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EVALUATING THE COST-EFFECTIVENESS OF CLINICAL AND PUBLIC HEALTH MEASURES*

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ABSTRACT

Cost-effectiveness analysis, an analytic tool that expresses as a ratio the cost of obtaining an additional unit of health outcome, can help decision makers achieve more health protection for the same or less cost. We characterize the state of the cost-effectiveness analysis literature by reviewing how this technique is applied to various clinical and public health interventions. We describe the results of cost-effectiveness analyses for over 40 interventions to reduce cancer, heart disease, trauma, and infectious disease. The cost-effectiveness ratios for these interventions vary enormously, from interventions that save money to those that cost more than $1 million per year of life gained. The methods used to derive the cost-effectiveness ratios also vary considerably, and we summarize this variation within each health area. Greater uniformity of analytical practice will be necessary if cost-effectiveness analysis is to become a more influential tool in debates about resource allocation.

Introduction

As pressures to control spending in the health sector accelerate, there is a need for the implementation of efficient therapeutic and preventive interventions. The trend toward managed care, for example, has caused an increased degree of scrutiny of the costs and effectiveness of surgical and pharmacologic interventions. Efforts at regulatory reform are also causing public health and environmental agencies to reevaluate whether the effectiveness of existing and proposed policies justifies anticipated costs. Thus, decision makers throughout the health sector of the economy are looking for insight into how to weigh the competing demands for reduced cost and enhanced effectiveness.

Cost-effectiveness analysis (CEA) is an analytic tool that can be used to evaluate the outcomes and costs of interventions designed to improve health. Unlike cost-benefit analysis, which seeks to express effectiveness as well as cost in a common unit (i.e. money), CEA provides ratios that show the cost (in monetary terms) of achieving one unit of health outcome (75). The measures of health outcomes most commonly employed are the number of lives, life-years (LYs), disability-adjusted life-years (DALYs), and quality-adjusted life-years (QALYs) gained. When interventions can vary in intensity (e.g. dosage) or periodicity (e.g. frequency), incremental cost-effectiveness (C/E) ratios are calculated, so that the ratio expresses the additional cost per each additional unit of outcome obtained. Interventions can be ranked according to their (incremental) cost-effectiveness ratios and a fixed budget can then be allocated to achieve maximum effectiveness.

In this article, we characterize the state of the CEA literature by reviewing how this analytic tool is applied to various clinical and public health interventions. We also report cost-effectiveness (C/E) ratios for selected interventions. The article focuses on specific interventions aimed at four important health problems in the United States: cancer, heart disease, trauma, and infectious disease. We chose these four health problems because they constitute the leading causes of death for the population. Annually, they account for more than 1.2 million deaths (9, 10) and 7 million hospital admissions in the United States (68).

Although we acknowledge the considerable contribution of the international CEA literature, we restricted our review to domestic analyses. Only studies that used lives saved, LYs, or QALYs as the health outcome were considered for review, although we recognize that studies using other measures of effectiveness can also provide useful information to policy makers. Where possible, we included examples of primary, secondary, and tertiary prevention measures. Our selected analyses were identified from one or more of the following sources: Medline, Current Contents and CancerLit for the years 1990–1996, the Harvard Center for Risk Analysis Life-Saving Database (63), and recent government

publications. We believe that the convenience sample presented here captures the current analytical practices in academia, government, and private industry.

In our review, we gave special attention to the nature of the intervention, the intervention against which it was being compared (i.e. the comparator), the population affected by the intervention (i.e. the target population), the health outcome used, the analytical assumptions (e.g. perspective, costs considered, discount rate), and the C/E ratios. We have summarized this review in four tables that describe the interventions, comparators, target populations, and C/E ratios for each analysis. We do not assess the overall quality of these studies (or the quality of the underlying data on effectiveness and cost) since this task is beyond the scope of this short survey. We evaluated the degree of consistency in the analytical practices among these studies, since the Panel on Cost-Effectiveness and Medicine (a group of experts commissioned by the US Public Health Service) has recently recommended more uniformity in the conduct of CEA in medicine and public health (23, 73).

For some interventions we recomputed the C/E ratios to improve the comparability among studies. Our recomputed C/E ratios included (depending on data availability): (*a*) updating the costs to 1995 US dollars using the all-items component of the Consumer Price Index (67); (*b*) discounting both future costs and health benefits by 3%; (*c*) computing LYs using the age distribution of the population affected by the condition and the US life expectancy tables (70); (*d*) computing QALYs using either quality weights as described in the Beaver Dam Health Outcomes Study (22) or the quality weights described in the Functional Capacity Index (42); (*e*) incorporating the morbidity benefits of the interventions; and (*f*) incorporating costs that had not been included in the original papers. Throughout the paper, costs and C/E ratios are presented in 1995 US dollars (unless otherwise noted) and have been rounded to two or three significant figures. The specific changes relevant to each of the recomputed C/E ratios are noted in the following sections.

Cancer

We reviewed analyses of 12 cancer interventions including three primary, five secondary, and four treatment interventions. The primary prevention studies were the US Food and Drug Administration's (FDA) analysis of the costs and benefits of regulations to restrict cigarette sales to minors (69); an assessment of the cost-effectiveness of initiatives to reduce exposure to indoor radon (43); and an analysis of the costs and effects of reducing exposures to methylene chloride in the workplace (71). The secondary prevention studies included analyses of Pap smears for women aged 20 to 75 (15), Pap smears for women older than 65 (18), annual fecal occult blood tests (FOBT) to screen for colorectal cancer

(16), annual mammography for women aged 55 to 65 (14, 41), and annual mammography for women aged 40 to 50 (14). The treatment interventions included treatment strategies for breast cancer (28, 60), metastatic non-small cell lung cancer (59), and chronic lymphocytic leukemia (72). A more detailed description of each study follows.

The FDA analysis of the cost-effectiveness of the restriction of cigarette sales to minors (69) was based on the premise that 25% of potential new smokers will not begin smoking due to the new restrictions. The health outcome used in the study was the number of LYs saved by the intervention. Costs to tobacco manufacturers, retailers, consumers, and federal agencies were estimated to be $172 million, implying a C/E ratio of about $840 per LY. Even if the new restrictions were assumed to prevent only 10% of potential smokers from starting the habit, the C/E ratio was $2000 per LY.

The CEA of programs to reduce exposure to indoor radon (43) based its intervention effectiveness on epidemiological studies of lung cancer in occupationally exposed uranium miners. Reducing residential radon levels to 20 pCi/liter or less was estimated to cost $130,000,000 and save 220 lives annually. The authors did not discount future health effects nor did they estimate the cost per LY saved. By applying a 3% discount rate and converting lives saved to LYs, we recomputed a C/E ratio of $47,000 per LY. Further adjustment of the LYs to reflect average health-related quality-of-life (22) yielded a C/E ratio of $57,000 per QALY.

