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ECONOMIC EVALUATION

DEVELOPMENT OF WHO GUIDELINES ON GENERALIZED COST-EFFECTIVENESS ANALYSIS

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SUMMARY

The growing use of cost-effectiveness analysis (CEA) to evaluate specific interventions is dominated by studies of prospective new interventions compared with current practice. This type of analysis does not explicitly take a sectoral perspective in which the costs and effectiveness of all possible interventions are compared, in order to select the mix that maximizes health for a given set of resource constraints.

WHO guidelines on generalized CEA propose the application of CEA to a wide range of interventions to provide general information on the relative costs and health benefits of different interventions in the absence of various highly local decision constraints. This general approach will contribute to judgements on whether interventions are highly cost-effective, highly cost-ineffective, or something in between. Generalized CEAs require the evaluation of a set of interventions with respect to the counterfactual of the null set of the related interventions, i.e. the natural history of disease.

Such general perceptions of relative cost-effectiveness, which do not pertain to any specific decision-maker, can be a useful reference point for evaluating the directions for enhancing allocative efficiency in a variety of settings. The proposed framework allows the identification of current allocative inefficiencies as well as opportunities presented by new interventions. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — cost-effectiveness analysis; guidelines; resource allocation

INTRODUCTION

The growing use of cost-effectiveness analysis (CEA) to evaluate the efficiency of specific interventions is dominated by studies of prospective new interventions compared with current practice [1–11]. This type of analysis does not explicitly take a sectoral perspective in which the costs and effectiveness of all possible interventions are compared, in order to select the mix that maximizes health for a given set of resource constraints. The estimated cost-effectiveness of a single proposed new intervention is compared either with the cost-effectiveness of a set of existing interventions derived from the literature [12–17] or with a fixed price cut-off point representing the assumed social willingness to pay for an additional unit of benefit [18–21]. The implicit assumption that, to improve overall efficiency, resources would need to be transferred to the more efficient intervention either from another health intervention or from another sector, is rarely discussed.

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On the other hand, much of the theoretical literature has taken a broader view of cost-effectiveness, exploring its use in allocating a fixed health budget between interventions in such a way as to maximize health in a society [22–34]. This we call sectoral CEA. Only a few applications of this broader use—in which a wide range of preventive, curative and rehabilitative interventions that benefit different groups within a population are compared in order to derive implications for the optimal mix of interventions—can be found. Examples include the work of the Oregon Health Services Commission [35–40], the World Bank Health Sector Priorities Review [41] and the Harvard Life Saving Project [42,43]. Of these, only the World Bank attempted to make international or global comparisons of sectoral cost-effectiveness.

At the heart of this broadened policy use is the notion that resources in the health sector should be allocated across interventions and population groups to generate the highest possible overall level of population health. If the calculations show that some current interventions are relatively cost-ineffective, and that some which are not undertaken fully are relatively cost-effective, resources could be reallocated across interventions to improve population health. In other words, the allocative efficiency of the health sector could be enhanced by moving resources from cost-ineffective interventions to cost-effective ones.[a] Interest in the promise of enhancing allocative efficiency of health systems has led to analytical efforts to study the cost-effectiveness of a broad range of interventions in a number of countries [44,45].

Several challenges have emerged to this wider use of CEA. First, analysts and decision-makers have correctly noted that resource allocation decisions affecting the entire health sector must also take into account social concerns, such as a priority for the sick [46–49], reducing social inequalities in health [50–53], or the well-being of future generations [54,55]. Vociferous debate on the use of CEA to prioritize the use of Medicaid resources in Oregon State is one indication of these concerns in the political arena [35–40]. So far there have been two proposed responses to this challenge: abandon the practice of using CEA to inform resource allocation decisions entirely or to progressively incorporate more of these social concerns into the methods of CEA [56].

Second, current CEA practice [57,58] often fails to identify existing misallocation of resources by focusing on the evaluation of new technologies or strategies. The very wide range of cost-effectiveness ratios found in the compendia of CEAs listed above suggest that addressing current allocative inefficiencies in many countries may yield substantial health gains, possibly more than identifying new technologies that will make small improvements in health.

