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Understanding cost-effectiveness

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Abstract

Healthcare delivery in the USA and abroad has changed dramatically over the last several decades. Along with the growth in diagnostic and therapeutic interventions, the costs of healthcare have escalated out of proportion relative to other aspects of the economy. This growth has fostered careful scrutiny of both the effectiveness and efficiency of healthcare delivery. Because of this emphasis on the economics of healthcare, physicians require an understanding not only of the efficacy and clinical utility of their interventions, but also of the relative value in an economic sense of their efforts. In other words, physicians in the modern era must now appreciate the concept of cost-effectiveness. Cost-effectiveness and cost–utility analyses are critical evaluative tools. Explicit data on comparative cost-effectiveness are useful for allocating the increasingly stretched healthcare resources. This article provides a primer for understanding the methods and applications of cost-effectiveness and cost–utility analyses.

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Introduction

Over the last several decades, healthcare expenditure in the USA has escalated disproportionately with regard to the general rate of inflation. Healthcare now accounts for a staggering $2.1 trillion annually, representing 16% of the US gross domestic product (http://www.oecd.org/dataoecd/48/4/33727936.pdf (last accessed 27 November 2006)). This means that for every $1 spent in the economy, 16 cents goes towards healthcare. This relative amount of spending exceeds the costs of healthcare in nearly every other nation, including those that provide universal healthcare to their citizens. These extensive healthcare expenditures are not necessarily inappropriate. To determine whether costs are 'appropriate', one key issue is value. Any level of spending may be acceptable, depending on the value provided by that investment. Unfortunately, emerging facts about medical errors and their costs [1], as well as our improved appreciation of the challenges of translating evidence into practice [2], underscore the fact that healthcare delivery is fraught with excess and waste.

Along these lines, and specifically for infectious diseases, there has been a growing focus on healthcare-associated infections (HAIs) as a marker of the quality of healthcare delivered. Recent data suggest that in the USA there are 1.7 million episodes of HAI annually, resulting in 99 000 excess deaths, costing the healthcare system over $35 billion [3,4].

These, and similar, revelations have prompted an increased examination of and changes in the practice of medicine, with an eye towards questions of resource allocation and efficiency. Moreover, there has been a general impression that a more vigorous move towards applying 'evidence-based medicine' could be a means for improving both clinical and economic outcomes [5]. In view of the sharply escalating costs, however, this effort to translate the results of clinical research into clinical practice must necessarily focus on efficiency. Conceptually, efficiency represents the notion of attempting to obtain the most value and output for every dollar spent. Hence, there is a growing interest in quantifying the value of our healthcare interventions, which necessarily relies on applying the methods of health economics. In this

article, we review some of the central methods of cost evaluation in healthcare, and provide examples of how they have been used in the recent literature.

Methods for Evaluating Healthcare Costs

There are five major types of cost analysis: (i) cost minimization; (ii) cost–benefit; (iii) cost–consequence; (iv) cost-effectiveness; and (v) cost-utility—the last two are encountered most frequently in the medical literature. Briefly, cost minimization compares two interventions that produce identical effects; such situations do not arise frequently. Cost–benefit analysis examines both costs and benefits in terms of monetary units, and cost–consequence is a type of analysis in which costs and consequences are listed separately. Cost–consequence analysis therefore allows the end-users to choose the costs and the consequences most relevant to their situations.

In medicine generally, and in infectious diseases specifically, most research has taken the form of either cost-effectiveness analyses (CEAs) or cost–utility analyses. Cost-effectiveness refers to analyses that examine the ratio of the cost of a particular intervention to a chosen unit of effectiveness. The need for CEAs and cost–utility analyses (these terms are sometimes used interchangeably) usually arises when the value proposition of a new intervention is unclear. When a new therapy, A, is cheaper and more effective than its comparator, B, it is said to 'dominate' the comparator—and in such a case (albeit rare in medicine) the decision to adopt therapy A is easy. Conversely, A is said to be dominated by B if A is less effective and more costly than B. As with the initial example, one's preference is clear and one does not require a formal evaluation. Ambiguity, on the other hand, arises when either: (i) new therapy A is more effective and more costly than comparator B; or (ii) new therapy A is less effective and less costly than comparator B. Under these circumstances, it becomes important to articulate the resource expenditure per unit of effectiveness. Put another way, one needs a formal means for balancing the trade-offs between the two interventions, so that one can make a rational decision that maximizes outcomes. Recognizing that CEAs had become an important evaluative tool in medicine, a Panel on Cost-effectiveness in Health and Medicine convened in the mid-1990s to 'develop consensus-based recommendations for the conduct of cost-effectiveness analysis' [6].