The costs and benefits of reducing the permissible exposure to methylene chloride in the workplace were assessed during an Occupational Safety and Health Administration rulemaking (71). Using data regarding the toxicity of methylene chloride in rodents, the agency estimated that lowering the exposure limit from 500 parts per million (ppm) in air to 25 ppm would prevent 31 cancer deaths and three acute toxicity deaths per year. The annualized cost of implementing the stricter exposure limits was estimated to be $101 million (1994 dollars). The authors of the analysis did not discount future health effects. We recalculated a C/E ratio of $160,000 per LY by applying a 3% discount rate and converting lives saved to life-years saved. Applying quality weights (22) to the LYs, we estimated a C/E ratio of $190,000 per QALY.

Eddy's analysis of breast cancer screening evaluated the effectiveness of adding annual mammography to annual physical breast exams (14). Two effectiveness estimates were available: the results of the Health Insurance Plan of Greater New York Study and the Breast Cancer Detection Demonstration Project. The C/E ratios depended heavily on the age group screened and the source of effectiveness estimates. Using results from the Health Insurance Plan study yielded an incremental cost per LY saved of $200,000 for annual mammography for women aged 40 to 50 (compared with annual clinical breast

exam only), whereas using the other effectiveness estimates yielded a C/E ratio of $43,000 per LY for the same age group and program frequency. The C/E ratios were more favorable for annual mammographic screening of women aged 55 to 65, with ratios of $32,000 and $120,000 per LY from the Breast Cancer Detection Demonstration Project and the Health Insurance Plan Study, respectively.

Lindfors & Rosenquist evaluated breast cancer screening using effectiveness estimates derived from observational data from a variety of sources, including trials conducted in the United Kingdom and Sweden and the Health Insurance Plan of Greater New York Study (41). The C/E ratios varied depending upon the frequency of screening and the age group screened. For women aged 50 to 79 the C/E ratio for a program of annual mammography was $31,000 per LY, and it fell to $19,000 per LY when the program was biennial. The reported C/E ratio of annual mammography is less favorable for women aged 40 to 50, with a ratio of $50,000 per LY. Comparisons of these ratios with those reported by Eddy (14) is limited because the C/E ratios in the Lindfors & Rosenquist study were based on a comparison to no screening, whereas those in the Eddy study were incrementally compared with less frequent screening and clinical exam. Neither of these two CEAs incorporated quality-of-life in the calculations.

The evaluation of screening tests to detect polyps and invasive cancers used a mathematical model to study the effectiveness of colorectal cancer screening strategies (16). The analysis compared a program of annual fecal occult blood testing with a program that combined annual testing plus sigmoidoscopy or barium enema at various frequencies. Coupling the effectiveness estimates with the costs of screening and follow-up procedures, Eddy estimated the C/E ratio of annual FOBT (compared with no screening) to be $14,000 per LY. The author did not incorporate quality-of-life adjustments. By applying quality weights to the years-of-life saved (22), we estimated a C/E ratio of $18,000 per QALY.

Two studies evaluated cervical cancer screening strategies. The analysis by Eddy employed a mathematical model using effectiveness data from a variety of sources (15). He estimated the C/E ratios of screening average-risk women with Pap smears at various frequencies, and his results highlight the importance of evaluating alternative screening strategies on an incremental basis. As the frequency of screening increases, the C/E ratio becomes remarkably less favorable: screening women aged 20 to 75 every four years compared with no screening yielded a C/E ratio of $14,000 per LY; screening every three years compared with every four years yielded a C/E ratio of $260,000 per LY; screening every two years and annually had incremental C/E ratios of $365,000 and greater than $1,000,000 per LY, respectively.

In the second study regarding cervical cancer screening, Fahs et al evaluated the effectiveness of screening in women older than 65 (18). They also used

a mathematical model to simulate the screening, diagnosis, and treatment of a hypothetical cohort of women. Effectiveness data came from a variety of studies, and the authors noted limitations due to the paucity of data on the natural history of cervical cancer among elderly women. Fahs et al reported both average and incremental C/E ratios for several Pap smear screening frequencies: one-time screening at age 65, every five years, every three years, and annually. They found more favorable C/E ratios than Eddy had and the same trend of increasing C/E ratios as screening frequency increases. Here we summarize only their incremental C/E ratios. Annual screening of elderly women yielded a C/E ratio of $51,000 per LY when compared with screening every three years. Using quality weights (22) to incorporate quality-of-life issues, we calculated a C/E ratio of $62,000 per QALY.

Smith & Hillner evaluated three strategies for treating early stage breast cancer: tamoxifen alone; standard cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy; or tamoxifen and CMF chemotherapy combined (60). They used a decision analysis model to evaluate the survival and quality-of-life of hypothetical cohorts of women who underwent each treatment option. The reported C/E ratios varied considerably depending on cancer node and estrogen receptor (ER) status. The most cost-effective strategy consisted of tamoxifen therapy for node-positive, ER-positive patients, with a C/E ratio of $5300 per QALY. The same treatment strategy in node-positive, ER-negative patients yielded a C/E ratio of $71,000 per QALY.

In a separate study, Hillner et al (28) constructed a similar model to compare standard chemotherapy and high-dose chemotherapy with autologous bone marrow transplantation for metastatic breast cancer. Effectiveness data were derived from a variety of sources including uncontrolled case series. The analysis was performed both with and without quality-of-life adjustments. Using a five-year time horizon, the authors found that autologous bone marrow transplantation increased life expectancy by six months compared with standard chemotherapy, for a C/E ratio of $110,000 per QALY. The authors noted that the period of time for which costs and effects are measured (i.e. the time horizon) was critical. The primary analysis evaluated costs and effects for a five-year time horizon based on the historical use of a five-year time horizon in oncology studies. In a secondary analysis, the authors used the more optimistic assumption that all patients in remission at five years had a normal life expectancy. With the longer time frame, the benefits of autologous bone marrow transplantation tripled, and the C/E ratio dropped to $32,000 per QALY.

Treatment strategies for metastatic non-small cell lung cancer were analyzed by Smith et al (59). They compared the costs and effectiveness of treatment with vinorelbine alone, vinorelbine plus cisplatin, and vindesine plus cisplatin. Their effectiveness data came from a randomized clinical trial. Compared with

vindesine plus cisplatin, vinorelbine plus cisplatin provided an additional 37 days of survival at a cost of about $1600 per patient, implying a C/E ratio of $16,000 per LY. Adjusting for quality-of-life increased the C/E ratio to $26,000 per QALY. The authors conclude that, despite chemotherapy's minimal impact on long-term survival of lung cancer patients, the C/E of treatment with vinorelbine plus cisplatin is within the limits of what is considered a reasonable societal investment for medical interventions.

Weeks et al studied the cost-effectiveness of prophylactically treating chronic lymphocytic leukemia patients with intravenous immunoglobulin (72). The authors developed a decision analysis model to compare their proposed treatment with no immunoglobulin therapy. Effectiveness estimates were derived from the results of a randomized trial. The authors found that prophylactic treatment with immunoglobulin resulted in an additional 0.0023 years of quality-adjusted life-expectancy at an additional cost of $14,000 per patient, which implies a C/E ratio greater than $7,000,000 per QALY.

