Population Survey, which includes employment rates, mean annual earnings, and the mean annual value of housekeeping—to estimate total mortality costs. Indirect costs often extend far into the future, so the wage data should reflect expected increases for future years.

Social Security Administration (SSA) data on disability by condition and National Health Interview Survey (NHIS) disability data can be combined with BLS earnings data to compute the losses attributable to disability. It should be noted that SSA data would lead to an underestimate of the number of disabled people because it provides data on the number of people who receive disability benefits. The number of people who are actually disabled exceeds the number who receive benefits. Productivity loss estimates due to absenteeism can be calculated by combining MEPS and NHIS data on lost workdays with BLS wage data. However, productivity losses due to presenteeism may require additional secondary data specific to the disease of interest.

Less Common Illnesses

For less common illnesses, MEPS and other national databases can suffer from small sample size problems, especially for some demographic groups.[16] A less common disease may

have too few occurrences in the national datasets to derive meaningful cost estimates. For these diseases, other more specific datasets may be required to obtain reliable data. Medicare claims data are very extensive and can provide useful data for some less common illnesses, especially those affecting the elderly population. The drawback to Medicare data, however, is that they are not readily accessible and they are expensive to obtain.

Other disease- or population-specific datasets can provide the necessary data on health care utilization rates. For example, it is difficult to estimate accurately the costs of Alzheimer's disease or Parkinson's disease from the previous national datasets. However, data from the National Long Term Care Survey, which gathers data on the health status and health care use of the elderly, can provide utilization rate data for Alzheimer's disease, Parkinson's disease, or other diseases that primarily affect the elderly, and thus may not be well represented in a general national survey.

For some less common illnesses (e.g., autism), the existing data on medical care utilization may not be adequate. In these cases, a survey may be required to gather the necessary data. Regardless of the method used to obtain data on the utilization of medical care for an illness, the unit costs of care can be estimated using reimbursement rates from the Medicare Standard Analytic Files. These costs are combined with utilization rates to obtain medical care cost estimates, using a method similar to that for more common illnesses.

An additional issue with less common illnesses, especially those affecting the elderly, is the relatively high rate of informal care use. Informal care is often not captured in the national datasets, which may lead to a significant underestimation of the costs of illness for diseases with high rates of informal care utilization. Disease-specific studies exist that estimate the costs of informal care. However, it may be necessary to perform a survey to obtain data on the rates of

informal care. McDaid[75] provided examples of studies and a discussion of some of the issues involved in estimating informal care costs for Alzheimer's disease.

The human capital method can still be used to estimate the indirect costs for less common illnesses. These costs can be calculated using the same mortality and wage data that are used with more common illnesses. However, rates of disability and lost work time may need to be estimated with disease-specific surveys or by performing original surveys.

Risk Factors

The costs of risk factors, such as smoking and obesity, are estimated slightly differently than costs of most illnesses. Risk factors have few costs themselves, but rather cause other illnesses that may have high costs. Thus, the risk factor is rarely listed as a diagnosis, which means many of the surveys of medical care utilization for more common illnesses are not appropriate. On the other hand, certain risk factors are common, such as smoking and obesity, meaning that national databases capture the appropriate data.

Some surveys, such as MEPS and NHIS, include responses to behavioral questions as well as height and weight information that can be used to estimate the cost of smoking and obesity, respectively. Because the cost of risk factors is measured largely by the illnesses they cause, a method of attributing the medical costs to the risk factor is necessary. Either an econometric or an epidemiological approach using a PAF is used. Thus, the top-down or econometric approaches are more appropriate than the bottom-up approach for measuring the costs of a risk factor.

Indirect costs can be calculated using the same human capital method that is used for other diseases. NHIS and MEPS data on absenteeism and CDC mortality data can be used, but a calculation must be made of the amount of missed work time and the number of premature

deaths that are attributable to the risk factor. These calculations are not trivial, and controversy exists about the correct figures to use.[76] BLS wage data can still be used in the indirect costs estimation. Data on attributable disability and absenteeism may have to be estimated from risk-factor-specific or original surveys for less common risk factors.

SENSITIVITY ANALYSIS

Sensitivity analysis is recommended anytime there is uncertainty.[77] Cost-of-illness studies rely on estimates with varying degrees of uncertainty and they should examine and vary the assumptions made to determine the range of possible values the costs of illness can take. A study should provide estimates with several different discount rates, illness prevalence rates, and any other variables that may have potentially different values. While point estimates are more useful for bringing attention to the costs of an illness, a range of possible costs has more credibility for health policy analysis.[27,37]

COST-OF-ILLNESS GUIDELINES: WHAT YOU NEED TO KNOW

COSTS

- Direct medical costs include hospital inpatient, physician inpatient, physician outpatient, emergency department outpatient, nursing home care, hospice care, rehabilitation care, specialists' and other health professionals' care, diagnostic tests, prescription drugs and drug sundries, and medical supplies.
- Direct nonmedical costs include transportation, relocation, and expenses to change diet, house, car, etc.
- Research, training, and capital costs of care are not included.
- Indirect costs include mortality costs, morbidity costs, informal care costs, and losses due to crime.

PERSPECTIVE

- The research question guides which perspective is appropriate.
- The societal and health care system perspectives are the most comprehensive and most often used. However, additional perspectives may also be used to provide information about the costs to a particular group.

INCIDENCE-BASED AND PREVALENCE-BASED STUDIES

- Incidence- and prevalence-based estimates will generally be equivalent if the costs all occur in one year.
- If the costs extend past one year, incidence-based estimates provide information about the cost of averting a case, whereas prevalence-based estimates provide a snapshot of current costs.

INDIRECT COSTS

- For practicality, the human capital method is generally recommended.

TOP-DOWN, BOTTOM-UP, AND ECONOMETRIC APPROACHES

- The top-down approach requires additional data about the causal pathway to calculate the population-attributable fraction.
- The bottom-up approach combines unit cost data with utilization data, which means it can be useful for less common illnesses.
- The econometric approach is most appropriate with a large, national dataset and is especially useful for risk factors.

DEFINITION OF ILLNESS AND COMORBIDITY

- For illnesses with significant comorbidities, an incremental approach is recommended to ensure the inclusion of all appropriate costs.

DATA

- Large national datasets are always appropriate, although they may suffer from small sample size for some less common illnesses.
- For less common illnesses, additional data are required, often in the form of population- or disease-specific datasets and surveys.

DISCOUNT RATE

- A 3 percent discount rate is most common, although using multiple rates is recommended to observe the effect of changing the discount rate.

SENSITIVITY ANALYSIS

- Applying different values for factors where uncertainty exists is recommended to determine the possible range of costs.

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