Perspective

'Perspective' refers to the point of view one takes when conducting a CEA. It is critical to establish the perspective utilized in any cost analysis. Perspective is crucial because it determines which costs and outcomes are likely to matter more than others. For example, in an intensive-care unit (ICU) study, the cost of averting one case of ventilator-associated pneumonia (VAP) is borne almost completely by the hospital, and this is therefore an outcome that is important from the hospital's perspective. To the patient, however, the development of VAP may affect morbidity but not necessarily the direct costs that the patient must pay. Other perspectives may represent those of payers, pharmacies, the ICU (as a cost centre) and others. Clearly, shifting of certain costs may be attractive to those whose costs are diminished, and far less so to those who must bear the additional cost burden. As one can see, the costs and benefits of any intervention may not be borne equally, and therefore if one does not look at these variables from a broad enough perspective, one might develop a skewed assessment of an intervention. Taking the broadest approach to perspective helps avoid a potential bias in CEA. This dilemma led to the principle in CEA that one should adopt a societal perspective. From a societal vantage, one can incorporate all costs, no matter on whom they individually fall. When reading CEAs, readers can quickly ascertain whether the authors have utilized a societal perspective. Generally, such articles will describe results in terms of a reference case. The reference case describes the baseline scenario that the analyst is exploring, and serves as the frame of reference for other comparisons. The reference case incorporates quality-adjusted life-years (QALYs) in the denominator of the cost-effectiveness ratio. This, by definition, represents the societal perspective, and is therefore most important for public health and overall resource allocation.

Recognizing the need to be explicit regarding the perspective taken, the Panel on Cost-effectiveness in Health and Medicine recommends that every CEA include a reference case [6]. The calculation of the reference case requires a longer-term evaluation of both costs (lifetime healthcare costs) and effectiveness outcomes. Included in the denominator are not only expected years of survival, factoring in the specific life-expectancy for survivors of the disease in question, but also the quality of life of those years. This is necessary because some interventions or therapies may restore a person to perfect health, whereas others, while extending life, still leave the person in a debilitated state. Reliance on the concept of QALYs is necessarily utilitarian from a philosophical perspective, and is fraught with ethical issues. This fact demonstrates why CEA cannot be applied either as a trump in policy analysis or in the absence of a framework for ensuring that important societal values are not vitiated.

The usual denominator in cost–utility studies is the QALY, and cost per QALY serves as the reference case. Additionally, reference cases are useful because they provide a baseline scenario against which to compare alternative resource allocation decisions—it is valid to compare the costs per QALY in reference cases across unrelated conditions and interventions. Whereas data regarding long-term outcomes for chronic conditions may be broadly available for researchers to apply in CEA, those for acute and short-lived episodes, such as those that arise with infectious disease, may not exist. To circumvent this challenge, investigators regularly adopt the technique of decision modelling.

Examples of modelling

A recent study by Angus *et al.* [7] of drotrecogin alfa (activated) in severe sepsis represents a CEA in the setting of an infection that incorporates both real-time data from a clinical trial and modelling. In this study, the investigators examined the incremental healthcare costs associated with one death averted at 28 days as a result of treatment with drotrecogin alfa (activated). To determine overall costs, the authors needed not only to establish the costs of drotrecogin alfa (activated), but also to take into account the fact that survivors require continued care and thus consume further healthcare resources. In other words, treatment with drotrecogin alfa (activated) has many implications beyond just the costs related to purchasing the drug. Angus *et al.* estimated that drotrecogin alfa (activated) cost society $160 000 per one life saved. In determining the reference case, which required estimating the life-expectancy of sepsis survivors and the quality of their additional years of life, the authors found that drotrecogin alfa (activated) cost $48 000 per QALY [7]. This ratio improved to $27 000 per QALY when the estimated risk of short-term death increased, and worsened dramatically, exceeding $100 000 per QALY, if the survivors had an overall estimated life-expectancy of <5 years.