Summary information from these cancer studies is presented in Table 1. The reported C/E ratios per QALY vary enormously, from less than $1000 (69) to over $1,000,000 (15, 72). Although it is tempting to make strict comparisons of the C/E ratios in Table 1, it is important to recognize the differences in how these studies were conducted and the nature of the information and assumptions that were employed.

From a methods perspective, most of the studies appeared to be performed from a societal standpoint, although few explicitly stated the analytical perspective. The number of lives saved was the metric of health outcome used in most of the primary prevention CEAs (43, 71). The analyses of secondary prevention measures were more likely to use LYs (14–16, 18), while QALYs were used in most of the analyses of tertiary measures (28, 60, 72). Quality weights were more likely to be based on physician (rather than community) preferences (60, 72) and were not routinely derived from standard gamble or time-trade-off techniques. Analysis of incremental costs was not performed uniformly. Discounting of future costs and health benefits was common but not universal (43, 72). When discounting was performed, a 5% rate was used most commonly, but a rate of 3% was also employed on occasion. The treatment of uncertainty varied considerably across studies with most including at least a limited univariate sensitivity analysis with respect to variables such as the effectiveness in mortality reduction the sensitivity and specificity of the screening tests, the costs, and the discount rate (if any).

Coronary Heart Disease

For this paper, we reviewed nine studies of coronary heart disease (CHD) interventions: three primary prevention, two secondary prevention, and four

Table 1 Cost-effectiveness ratios for selected cancer prevention interventions (1995$)

Reference	Intervention	Comparator	Target population	$ per QALY	$ per LY
69	Restriction of cigarette sales to minors	No restriction	Children <18	950*	840
60	Adjuvant tamoxifen chemotherapy	No adjuvant chemotherapy	Women, 45, with early stage breast cancer	5300	N/R
15	Pap smear every four years	No screening	Women 20–75	16,000*	14,000
16	Annual FOBT[a] screen for colorectal cancer	No screening	Population 50–75	18,000*	14,000
59	Vinorelbine + cisplatin chemotherapy	Vindesine + cisplatin chemotherapy	Patients with non-small-cell lung cancer	26,000	16,000
43	Mitigation of radon in homes	No testing or mitigation	Residents of homes with radon >20 pCi/liter	57,000*	47,000
18	Annual Pap smear	Pap smear every three years	Women >65	62,000*	51,000
28	Autologous bone marrow transplantation	Standard CMF[b] chemotherapy	Women, 45, with metastatic breast cancer	110,000	135,000
14	Annual mammography	Annual clinical breast exam	Women 55–65	150,000*	120,000
71	Methylene chloride exposure limit of 25 ppm	Methylene chloride exposure limit of 500 ppm	Workers exposed to methylene chloride	190,000*	160,000
14	Annual mammography	Annual clinical breast exam	Women 40–50	240,000*	200,000
15	Annual Pap smear	Pap smear every two years	Women 20–75	>1,600,000	>1,300,000
72	Prophylactic intravenous immunoglobulin	No prophylaxis	Patients with chronic lymphocytic leukemia	7,400,000	N/R

Notes: *QALYs were calculated by applying quality-of-life weights from the Beaver Dam Health Outcomes Study (22) to the authors' estimate of LYs saved by the intervention.
N/R = not reported.
[a]FOBT = fecal occult blood test.
[b]CMF = Cyclophosphamide, Methotrexate, and Fluorouracil.

treatments of established CHD. The three primary prevention studies involved strategies to reduce risk factors: diet modification in the community (66); antihypertensive medication (17); and pharmacological cholesterol lowering (24). The secondary prevention studies evaluated the cholesterol reduction effect of statines among patients with established coronary heart disease (24, 35). The four treatment CEAs evaluated strategies to revascularize patients with established CHD: coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) in patients with stable angina (29, 77); diagnostic coronary angiography in postinfarction patients with or without symptoms (39); and use of two leading thrombolytic agents during acute myocardial infarction (45).

The cost-effectiveness evaluation of a program to modify the diet in the community (66) used cost and effectiveness data from three community-based trials: the Stanford Three-Community Study, the Stanford Five-City Project, and the North Karelia Study. Each of these intervention studies evaluated a media-based educational approach to diet and lifestyle change involving television, radio, newspaper, and direct face-to-face education. Cholesterol reductions of 1% to 4% at per capita costs of $4.95 to $16.55 were obtained. Tosteson et al (66) used these findings as inputs to the CHD Policy Model, a computerized, state-transition model of CHD in the US population (32, 74). The CHD Policy Model employs logistic regression equations linking risk factors including cholesterol to CHD incidence, based on data from the Framingham Heart Study and other sources. Using a cost of $4.95 per person and a 2% cholesterol reduction, the resulting C/E ratio was $3400 per LY. Even at a cost of $16.55 per person, a 2% average cholesterol reduction would result in a cost per LY just over $40,000.

This analysis was limited because only total cholesterol changes were available from the source studies. It has been shown recently that diet-mediated cholesterol changes tend to reduce both serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL), the effects of which are offsetting. Thus the assumption that total cholesterol reductions observed in the community trials reduced CHD risk as much as predicted by the model could be questioned, but there is no way to infer the HDL and LDL changes that occurred in these community trials from the 1970s and early 1980s.

Edelson et al (17) assessed the cost-effectiveness of five drug classes for blood pressure reduction: a diuretic; a beta-adrenergic blocker; an angiotensin-converting-enzyme inhibitor; an alpha-adrenergic blocker; and a calcium channel blocker. Blood pressure reductions and lipid changes attributable to each monotherapy were evaluated by a meta-analysis of clinical studies of each drug. The CHD Policy Model was used to extrapolate the LYs gained and net costs in the US population aged 35 to 64. All drugs were compared individually with

no treatment. Net costs per LY were: $15,000 for the beta-adrenergic blocker; $22,000 for the diuretic; $43,000 for the calcium channel blocker; $83,000 for the alpha-adrenergic blocker; and $96,500 for the angiotensin-converting-enzyme inhibitor. Since health-related quality-of-life was not included, the differential effects of the monotherapies in this regard were not considered. Nor were the cost offsets due to diseases other than CHD considered, including stroke and end-stage renal disease.

Goldman et al (24) studied the effects of lovastatin (an HMG CoA reductase inhibitor) for cholesterol reduction. Their data on cholesterol reduction using per diem lovastatin doses of 20 mg, 40 mg, and 80 mg were based on clinical studies, but the link from serum cholesterol to CHD incidence (for primary prevention) and recurrent CHD event rates (for secondary prevention) were based on the Framingham Heart Study. Primary prevention was found not to be very cost-effective, except in population subgroups with two or more other risk factors (among smoking, hypertension, and overweight). For men aged 45 to 74, with no prior heart disease, a total cholesterol of greater than 300 mg/dl, and no other risk factors, the C/E ratio was $71,000 to $135,000 per LY, depending on age. For women with similar characteristics, the ratios were $84,000 to $390,000 per LY. The ratios were even higher for persons with serum cholesterol within the range 250 to 299 mg/dl ($105,000 to $270,000 per LY for men).