Third, for all but the richest societies, the cost and time required to evaluate the large set of interventions required to use CEA to identify opportunities to enhance allocative efficiency may be prohibitive. The results of many, if not most, CEA studies are so context-specific that they cannot be used to inform policy debate in another population—as reflected in the debate about the use of league tables, which include the results of studies using a variety of methods and which were undertaken to answer a variety of context-specific questions [12,14–17,59–68]. For low- and middle-income countries and smaller high-income countries, there has been little progress towards the goal of affordable and timely information on the costs and effects of a wide array of interventions to inform policy.

Fourth, the difficulties of generalizing context-specific CEA studies have been institutionalized by the proliferation of multiple national or sub-national guidelines for CEA practice, all using slightly different methods [69–91]. International guidelines have not to date been developed.

As part of the reorganization of the World Health Organization (WHO) following the election of Dr Gro Harlem Brundtland as the Director-General in May 1998, a new programme, Choosing Interventions: Effectiveness Quality, Costs, Gender and Ethics, part of the Global Programme on Evidence for Health Policy, has been established. This group is attempting to address some of the challenges of providing decision-makers with timely information on the technical and ethical characteristics of different interventions to inform health policy debates. It is collaborating with other international organizations to develop international guidelines for CEA intended in part to address some of the challenges listed here. In this paper, we outline some of the uses of CEA, the limitations of current methods, directions for revising these methods and some of the remaining technical challenges facing this revision.

TWO SECTORAL USES OF CEA

The appropriate methods, transferability of results and policy applicability of CEA depend critically on the intended use. CEA can have many applications beyond informing health sector resource allocation decisions across interventions, however, the focus of this paper is on two potential applications. They will be outlined briefly, after which the strengths and weaknesses of current methods of undertaking CEA will be discussed in relation to the two uses.

First, *CEA of a wide range of interventions can be undertaken to inform a specific decision-maker. This person faces a known budget, a set of options for using the budget, and a series of other (resource, ethical or political) constraints*. The set of constraints in this highly context-specific use of CEA for sectoral decision-making will vary tremendously from setting to setting. A decision-maker may be able to reallocate an entire budget or only allocate a budget increase; the decision-maker might be a donor, a minister of health, a district medical officer, or a hospital director. The choices available, at least in the short- to medium-term, might be limited by factors such as the currently available physical infrastructure, human resources or political considerations—for example, in systems with substantial public provision there is a relatively fixed stock of hospital beds that cannot be increased or decreased easily. Decisions could also be constrained by the current mix of interventions that are delivered; perhaps for political reasons specific interventions may not be reduced or eliminated without providing some alternative for that class of health problem. The set of constraints facing a decision-maker defines the decision space or the set of possible options from which choices can be made [92].

Second, *CEA of a wide range of interventions can be undertaken to provide general information on the relative costs and health benefits of different technologies or strategies that are meant to contribute through multiple channels to a more informed debate on resource allocation priorities*. Such general information should be seen as only one input into the policy debate on priorities. Because it is not meant to provide a formulaic solution to resource allocation problems, it need not be highly contextualized. This general approach will contribute to judgements on whether interventions are highly cost-effective, highly cost-ineffective, or something in between. Such general perceptions of relative cost-effectiveness can have far-reaching and constructive influence on policy formulation, defining the set of options that are debated without defining the allocation of resources in a precise or mechanical fashion. An alternative way to conceptualize this more general use of sectoral CEA is that the results define the mix of interventions that would be health maximizing in the absence of any constraints on possible decisions, except a finite budget. That health maximizing mix of interventions, which does not pertain to any specific decision-maker, can be a useful reference point for evaluating the directions for enhancing allocative efficiency in a variety of settings.