For this study, the cost per death avoided was calculated on the basis of the actual data collected in the trial, but the cost–utility ratio was based on a modelling exercise. In the model, assumptions about long-term outcomes, based on previous work in septic populations, were put into a mathematical formula, which, in turn, generated the outcome estimates of interest. This is a preferred approach to building a reference case, as practical considerations, such as the urgency of the need for cost-effectiveness information and the enormous resources required, preclude real-time collection of the actual long-term outcomes.

CEAs in infectious disease have also dealt with issues that inform public policy decisions when society is faced with a novel health threat. For example, Khazeni *et al.* [8] examined the costs and effectiveness of a public health intervention—vaccination against pandemic influenza (H1N1). Utilizing a compartmental epidemic model along with a Markov analysis, and inputting well-documented assumptions, the authors concluded that vaccinating approximately 40% of the population of a hypothetical US city (population 8.3 million) in October or November 2009 would not only be life-saving, but also cost-saving. In the reference case, for instance, vaccinating 40% of the at-risk population in October would add nearly 70 000 QALYs and save $469 million [8].

Another example of using modelling to arrive at a reasonable epidemic response is a recent study by Dan *et al.* [9]. In their model, the investigators attempted to define the most balanced approach to H1N1 hospital outbreak prevention in Singapore. They began their analysis by taking into account their local experience with the SARS epidemic. The authors examined the cost-effectiveness of a five-level response, considering both viral and outbreak characteristics. The five levels of response ranged from Green, representing the situation when no active virus is circulating, to Red, when a pandemic is underway and viral import into Singapore is inevitable. In this simulation exercise, based on assumptions about the infectivity and case-fatality rate of H1N1, with the Green level of response (e.g. corresponding to personal protective equipment for healthcare workers in direct contact with infected patients) all but a single death in the population would be averted in the model. They estimated that this would occur at a cost of $23 000. Although, under their proposed Yellow level of response, all H1N1 deaths would be averted, preventing each additional death would cost $828 000. Escalating the alert to Red level would reduce further infections, but would not have an additional impact on mortality. In this scenario, the overall costs would reach an untenable $2.5 million to avert one H1N1-related death. Clearly, the model by Dan *et al.* illustrates the usefulness of defining different scenarios explicitly and transparently in order to model the implications of alternative options and thus to allow one to institute the most sensible healthcare policy [9].

Incremental cost-effectiveness ratio

Comparative effectiveness research (CER) represents a useful application of CEAs and cost–utility analyses. The purpose of CER is to compare explicitly the effectiveness of two interventions used for the same condition. Although, as a point of policy in the USA, the place of cost analyses remains vague, some have advocated that cost-effectiveness is an essential component of CER [10]. The single value representing comparative cost-effectiveness is the incremental cost-effectiveness ratio (ICER).

Shorr *et al.*, for example, explicitly examined the cost-effectiveness of linezolid as compared with vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* VAP [11]. Here, the ICER was calculated as the ratio of the differences in costs to the differences in effectiveness measures of the two therapies being compared. By definition, the lower the ICER, the better the cost-effectiveness profile. Methodologically, Shorr's study relied fully on a model-building approach, examining multiple outcomes of interest. In the base-case analyses, the estimates were approximately $67 000, $22 000 and $30 000 for incremental costs per survivor, per life-year saved, and per QALY, respectively [11].