The cost-effectiveness of cholesterol reduction with lovastatin among persons with prior coronary events was markedly better. In fact, for men aged 45 to 74 who have a serum cholesterol greater than 250 mg/dl and prior CHD, use of 20 mg/day of lovastatin was found to be cost saving. For women, the C/E ratio ranged from $9800 to $18,500 per LY. Even with serum cholesterol levels lower than 250 mg/dl, secondary prevention produces favorable C/E ratios in both men ($20,000 to $31,000 per LY) and women ($37,000 to $90,000 per LY).

Like the Tosteson et al study (66) of community-based lipid lowering, the Goldman study used an early version of the CHD Policy Model that did not separate out HDL and LDL as risk factors. Nonetheless, their results were recently corroborated by a prospective randomized clinical trial of secondary prevention with simvastatin, a compound similar to lovastatin. In the Scandinavian Simvastatin Study (35), the C/E ratios ranged from $3800 per LY for 70-year-old men with cholesterol levels averaging 309 mg/dl, to $27,000 per LY for 35-year-old women with cholesterol levels averaging 213 mg/dl. This latter analysis also involved modeling of survival and costs after the conclusion of the trial.

The C/E studies of revascularization for patients with stable angina included one based solely on modeling from secondary data (77) and one based directly

on a clinical trial (29). Using decision analysis with a Markov model, Wong et al assessed the incremental cost effectiveness of angioplasty (PTCA) compared with medical therapy and CABG in different patients (77). For one-vessel disease, Wong estimated that CABG was dominated by PTCA in all groups considered. The incremental C/E ratio for PTCA compared with no revascularization was $108,000 to $112,000 per QALY in patients with mild angina, but only $7700 to $10,000 per QALY in patients with severe angina, regardless of left ventricular function. For two-vessel disease, CABG remained dominated except in patients with both normal left ventricular function and severe angina, but the incremental C/E ratio compared with PTCA was $450,000 per QALY. PTCA remained cost-effective for patients with severe angina, at $9000 to $11,000 per QALY compared with medical therapy. For patients with mild angina, the incremental C/E ratio for PTCA was $81,000 to $97,000 per QALY. For three-vessel disease, CABG remained dominated by PTCA for patients with depressed left ventricular function, but had incremental C/E ratios of $84,000 to $110,000 per QALY, compared with PTCA, in patients with normal cardiac function. PTCA had a C/E ratio of $9000 to $14,000 per QALY for patients with severe angina and $53,000 per QALY for patients with mild angina, although CABG emerges as a reasonable alternative in the subgroup with normal cardiac function.

The Bypass Angioplasty Revascularization Investigation followed the Wong analysis in 1997, and its results were quite different (29). This Investigation was a randomized experiment comparing PTCA and CABG, on an intention-to-treat basis, in patients with disease of one or two coronary vessels. The economic substudy was limited to the follow-up period of the trial itself (i.e. no LYs were assumed to be gained after the end of the trial). Thus, the gains in life expectancy for both PCTA and CABG were probably underestimated. Subject to this limitation, but with the advantage of primary data from a randomized trial, Hlatky et al (29) found that CABG was somewhat more expensive and more effective than PCTA, at an incremental C/E ratio of $26,000 per LY.

Kuntz et al (39), using a decision analysis, assessed the cost-effectiveness of coronary angiography to identify candidates for revascularization after acute myocardial infarction (AMI). Data on effectiveness were based on randomized trials comparing CABG with medical therapy, since there had been no completed trials involving PTCA at the time. The C/E ratios varied considerably as a function of patient characteristics, most notably age, prior myocardial infarction, and evidence of exercise-inducible postinfarction ischemia. C/E ratios ranged from $17,500 to $45,000 for patients 45 to 74 years old with prior AMI and exercise-inducible ischemia. The ratios increased from $63,000 to $340,000 per QALY for 45 to 74 year-olds with no prior AMI, negative stress tests, and no post-AMI angina.

The controversy over which thrombolytic (clot-busting) drug to use within a few hours after a AMI was hoped to be resolved by the trial conducted by the Global Utilization of Streptokinase and Tissue Plasminogen Activator (t-PA) for Occluded Coronary Arteries (GUSTO) group of investigators (45). The trial did not fully resolve the controversy, but it did provide an important cost-effectiveness assessment. Costs were obtained during the one-year follow-up period of the trial, and survival was extrapolated beyond the one-year follow-up using a model based on the Duke Cardiovascular Disease Database. The trial demonstrated that t-PA resulted in a gain of survival and an increased cost relative to streptokinase, with a C/E ratio of $34,500 per LY. Virtually all of the incremental cost was due to the difference between the costs of the drugs ($425, in favor of streptokinase), with a very small difference between the follow-up costs.

Table 2 contains a summary of selected items from these studies. The C/E ratios vary from less than zero (24) to $270,000 (24) per LY and from $7700 (77) to $340,000 (39) per QALY.

From a methods perspective, most of the studies appeared to be performed from a societal perspective. The number of LYs was the metric of health outcome used in all the primary and secondary prevention CEAs (17, 24, 29, 66). The analyses of tertiary prevention measures were more likely to use QALYs (29, 39, 45). Quality weights were likely to be based on physician or patient (rather than community) preferences (77). Analysis of incremental costs was performed properly. Discounting of future costs and health benefits was common at 5%, except in the study that truncated the analysis after a clinical trial (29). As the review of these studies indicates, the application of CEA to CHD interventions is becoming more common, more rigorous, and somewhat more standardized. In the future, the estimates reported here need to be updated based on new cost and effectiveness information.

Trauma

Historically, CEA of trauma prevention (also referred to as injury control) has been hampered by a paucity of effectiveness, incidence, quality-of-life, and cost information. Developments in three areas have led to an increased number of analyses over the past several years. First, studies have enhanced our understanding of the incidence and costs of injuries by body region, severity, and cause (4, 48, 57). It is now feasible to estimate resource savings associated with implementation of injury prevention policies. Secondly, there has been progress in quantifying the long-term functional limitations induced by trauma, leading to the development of the Functional Capacity Index (FCI) and other injury scaling systems (42, 61). Although it is still undergoing validation, the FCI provides preference ratings for various injuries that can be used to derive

QALYs. Thirdly, a burgeoning literature on the effectiveness of injury control interventions has accumulated. Although randomized clinical trials are rarely feasible, a variety of observational approaches are being used. In some areas, the literature is substantial enough to support initiation of meta-analyses.