Although all CEA runs the risk of being used in a formulaic way, we believe that the first use of sectoral CEA—to inform a given decision-maker in a specific context—is more likely than the second to be used in this way to determine resource allocation. In context-specific CEA, the challenges of incorporating explicitly other social concerns are more pressing, but efforts to incorporate legitimate context-specific social concerns into the calculation of cost-effectiveness through devices such as equity weights inevitably make the results more difficult to communicate to some decision-makers and to the public. Such efforts also decrease the transferability of results. At some point in the continuum of complexity, the goal of informing a given decision-maker in a specific context may become impossible because of the cost and time required to generate the information [18].

We believe that the more general use of CEA, to inform sectoral debates on resource allocation, is where CEA can make the greatest contribution to health policy formulation. Such analysis indicates the general directions for resource reallocation required to enhance allocative efficiency. The results can be weighed alongside other social goals and considered together with the other constraints on decision-makers, which are inevitable in specific contexts. The more generalized approach will enhance transferability and will make it possible to provide useful, timely and affordable information on the health generating characteristics of interventions.[b] In some sense, there is a trade-off between making CEA information precisely relevant to a given context and the time and resources required for that contextualization. Our

preference for the more general use of CEA is an indication of how we see the outcome of that trade-off.

INTERVENTION MIX CONSTRAINED COST-EFFECTIVENESS

Various attempts have been made to codify a standard practice for CEA [14,57,58,93–125]. These guidelines differ for certain technical assumptions, such as standard discount rates, the treatment of unrelated medical costs or the valuation of health outcomes. The broad approach, however, is similar. Intervention costs and health benefits are evaluated with respect to current practice, so that the numerator in the cost-effectiveness ratio is the change in cost due to the application of an intervention compared with the change in health benefit. For the development of league tables, decision rules have been developed for both independent and mutually exclusive interventions to be ranked in a single league table [22,28]. When applied to a wide range of interventions in a population, the results inform decision-makers faced with a single constraint, the budget. The results of this type of analysis do not lead to recommendations to change the current mix of interventions unless the new intervention is accepted over current practice. For this reason, we will refer to this standard practice as intervention mix constrained CEA or IMC-CEA. Interestingly, IMC-CEA as currently practised does not consider other possible constraints on decision making. It is worth noting that the policy environment in which decision-makers come closest to facing a constraint to continue current practice (or expand benefits in areas where there are existing interventions) but face no physical infrastructure, human capital or other constraints, is the United States, where most provision of interventions is in the private sector and ethical guidelines on standards of care tend to automatically adopt all health enhancing interventions.

To further explicate the advantages and disadvantages of standard cost-effectiveness methods, consider Figure 1, which depicts the costs and benefits of six mutually exclusive interventions. Following standard practice [58], intervention costs are on the y-axis and health benefits on the x-axis. In this and subsequent diagrams, each intervention should be thought of as a national programme or policy, which can be purchased at only the point on the figure shown.[c] If a population has purchased intervention a1, then IMC-CEA would evaluate the cost-effectiveness of interventions a2–a6 with respect to the origin set equal to a1—indicated by the light grey axes. Average cost-effectiveness for each intervention is equal to the slope of the line joining the point to the currently delivered intervention a1, illustrated for intervention a2—this slope is labelled as $\alpha 1 \alpha 2$. Incremental cost-effectiveness for moving