Sensitivity analyses

Because model inputs are based on assumptions, albeit optimally derived from the literature, they necessarily include a degree of uncertainty. Sensitivity analyses are designed to estimate how this uncertainty in the assumptions may impact on the precision of the outcome estimates [6]. These sensitivity analyses usually include univariate (where one input is varied at a time), two-way (where two of the inputs with the strongest effect on the outcome variability are varied at the same time) and multivariate (where all of the inputs are varied at the same time across their plausibility ranges) analyses. Readers should look sceptically at CEAs that do not report sensitivity analyses. For example, in a recent cost-effectiveness simulation of the silver-coated endotracheal tube as a VAP-preventive measure, the authors found the intervention to be overall cost-saving in the base case [12]. Because univariate analyses indicated that VAP costs and the risk reduction resulting from use of the novel endotracheal tube accounted for most of the uncertainty in the model, a two-way sensitivity analysis was performed in which these parameters were altered simultaneously across their respective ranges of uncertainty. The extent of uncertainty employed in sensitivity analyses is most appropriate if derived from actual clinical data, and should represent the 95% CIs around various point estimates. In the endotracheal tube study, the sensitivity analysis revealed outcome estimates ranging from savings of $34 000 to an expenditure of $205 to prevent one case of VAP [12].

Another useful sensitivity analysis is a worst-case scenario analysis, where all inputs are biased against one of the comparators (usually the novel intervention). In a study of the cost-effectiveness of micafungin as compared with fluconazole for empirical treatment of cadidaemia in the ICU, the calculated cost per QALY was $35 000. In the worst-case scenario, the cost–utility ratio gave a cost of $72 000 to save one additional QALY [13]. A further threshold analysis was performed in the same study [13]. Because cost estimates can be exquisitely sensitive to the population studied, the authors sought to evaluate the threshold impact of azole resistance that would push the cost–utility ratio into the traditionally non-cost-effective range of >$100 000 per QALY. Gradual adjustment of this input suggested that when the prevalence of azole resistance reached 1.5%, micafungin was no longer cost-effective relative to fluconazole [13].

Inflation adjustments and discounting

Two other recommendations by the Panel on Cost-effectiveness in Health and Medicine, to adjust costs for inflation and to discount both future costs and effectiveness estimates, can be used as markers of the study's quality [6]. Inflation adjustment is necessary for several reasons. Because medical cost inflation shifts rapidly, costs need to be adjusted to the current time. In other words, a dollar spent today is not of the same true value as a dollar spent in the future. More importantly, because cost parameters may be derived from varied sources that make calculations in different years, inflation adjustment to the same year is applied for the sake of uniformity and to simply be able to 'compare apples with apples'.

Furthermore, humans value money and other goods more in the current time than in the future. This also explains why one needs to discount future costs and outcomes. Therefore, any analysis quantifying future costs (e.g. lifetime healthcare costs) and outcomes (e.g. QALYs) needs adjustment for this factor. More importantly, these adjustments must be made in both the numerator and the denominator of any cost-effectiveness ratio. The recommended annual base discount rate is 3%, with the range around it being between 0% and 7% [6].

Types of cost

There are several terms that readers should understand as they relate to types of cost. An important distinction exists between charges and costs. Charges reflect the desired reimbursement rates for a hospital or a healthcare provider. Included in this value may be not only the true expenditures for the care along with some measure of reasonable profit, but also profit-maximizing strategies [14]. Because of this and the highly variable nature of charges, costs are the preferred numerator for CEAs. Costs are meant to represent the actual consumption of resources, whereas charges simply represent an accounting tool.

Costs can be derived from charges on the basis of the published hospital-specific cost/charge ratios from Medicare. Costs can also be direct, indirect or intangible. Similarly, they can be either fixed or variable. Direct costs are those of

labour and goods utilized in the delivery of the intervention. Indirect costs, on the other hand, are those attributable to lost productivity resulting from illness. Intangible costs incorporate the pain and suffering resulting form the disease and/or intervention. Fixed costs are those that remain the same regardless of the amount of production output. In a hospital setting, these include costs associated with running the physical plant and equipment. Variable costs are those that do tend to change in the short term with the changes in production output, such as costs of having to increase the number of nursing staff because of a temporary surge in ICU volume.