We identified several evaluations of primary, secondary, and tertiary prevention interventions. Examples of primary prevention interventions are the regulation of motorcycle helmet use (50); the promotion of bicycle helmet use via legislation, education, and/or subsidization (26, 27, 64); the strengthening of side door beams in motor vehicles (51); the installation of lap-only belts in the rear-center seating position of passenger vehicles (51); the installation of lap and shoulder belts in five different seating positions (i.e. driver, front-right, outboard rear, and center-rear) (25, 51); the installation of airbags in the driver and front-right seats (25); the implementation of daytime running lights (76); the use of child restraint devices (58); and the regulation of speed limits (37). Additionally, we found several studies that evaluate the ability of hormone replacement therapy to reduce the incidence and severity of fractures (19, 36, 65). The two secondary prevention interventions evaluated the use of diagnostic procedures for blunt aortic trauma (6, 33). Tertiary prevention interventions that we reviewed included routine screening for proximal deep venous thrombosis in acquired brain injury patients (47) and an accelerated rehabilitation program after proximal femoral fracture (8).

Owing to space limitations, we selected for presentation here a subgroup of 13 primary prevention interventions from the 19 interventions listed above. Two of the interventions are aimed at preventing vehicle accidents: speed limits and daytime running lights. In his evaluation of the 55-mph speed limit (compared with a 65-mph limit) on rural interstates, Kamerud (37) reported a C/E ratio of $2,900,000 per life saved. Costs considered in the analysis include costs of enforcement, extra travel time, and vehicle wear as well as savings from lower fuel expenses. We recomputed the ratio using life expectancy data and quality-of-life weights (42) and incorporating morbidity reduction. The recomputed C/E ratios were $220,000 per LY and $82,000 per QALY.

Williams & Lancaster (76) evaluated the C/E of mandatory use of daytime running lights (compared with the current nighttime-only requirement). Due to the extremely low cost of the intervention (less than $3 per car per year in extra fuel consumption), even small reductions in the number of crashes led to cost savings (the authors assumed a 10% reduction). When we recomputed cost per LY as cost per QALY (42), the intervention became even more cost saving, since the benefits from morbidity reduction were also considered.

The remaining interventions that we reviewed involve reducing the risk of injury once the event that could lead to an injury has been initiated (e.g. a crash). Stronger side-door beams, lap or lap/shoulder belts, airbags, helmets, and child

Table 2 Cost-effectiveness ratios for selected coronary heart disease prevention interventions (1995$)

Reference	Intervention	Comparator	Target population	$ per QALY	$ per LY
77	PTCA[a]	No revascularization	Patients with severe angina and one-vessel disease	7700–10,000	N/R
39	Coronary angiography and revascularization if indicated	Medication only	AMI[d] patients, 45–74, positive exercise test or angina, and prior AMI[d]	17,500–45,000	N/R
45	t-PA[c]	Treatment with streptokinase	Eligible patients post-AMI[d]	38,000	34,500
39	Coronary angiography and revascularization if indicated	Medication only	AMI[d] patients, 45–74, negative exercise test and no prior AMI[d]	63,000–340,000	N/R
29	PTCA[a]	No revascularization	Patients with mild angina and one-vessel disease	108,000–112,000	N/R
66	Education to promote cholesterol reduction	No intervention	General population, ages 35–84	SA only	3400
17	Diuretic	No treatment	Patients, 35–64, DBP[e] > 95 mm Hg	SA only	22,000
17	Beta-adrenergic blocker	No treatment	Patients, 35–64, DBP[e] > 95 mm Hg	SA only	15,000
17	Angiotensin-converting enzyme inhibitor	No treatment	Patients, 35–64, DBP[e] > 95 mm Hg	SA only	96,500

17	Calcium channel blocker	No treatment	Patients, 35–64, DBP[e] > 95 mm Hg	SA only	43,000
17	Alpha-adrenergic blocker	No treatment	Patients, 35–64, DBP[e] > 95 mm Hg	SA only	83,000
29	CABG[b]	PTCA[a]	Eligible patients with multi-vessel disease	N/R	26,000
24	Lovastatin, 20 mg/day	No treatment	Men, 45–74, no prior CHD[f], cholesterol > 300 mg/dl	N/R	71,000–135,000
24	Lovastatin, 20 mg/day	No treatment	Men, 45–74, no prior CHD[f], cholesterol 250–299 mg/dl	N/R	105,000–270,000
24	Lovastatin, 20 mg/day	No treatment	Men, 45–74, prior CHD[f], cholesterol > 250	N/R	<0
24	Lovastatin, 20 mg/day	No treatment	Men, 45–74, prior CHD[f], cholesterol < 250 mg/dl	N/R	20,000–31,000
34	Simvastatin	No treatment	Men, 70, average cholesterol 309 mg/dl and prior CHD[f]	N/R	3800
35	Simvastatin	No treatment	Men, 35, average cholesterol 213 mg/dl and prior CHD[f]	N/R	11,400

Notes: N/R = not reported.
SA only = ratios reported in sensitivity analysis of original paper.
[a]PTCA = percutaneous coronary angioplasty.
[b]CABG = coronary artery bypass graft.
[c]t-PA = tissue plasminogen activator.
[d]AMI = acute myocardial infarct.
[e]DBP = diastolic blood pressure.
[f]CHD = coronary heart disease.

restraints belong to this category. The strengthening of vehicle side-door beams to minimize intrusion into the passenger compartment was analyzed in a regulatory analysis from National Highway Traffic Safety Administration (51). The fatality reduction effectiveness was estimated to be 18%. The outcomes used in the analysis were lives and equivalent-lives saved. The reported C/E ratio was $160,000 per LY. We recomputed the ratio by incorporating the morbidity and mortality consequences into QALYs (42); the resulting cost per QALY was $53,000.

The costs and effects of seat belts were evaluated in two studies (25, 52). Due to the different rates of occupancy by seating position, seat-belt effectiveness varied considerably by seating position (even if the belts were equally efficacious and costly at each seating position). Both lap-only and a lap and shoulder belt combination were reported to be cost saving for front-seat occupants (25, 52), even assuming only a 50% usage rate. Belts in the rear offered a different result. When lap-only belts were compared with no restraints, a C/E ratio of $430,000 per LY was derived (52). Incorporating morbidity benefits and quality-of-life weights (42) yielded a recomputed ratio of $270,000 per QALY. The addition of a shoulder belt generated an incremental C/E ratio of $420,000 per LY (or $160,000 per QALY after our recomputation). These high C/E ratios were driven by the low occupancy rates and the low seat belt use among rear seat occupants (a 9% usage rate was used). The C/E ratios were particularly high when we analyzed the rear-center only belts. Lap-only belts (when compared with no belts) had a C/E ratio of $1,300,000 per LY and $830,000 per QALY. The incremental C/E ratio of adding a shoulder belt to the lap belt led C/E ratios of $6,000,000 per LY or $2,400,000 per QALY. QALYs were computed incorporating morbidity reduction and quality-of-life (42). In the future, the cost-effectiveness ratios for safety belts in the rear seats will improve if children use the rear seats more frequently and if states adopt primary enforcement legislation that increases the rate of safety belt use in the rear seat.