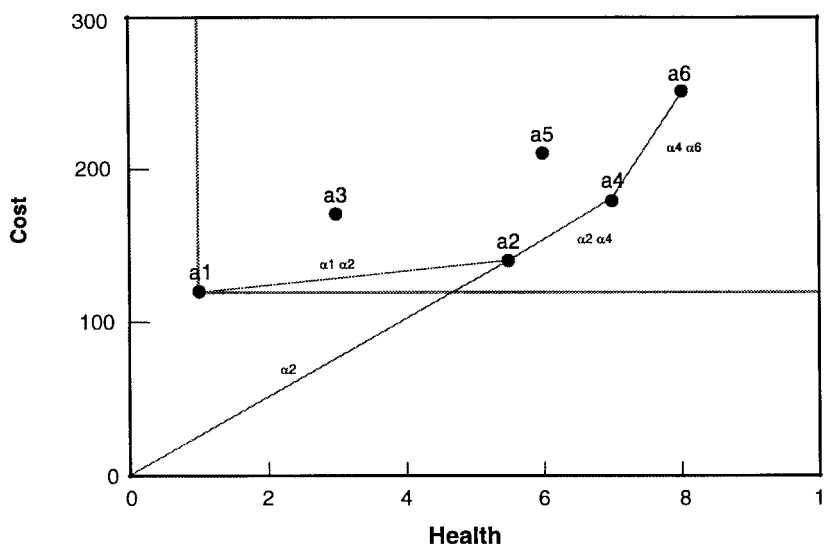


Figure 1. Costs and benefits of six mutually exclusive interventions

from a2 to a4 is shown as the slope $\alpha 2\alpha 4$. For reasons that will be discussed in detail below, the origin in Figure 1 has been set as the costs and health benefits in the absence of any of the interventions a1–a6. The line joining intervention a2 to the origin is the average cost-effectiveness with respect to the null set of interventions a1–a6, labelled simply $\alpha 2$. This format follows standard practice in the literature.

Figure 2 will be used to illustrate one of the main limitations of IMC-CEA. Eleven different interventions to those of Figure 1 are divided into three sets of mutually exclusive interventions, a1–a4, b1–b3 and c1–c4. Costs and health benefits for each intervention are shown with respect to the null set of this set of 11 interventions—health benefits could be denominated in QALYs gained, DALYs averted or some other general measure of health. In other words, costs and benefits are shown compared with the costs and benefits in the absence of any of these interventions. Table 1 provides the costs and benefits for each intervention and the average cost-effectiveness of each with respect to the null set.

Consider a population where a budget of 170 is currently spent to purchase a1 and c1 producing 23 units of health. Next, consider an increase in the budget from 170 to 190. The remaining set of mutually exclusive interventions with respect to a1 would be evaluated. It shows that a3 is dominant

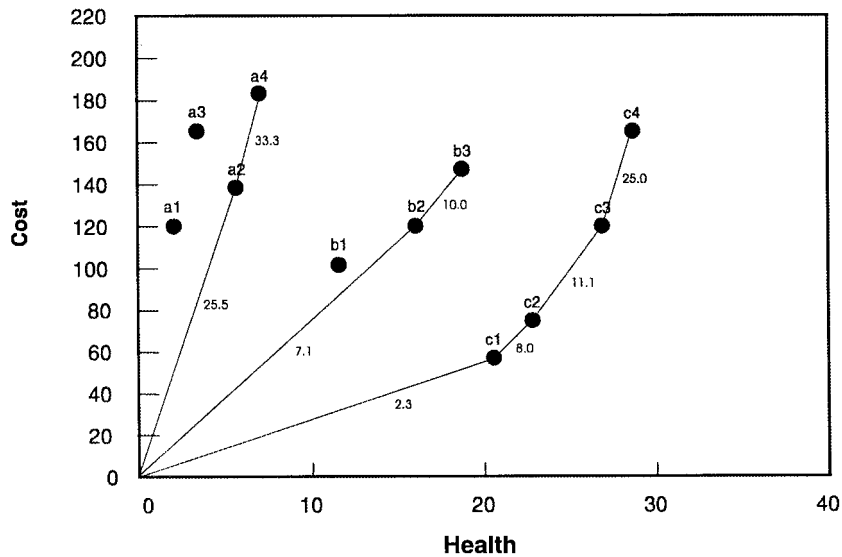


Figure 2. Costs and benefits of three sets of mutually exclusive interventions

Table 1. Average cost effectiveness for 11 interventions

Intervention	Costs	Health benefits	Average cost-effectiveness
a1	120	1	120
a2	140	5.5	25.45
a3	170	3	56.67
a4	190	7	27.14
b1	100	12	8.33
b2	120	17	7.06
b3	150	20	7.5
c1	50	22	2.27
c2	70	24.5	2.86
c3	120	29	4.14
c4	170	31	5.48

and yields the incremental cost-effectiveness ratios in Table 2, which also shows similar calculations for the independent sets of interventions. A decision-maker would choose to purchase a2 instead of a1 because moving from a1 to a2 has the lowest incremental cost-effectiveness ratio. The final combination of a2 and c1 yields 27.5 units of health.