There is controversy regarding whether CEA should address fixed, variable or total (the sum of fixed and variable) costs. This dilemma is particularly acute when costing out a disease or an intervention in the ICU. Although most studies take the total cost approach, it appears that variable costs may be more subject to being influenced by interventions [15]. In other words, one cannot save 'fixed' costs—they will accrue no matter what transpires. At the same time, however, fixed costs are also subject to external pressures, albeit over longer periods of time. Therefore, they need to be taken into account. Analysing fixed vs. variable costs can result in vastly different estimates of the cost of an illness. For example, according to a study by Dasta *et al.* [16], the total cost for the first day of ICU care in the USA for a patient with respiratory failure approaches $8000. However, this cost diminishes for subsequent days to $3600–3900 (2002 $US). Conversely, Kahn *et al.* [15] calculated that the direct variable costs of the last ICU day in a cohort of similar patients who survived beyond ICU day 3 was $400, with the first ward day cost totalling only $280. On the basis of this accounting, a hypothetical intervention that reduces the ICU length of stay (LOS) by 1 day saves the hospital only $120. Alternatively, if the data from Dasta *et al.* were utilized in a CEA, entirely different conclusions might be drawn.

Are bundled interventions cost-effective?

Translating evidence into practice generally relies on adopting a conglomeration of interventions, rather than a single treatment. Hence, it is important to ask whether some of the currently recommended bundled interventions for quality improvement are cost-effective. Two such potentially costly bundled strategies include early goal-directed therapy (EGDT) for sepsis and a shift to a 24-h intensivist model for ICU staffing. Huang *et al.* examined the cost-effectiveness of EGDT from both the hospital and societal perspectives. They concluded that EGDT had a nearly 100% probability of being cost-effective at a value of <$20 000 per QALY [17]. On the other hand, the cost-effectiveness of different models of ICU coverage remains poorly understood. For example, a 24-h intensivist model for ICU coverage is thought to be cost-saving from the perspective of the hospital—the intensivist approach can improve outcomes, enhance patient flow, and focus on prevention [18]. However, this policy's cost-effectiveness from the societal perspective has not been definitively shown. The savings associated with implementation of this model derive largely from an anticipated reduction in the ICU and hospital LOS. On the one hand, it seems quite reasonable to believe that a 24-h intensivist model will not alter post-ICU survivorship, either in the intermediate or in the long term. As a result, any savings from a near-term shortening of LOS may be offset by an increase in post-hospitalization mortality or a reduced duration of survival [19]. Again, this conundrum illustrates the need to be explicit about perspective and sensitivity analyses when conducting CEA.

Strikingly, some of the bundled interventions for HAI prevention, which many strictly advocate, have not been evaluated either for their effectiveness or for their cost-effectiveness. One such example includes the Institute for Healthcare Improvement's ventilator bundle [20]. In a recent systematic review of studies evaluating bundled interventions for prevention of VAP, the authors found weak evidence for the effectiveness of this approache. More importantly, they found no rigorous evaluations of the cost-effectiveness of ventilator bundles for avoiding VAP [21]. As more and more bundled strategies are promoted as quality measures and criteria for reimbursement, a critical approach to their cost-effectiveness becomes essential. Although, for example, preventing VAP is important, the resources available to accomplish this are limited, and reflexive adoption of some strategies for this might result in the diversion of resources from more cost-effective approaches.

Conclusions

The rapid growth in healthcare expenditure has engendered careful scrutiny of the practice of medicine with regard not only to effectiveness, but also to efficiency. This shift necessitates that physicians understand the effectiveness of their interventions and the cost at which this effectiveness is obtained. CEAs and cost–utility analyses have become critical evaluative tools in medicine. Explicit articulation of comparative cost-effectiveness facilitates the determination of how to allocate limited resources. As physicians encounter CEA in the literature, they must evaluate such studies as they would any clinical study—with caution, scepticism, and attention to the methods utilized.

Transparency Declaration

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