Airbags offer supplemental restraint in addition to the lap/shoulder belt systems for the driver and front-right passenger. A recent analysis by Graham et al (25) that used the recommendations from the US Panel on Cost-Effectiveness in Health and Medicine (23) reported C/E ratios of $96,000 per LY and $24,000 per QALY for the driver-side airbag, and an incremental $213,000 per LY and $61,000 per QALY for the front-right airbag (compared with the driver-only airbag system).

Shew & Dardis evaluated the cost-effectiveness of child restraints for a cohort of children aged 0 to 4 years old in 1987 (58). They reported a combined C/E ratio for infant and toddler restraints. Fatality reduction effectiveness rates of 69% and 47% were assumed for infant and toddler restraints, respectively. The reported C/E ratio was $33,000 per LY. Due to the long life expectancy of the

target population, the authors performed sensitivity analysis of the discount rate. Using a 10% discount rate rather than a 5% rate slightly more than doubled the C/E ratio.

Hatziandreu et al compared the cost and effectiveness of three different strategies to increase use of bicycle helmets among children: legislation, a community-wide program, and a school-based program (27). Their outcome measure was the number of head injuries avoided among children ages 5 to 16. Using a 85% effectiveness rate in reducing the risk of head injuries, the authors reported costs per head injury avoided of $37,000, $38,000, and $144,000 for the legislative, community-wide, and school-based programs, respectively. For the legislative strategy, we recomputed a C/E ratio of $1,000,000 per LY.

Muller calculated the cost and benefits of mandatory use of motorcycle helmets (50) (compared with voluntary use). Using a 40% to 50% increase in helmet use and effectiveness rates ranging from 67% for mortality reduction and 7% for moderate injuries (and a 32% increase in minor injuries), the intervention was cost saving, whether including only mortality or both mortality and morbidity reductions.

Summary information from these studies is presented in Table 3. Readers are cautioned that the ratios reported in Table 3 are illustrative and should not be considered definitive. The reported C/E ratios per QALY for these primary prevention interventions vary from less than $0 (25, 52, 76) to more than $2,400,000 (52).

From a methods perspective, all of the CEAs reviewed employed a societal perspective. The effectiveness information was usually based on real-world observational information, though engineering judgment was sometimes employed (51). All but one of the studies (27) used lives saved as the outcome measure. Additionally, some studies used equivalent-lives saved when analysts sought to combine information on nonfatal injury with fatality information (51, 52). This method is based primarily on the relative productivity losses associated with fatalities and nonfatal injuries of different levels of severity. None of the studies used years-of-life saved or QALYs as an outcome measure. Most studies excluded intangible costs, which are an important concern about these measures (e.g. it is difficult to quantify in dollar terms the hassle associated with remembering to wear a safety belt or the discomfort of wearing a helmet on a hot day). The studies were typically careful about performing incremental analysis (25, 50, 52). Discounting of future costs was common, but not the discounting of future lives saved (50–52). When discounting was performed, rates between 3% and 10% were used. The treatment of uncertainty varied considerably across studies, with most including at least a univariate sensitivity analysis with respect to variables such as the effectiveness in mortality and morbidity reduction estimates, the costs, and the discount rate (if any).

Table 3 Cost-effectiveness ratios for selected injury prevention interventions (1995$)

Reference	Intervention	Comparator	Target population	$ per QALY	$ per LY
25, 52	Lap/shoulder belts (50% use)	No restraints	Drivers (passenger vehicles)	<0	<0
25, 52	Lap/shoulder belts (50% use)	No restraints	Passenger car front-right occupants	<0	<0
15	Compulsory helmet use	Voluntary helmet use	Motorcyclists	<0	<0
76	Daytime running lights	Nighttime lights only	All motor vehicle occupants	<0	<0
25	Frontal airbags	Manual belts (50% use)	Passenger car drivers	24,000*	96,000
51	Strengthened side door beams	Status quo occupants	Light truck	53,000*	160,000
25	Frontal airbags	Driver-only airbags	Passenger car front-right occupants	61,000*	213,000
37	55-mph limit	65–mph limit	Rural interstate travelers	82,000*	220,000
52	Lap/shoulder belts (9% use)	Lap belts	Passenger car rear seat occupants	160,000*	420,000
52	Lap-only belts (9% use)	No restraints	Passenger car rear seat occupants	270,000*	430,000
52	Lap belts (9% use)	No restraints	Passenger car rear-center occupants	830,000*	1,300,000
52	Lap/shoulder belts (9% use)	No restraints	Passenger car rear-center occupants	2,400,000*	6,000,000
58	Child seats	No child seats	Children <4	N/R	33,000
27	Mandatory bicycle helmet	No program	Children 5–16	N/R	1,000,000

Notes: *QALYs were calculated by applying quality-of-life weights from the Functional Capacity Index (42) to the author's estimate of lives saved by the intervention.

N/R = not reported.

Infectious Diseases

We restricted our review of the infectious disease-related literature to primary and secondary prevention strategies intended to reduce diseases caused by two viral infectious agents: the human immunodeficiency virus (HIV), and the hepatitis B virus (HBV). HIV causes the acquired immunodeficiency syndrome (AIDS), a disease with high mortality; hepatitis B causes a very severe form of hepatitis.

Among the hepatitis B–related studies, the primary prevention studies included the screening and/or vaccination of persons in different age groups (5, 38, 44), and the screening of blood specimens (see below). Among the HIV-related studies, the primary prevention studies evaluated behavioral interventions to prevent HIV transmission (30, 31, 56) and the screening of blood specimens (see below). The secondary prevention studies evaluated screening for HIV in acute care settings (11, 53, 54); screening for HIV in populations with varying prevalence rates (46); and alternative clinical management strategies for patients already infected (20, 21). Lastly, there were four studies that dealt simultaneously with the primary prevention of HIV and hepatitis B through the screening of blood specimens (1–3, 7).

Margolis et al (44) analyzed the prevention of HBV transmission by modeling an immunization strategy for the 1991 birth cohort. C/E ratios were assessed for three age groups: 0 to 12 months (perinatal), 1 to 5 years (infants), and 6 years and older (adolescents). Adopting the societal perspective, the authors found that immunizing all three target populations was cost saving. When indirect costs were excluded, the intervention still had relatively attractive C/E ratios: $2900, $22,000, and $29,500 per LY for the three age groups, respectively. Using quality-of-life weights (22), we recomputed the cost per QALY saved to be $3300, $25,000, and $33,000, respectively.