Consider another population where a budget of 170 is currently spent on a3 yielding only 3 health units. In this population, incremental CEA of the remaining interventions with respect to the starting point of a3 would yield the ratios in Table 3. If the budget now increases from 170 to 190, the decision-maker would first choose to save money and increase health output by moving to a2. With the savings of 30 and the increased budget of 20, the next most attractive intervention would be to purchase c1, with the resulting allocation of resources being a2 and c1 yielding 27.5 units of health.

In both examples, IMC-CEA identified health enhancing resource allocations but the basic fact that the C and B category interventions are much more cost-effective than the A category interventions does not emerge from the analysis. This is because the cost-effectiveness of the starting point is not evaluated in current practice. As detailed below, it is relatively straightforward to identify the health maximizing combination of interventions for a budget of 170 as c1 and b2, which yields 39 health units and the health maximizing combination of interventions for a budget of 190 is c2 and b2 yielding 41.5 health units.[d] In reality there is likely to be substantial allocative inefficiency in current allocations of health resources in many settings, and this example demonstrates that the application of IMC-CEA may fail to identify major opportunities for enhancing the overall cost-effectiveness of the health system.[e]

Table 2. Sequential incremental cost-effectiveness ratios starting from a1–c1

Category A		Category B		Category C	
$\Delta C/\Delta E$		$\Delta C/\Delta E$		$\Delta C/\Delta E$	
a2	4.4	b1	8.3	c2	8.0
a3	Dominant	b2	7.1	c3	11.1
a4	33.3	b3	10.0	c4	25.0

Table 3. Sequential incremental cost-effectiveness ratios starting from A3

Category A		Category B		Category C	
$\Delta C/\Delta E$		$\Delta C/\Delta E$		$\Delta C/\Delta E$	
a2	−12	b1	8.3	c2	2.3
a4	33.3	b2	7.1	c3	8.0
		b3	10.0	c3	11.1
				c4	25.0

The intervention mix constraint on CEA means that major allocative inefficiencies may not be evaluated and thus identified. If the current intervention mix is an unavoidable constraint on decision-makers in a given context, then this is appropriate for context-specific CEA analyses. In most situations, however, other constraints on decision-makers may be more pervasive. As described above, in many health systems with a large share of public provision there is a fixed stock of community and referral hospitals, which cannot be modified in the short- to medium-term for powerful political reasons. Likewise, in many countries the supply of different types of health providers (nurses, general practitioners, specialists or community health workers) may limit the set of interventions that can be delivered. These decision constraints may be more common than the strict commitment to the current mix of interventions assumed in current practice—it may be easier to shift spending from the treatment of ischaemic heart disease to childhood immunization programmes than to shut district hospitals or import ophthamologists.

If the focus of sectoral CEA is to inform context-specific decision making, then methods need to be developed to incorporate these and other constraints on the set of possible decisions. This can be achieved relatively easily through the use of optimal resource allocation planning models adapted to the health sector [22,26–34]. For example, Table 4 illustrates using a simple resource allocation model that the health maximizing resource allocation in the setting of two binding constraints (physical capacity of health facilities and fungible dollars[f]) is substantially different than the health maximizing resource allocation in the setting of only a dollar constraint. Using the data from Table 1, the total budget is set at 170, 70 of which is fungible dollars and the rest is the constraint on infrastructure or the physical capacity of health facilities valued at 100. For each