Bloom et al (5) assessed the cost effectiveness of two hepatitis B–prevention strategies—a screen and vaccinate program and a vaccinate-all program (without prior screening). The researchers concluded that the vaccinate-all strategy was more cost-effective. The screen and vaccinate strategy, when compared with no program, led to C/E ratios of $52,000 per LY for ages less than 3 months (newborns) and $340,000 per LY for ages 12 to 50 years (adults). We recomputed these ratios by incorporating quality-of-life weights (22); the updated costs per QALY were $58,000 for newborns and $420,000 for adults. The comparison of the vaccinate-all strategy with no program generated C/E ratios of $47,500, $120,000, and $320,000 for newborns, adolescents (10 years old), and adults, respectively. Using quality-of-life weights (22), we estimated C/E ratios of $52,000, $137,000, and $385,000 per QALY.

Modeling a similar strategy, Krahn & Detsky (38) assessed the cost-effectiveness of a universal vaccination program to protect infants from HBV. Their

analysis incrementally compared a universal screening strategy to a selective strategy that first screened pregnant women and vaccinated only the infants of mothers who tested positive. The authors reported an incremental C/E ratio of $35,000 per LY for the universal strategy compared with the selective screening strategy, and an incremental C/E ratio of $40,000 per LY for the selective strategy compared with no program.

Differences in results among these three studies stem from varying methods and data (5, 38, 44). For example, Margolis and Krahn included direct medical and nonmedical costs and indirect costs associated with lost productivity, while Bloom included direct medical costs only. Further, these studies utilized different base case input values in their calculations (e.g. the transmission rate estimated by Krahn was 38% vs 42% by Margolis).

Several studies evaluated HIV-related primary prevention strategies. Pinkerton et al (56) based their analysis on a retrospective assessment of a skills-training (i.e. condom usage) component of a cognitive-behavioral intervention for homosexual and bisexual men. Using an incremental approach, a group receiving a skills training lecture in conjunction with a safer sex lecture was compared with a group that received a safer sex lecture only. The baseline seroprevalence among the group's sex partners was estimated at 15%. A model was used to translate the observed behavior change into the number of HIV infections averted, and the number of HIV infections averted into the number of QALYs saved. The skills training intervention saved a total of 21 (discounted) QALYs as well as $185,000 in direct medical costs, suggesting that it was cost saving. In a CEA of a behavioral intervention targeting a comparable population, Holtgrave & Kelly (31) also concluded that the prevention strategy was cost saving. In a high-risk female population with a lower seroprevalence rate among sex partners (3%), another study (30) computed a C/E ratio of $2200 per QALY.

Prevalence of HIV in the general population influences the cost-effectiveness of screening and treatment interventions. For example, McCarthy et al (46) modeled the cost-effectiveness of an HIV screening program varying prevalence from a low-risk rate (0.0023% for female first-time blood donors) to a high-risk rate (50% for intravenous drug users). The incremental C/E ratio, compared with a no screening strategy, was $1,500,000 per LY for the low-risk population and $11,000 per LY for the high-risk population.

Secondary prevention aimed at screening and treating health care workers to prevent occupational transmission of HIV to patients yielded C/E ratios greater than $100,000 per QALY. Owens et al (54) found that annual, mandatory screening of surgeons costs over $1,000,000 per LY if the prevalence of HIV and the transmission rate are estimated at 0.9% and 0.29%, respectively. Mandatory screening every 10 years resulted in a C/E ratio of $4,100,000 per QALY and mandatory one-time screening resulted in a C/E ratio of $1,600,000 per QALY

(54). One study evaluated screening of all health care workers in an acute-care setting (11). Incorporating direct costs of screening only, they found a C/E ratio of $490,000 per QALY when the prevalence was estimated at 0.4% and the transmission rate was estimated at 0.24% (11). Voluntary screening and counseling for patients in an acute care setting was also found to have very high C/E ratios. With a prevalence of 1%, the C/E ratio was $97,000 per QALY if only the benefits to the patient screened were considered; if benefits to the partners of the patients were included, the C/E ratio decreased to $59,000 per QALY (53).

The quality weights used in the HIV-related studies were derived in a variety of ways. Two of the studies (53, 54) used quality weights assessed by 128 physicians and 22 AIDS patients utilizing the time trade-off methodology. Three studies (30, 31, 56) used quality weights elicited from 31 AIDS patients using a version of a rating-scale measurement.

The cost-effectiveness literature on strategies to manage and control HIV has grown as treatments and therapies to prevent the onset of AIDS in HIV-infected persons have become available. Freedberg et al (21) evaluated the impact of prophylaxis for first episodes of *Pneumocystis carinii* pneumonia (PCP) in HIV-infected individuals with CD4 counts less than 200/mm^3 and no prior history of PCP infection or AIDS diagnosis. Compared with no prophylaxis, treatment with Dapsone followed by Apent yielded a C/E ratio of $16,500 per LY. When compared with the Dapsone-Apent treatment combination, treatment with trimethoprim-sulfamethoxazole (TMP-SMX) was less effective and more costly. When compared with the TMP-SMX strategy, Apent followed by Dapsone resulted in a cost savings. In AIDS patients who had completed 21 days of PCP therapy, TMP-SMX had C/E ratios of $350 to $720 per LY, compared with no prophylaxis (20). Treatment in the same group with Apent was less effective and more costly; therefore, dominated by the TMP-SMX strategy (20).

Four studies dealt with the prevention of HBV and HIV transmission through blood donations. (These studies also incorporated the costs and benefits of detecting hepatitis C virus (HCV), another virus that produces a serious type of hepatitis.) C/E ratios from these studies ranged from $180,000 (3) to $8,100,000 per QALY (7). The latter C/E ratio was reported by Busch et al (7), who adopted a societal perspective for the inclusion of costs in their evaluation of the alanine aminotransferase (ALT) screening vs the implementation of HCV screening alone. All four studies used QALY weights derived from a consensus panel of senior clinicians and medical decision makers using a rating-scale method.

Summary information from these infectious disease studies is presented in Table 4. These interventions had C/E ratios ranging from less than zero (31, 56) to $8,100,000 per QALY (7) and from less than zero (44) to $1,500,000 per LY (46).

Table 4 Cost-effectiveness ratios for selected infectious disease prevention interventions (1995$)

Reference	Intervention	Comparator	Target population	$ per QALY	$ per LY
56	Safer sex program with skills training to prevent HIV[e] transmission	Safer sex program only	Homosexual and bisexual men	< 0	N/R
31	Behavioral intervention to increase condom usage to prevent HIV[e] transmission	No program	Self-identified gay men	< 0	N/R
30	Behavioral intervention to increase condom usage to prevent HIV[e] transmission	No program	High-risk women attending a primary health clinic	2200	N/R
44	Immunization to prevent HBV[f]	No program	Perinatal, infants, adolescents	3300–33,000*	< 0
5	Vaccinate-all to prevent HBV[f]	No program	Newborns, adolescents, adults	52,000–385,000*	47,500–320,000
53	Voluntary screening and counseling to prevent HIV[e] transmission	No screening	Patients 15–54 in an acute care setting and partners	59,000	39,000
5	Screen and vaccinate strategy to prevent HBV[f]	No program	Newborns, adults	58,000–420,000*	52,000–340,000
3	Preoperative autologous blood donation to prevent HBV[f], HCV[g] and HIV[e]	No autologous blood donation	Patients undergoing hip or knee replacement	180,000	N/R
1	Solvent-detergent to eliminate HBV[f], HCV[g] and HIV[e]	No solvent-detergent	Patients undergoing plasma transfusion	310,000	N/R
11	Screening to prevent HIV transmission to patients	Universal precautions	Health care workers in an acute care setting	490,000	N/R