Table 4. Optimal solutions with two constraints

Interventions	Total cost	Current budget = 70	Infrastructure = 100	Benefit	Average cost-effectiveness	Benefit at current use
a1	120	60	60	1	120.00	
a2	140	80	60	5.5	25.45	
a3	170	90	80	3	56.67	
a4	190	110	80	7	27.14	
b1	100	35	65	12	8.33	12
b2	120	60	60	17	7.06	
b3	150	75	75	20	7.50	
c1	50	15	35	22	2.27	
c2	70	35	35	24.5	2.86	24.5
c3	120	50	70	29	4.14	
c4	170	85	85	31	5.48	
				Total benefit		36.5
				Slack in the current budget		0
				Slack in the infra budget		0

intervention, we have divided the costs of Table 1 into two components—fungible dollars and infrastructure. With a single budget constraint of 170, optimal allocation required provision of b2 and c1 with a benefit of 39. The dual constraints of Table 4 now require b1 and c2 to be carried out at a benefit of 36.5, because the two constraints must be met. With multiple constraints, there is no easy way of developing a cost-effectiveness league table and more complex programming models should be used to allocate resources. In this case, the solution was obtained with 0–1 linear programming solved using the programming language LINGO®.

GENERALIZED CEA

For some decision-makers, the development of complex resource allocation models that explicitly incorporate a range of decision constraints and multiple objectives may be very useful. However, such efforts are information intensive, time consuming, costly and very often difficult to communicate to the full set of actors in any health policy dialogue [18]. We believe that CEA can be most useful with more modest goals by focusing on the more general use of cost-effectiveness information to inform health policy debates without being completely contextualized. Moreover, sectoral CEA should identify current allocative inefficiencies as well as opportunities presented by new interventions. For this reason, WHO will propose a modification of the standard ICM-CEA lifting the constraint on the current mix of interventions to evaluate the cost-effectiveness of all options including currently funded interventions.

In brief, the basic modification can be summarized in two propositions.

1. The costs and benefits of a set of related interventions should be evaluated with respect to the counterfactual of the null set of the related interventions. This is illustrated in Figure 2 for the 11 interventions. This provides the complete set of information for evaluating both independent and mutually exclusive options to identify the health maximizing combination of interventions for any given budget.
2. Results of CEA should be presented in a single league table. For each set of mutually exclusive interventions, the intervention with the lowest average cost-effectiveness ratio (the lowest slope in the figure of cost versus benefit) with respect to the null set appears first in the league table. The second intervention from the set (if there are at least two) that appears in the league table is the one with the lowest slope with respect to the intervention with the lowest CE ratio that already appeared in the table. The third intervention is the one with the lowest slope with respect to the second intervention, etc. Weakly dominated interventions do not appear in the league table. The results for all sets of mutually exclusive

interventions are shown in the same league table according to the same principles. The application of this simple approach to the 11 interventions example in Figure 2 is shown in Table 5. Interventions a1, a3 and b1 are weakly dominated and do not appear. For heuristic purposes, the health maximizing combination for any budget level can be selected from the table. These decision rules are similar to those that have been derived for IMC-CEA but the analysis starts from the origin [18,68,126–133].

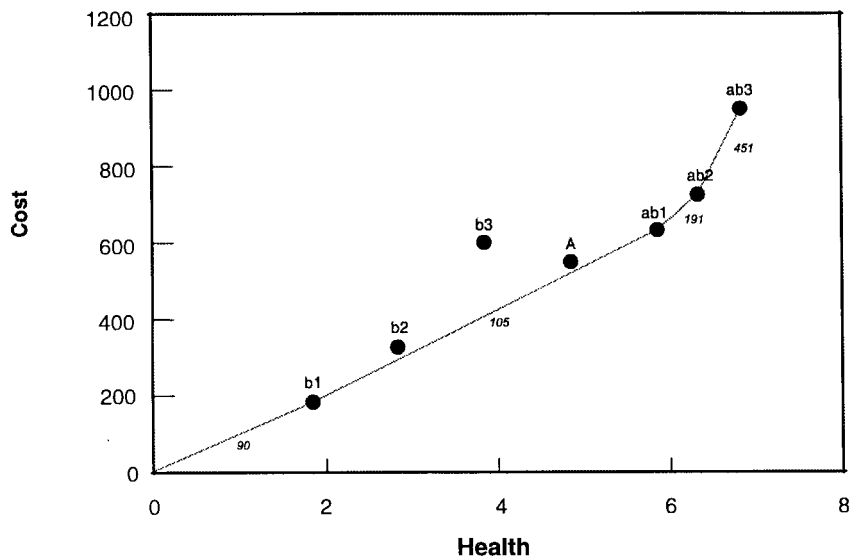
A key issue in this or any other approach to CEA is defining an intervention. If the comparator for a set of related interventions is the null set then each intervention must be defined with respect to that null set. Thus, if a new drug shortens the length of stay and reduces complication rates post coronary artery bypass graft operations, the drug is not the intervention. The intervention is coronary artery bypass graft plus the new drug.