2	Preoperative autologous donation of 3 units of blood to prevent HBV[f], HCV[g] and HIV[e]	Donation of only 2 units of blood	Patients undergoing CABG[a]	1,000,000	N/R
54	Screening and treatment to prevent HIV[e] transmission	No screening	Surgeons, one time only	1,600,000	480,000
54	Screening and treatment to prevent HIV transmission	No screening	Surgeons, every 10 years	4,100,000	630,000
7	ALT[b] screening of Hepatitis HBV[f] and HCV[g]	Screening for HCV[g] only	Blood donors with normal and elevated ALT[b]	8,100,000	N/R
21	Apent/Dapsone prophylaxis for PCP[d]	TMP-SMX[c] prophylaxis	HIV[e]-infected persons with CD4 <200, followed for 3 years	SA only	<0
20	Secondary prophylaxis with TMP-SMX[c] for PCP[d]	No prophylaxis	AIDS patients who have completed 21 days of PCP[d] therapy	N/R	350–720
46	Screening and treatment for HIV[e]	No screening	High-risk population (p = 50%)	N/R	11,000
21	Dapsone/Apent prophylaxis for PCP[d]	No prophylaxis	HIV[e] infected persons with CD4 <200, followed for 3 years	SA only	16,500
38	Universal vaccine to prevent HBV[f]	Selective vaccination	1991 birth cohort	N/R	35,000
38	Selective vaccination to prevent HBV[f]	No program	1991 birth cohort	N/R	40,000
46	Screening and treatment for HIV	No screening	Low-risk population (p = 0.0023%)	N/R	1,500,000

Notes: *QALYs were calculated by applying quality-of-life weights from the Beaver Dam Health Outcomes Study (22) to the authors' estimate of LYs saved by the intervention.
N/R = not reported.
SA only = ratios only reported in the sensitivity analysis of the original paper.
p = prevalence.
[a] CABG = coronary artery bypass graftig.
[b] ALT = alanine aminotransferase.
[c] TMP-SMX = Trimethoprim-Sulfamethoxazole.
[d] PCP = *Pneumocystis carinii* pneumonia.
[e] HIV = Human immunodeficiency virus
[f] HBV = Hepatitis B virus
[g] HCV = Hepatitis C virus

All of the infectious disease studies reviewed used a 5% rate to discount future costs and health outcomes in the base case analysis. Two HBV studies (5, 44) discounted benefits only when LY saved was the outcome measure of interest. Hard-to-quantify costs, such as overhead expenses, start-up (as opposed to operating) costs, and nonmedical costs were often omitted. In the estimation of health care costs for infectious diseases, a failing of the C/E literature is the omission of costs associated with chronic sequelae. Further, some studies use charges rather than costs as the basis for cost estimation, leading to considerable (yet often subtle) variation across studies. In most cases, it was not feasible to discern the quality of the effectiveness data used in these CEAs. The sources of effectiveness data included randomized controlled trials, meta-analyses of trials, and observational data from ongoing studies. The analytic treatment of uncertainty varied considerably across studies. Almost every study performed at least a limited sort of univariate sensitivity analysis with respect to main uncertain variables such as incidence of disease, disease progression rates, effectiveness values, and program costs. Several authors varied all uncertain parameters using one-way sensitivity analysis (20, 21, 31, 53, 54, 56). Although a few studies conducted multivariate sensitivity analysis (31, 53, 56), none employed probabilistic or value-of-information methods.

Conclusions

The analytical community is responding to society's demands for more and better analyses of the effectiveness and cost of clinical and public health measures. Although there is increasing interest in formal cost-benefit analysis of programs where health effects are valued in monetary terms by willingness-to-pay (34, 55), the method of CEA appears to be the most popular method of economic evaluation in the health sector (23). CEA can assist decision makers in achieving more health protection at less cost than is being accomplished under current resource allocation strategies.

It is encouraging that some of these interventions, such as the installation of lap/shoulder belts in the front seats of passenger vehicles (25) and behavioral interventions to increase condom usage in high-risk populations (31, 56), are cost saving, a fairly rare outcome in CEA studies (63). Most of the C/E ratios reviewed here clustered in the range of $10,000 to $100,000 per QALY.

The influence of CEA on resource allocation decisions is most direct when alternative interventions for a specific health problem are explicitly and rigorously analyzed in a particular study. For example, the analyst may compare different screening intervals for breast cancer, drug therapies for hypertension, strategies for increasing bicycle helmet use, or approaches to educate the populations at risk for HIV infection. A recent example of a CEA that strongly

influenced policy decisions is Lieu et al's analysis of management and treatment strategies related to the new varicella vaccine (40). At the present time, CEA is probably exerting most of its influence in these important yet narrow comparisons of interventions.

There is also interest, however, in broader uses of CEA (12, 62). CEA might be used to compare diverse interventions within a problem area (e.g. behavioral vs technological approaches to trauma prevention) or a particular target population (e.g. enhanced child health through toxin control vs trauma prevention). Should marginal dollars be transferred from cancer to heart disease interventions? In the allocation of limited research funds, marginal dollars could be transferred from one disease to another or from secondary and tertiary to primary prevention interventions. These kinds of questions are only beginning to be asked by decision makers. Managed care may offer enhanced incentives to consider resource allocation decisions more broadly at the community (covered population) level. Moreover, Congress may compel comparative CEA of agency programs in comprehensive regulatory reform legislation. So-called league tables of C/E ratios for diverse interventions are often published and used by advocates interested in supporting or opposing particular reallocations of resources. Questions have been raised about the utility of these league tables, given the current state of the art of CEA (13).

If CEA is to become a more influential tool in debates about broad-based resource allocation (either within disease categories or throughout the health sector of the economy), the analytical community needs to achieve more consensus about the methods and conventions employed in CEA. The Panel on Cost-Effectiveness in Health and Medicine of the US Public Health Service has recommended a uniform set of analytic practices that should govern Reference Case analyses in future CEAs. As this article has indicated, the analytical community has a ways to go yet to achieve the kind of uniformity in analytical practice that is necessary to inform decision makers interested in intersectoral reallocation of limited health resources.

We conclude by emphasizing what is obvious but sometimes forgotten: Cost-effectiveness is only one of the considerations that should inform allocations of limited resources. Other important factors include: notions of justice, equity, personal freedom, political feasibility, and the constraints of current law. It is important for advocates of CEA to recognize that what they have to offer should inform rather than dictate allocation of resources within the health sector of the economy.

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