Table 5. Generalized cost-effectiveness league table

Intervention	Cost-effectiveness ratio
c1	2.3
b2	7.1
c1–c2	8.0
b2–b3	10.0
c2–c3	11.1
c3–c4	25.0
a2	25.5
a2–a4	33.3

This logic in defining interventions allows for complex interactions in costs and health benefits to be easily captured and represented in a league table.

Figure 3 illustrates such an evaluation for four interventions for tuberculosis: passive case detection and treatment with directly observed short



	Costs	Benefits	CE
A	550	500	110
b1	180	200	90
b2	325	300	108.3
b3	600	400	150
Ab1	631	600	105.2
Ab2	726.5	650	111.8
Ab3	952	700	136

Figure 3. Costs and benefits of interventions with cost and effectiveness interactions

course therapy (DOTS), BCG vaccination at 50% coverage, BCG at 75% coverage and BCG at 100% coverage. In addition, three other mutually exclusive options are presented: passive case detection and treatment with DOTS combined with the three different levels of BCG coverage. Costs interact, in that, if BCG is delivered, the number of cases of tuberculosis that will occur, be detected and accept treatment will decline so that the variable cost component of the treatment programme will decline but the fixed cost component will not. Likewise, the health benefits of BCG in the presence of a treatment programme will be less because many of the deaths from tuberculosis expected in the absence of treatment will be avoided.

Using a multiplicative model, the interaction of the benefits of the two programmes can be estimated. The lines in Figure 3 indicate graphically the league table for this set of mutually exclusive interventions, in order: BCG at 50% coverage, BCG at 50% coverage combined with passive detection and treatment, BCG 75% with detection and treatment and BCG 100% with detection and treatment. BCG 75%, BCG 100% and passive detection and treatment alone do not appear in the list as they are dominated by the other alternatives.

In the literature on cost-effectiveness [23,30,34] there has been considerable concern about non-linear cost-effectiveness functions; for example, the cost per DALY averted through the expansion of measles coverage from 50% to 90% is likely to be much lower than the cost per DALY averted through the expansion of coverage from 90% to 99%. Because interventions at different levels of coverage are clearly mutually exclusive at the population level, then the same approach outlined above can be used to capture in a series of discrete points a non-linear cost-effectiveness function. In Figure 2, the set of interventions c1–c4 could be different strategies or different levels of coverage for the same strategy. By picking a parsimonious set of coverages, a set of indivisible and mutually exclusive interventions can be defined and the key consequences of non-linear cost-effectiveness functions captured in a single league table. The tuberculosis example of Figure 2 clearly does not by itself represent an example of generalized CEA, but would be part of the larger league table used to inform the policy debate.

By analysing the costs and benefits of sets of related interventions with respect to the null set of those interventions, the results are likely to be more transferable from one population to another—though only through experience will we learn if this is true. Clearly, the costs of different resource inputs to the production of a given intervention vary across populations as do some of the determinants of effectiveness [15,59,60,63–68].[g] However, one major factor limiting the relevance of ICM-CEA results in one population to another population, namely different current mixes of interventions, can be removed by using the generalized CEA approach. To put it another way, the null set for a group of related interventions is more comparable across populations (or at least sets of populations) than the current mix of interventions. Nevertheless, there are clear limits to the comparability across populations of the counterfactual null set. It will depend on the development of the health system and on the epidemiological pattern. Clearly, global comparisons of the cost-effectiveness of interventions with respect to the null set even if input costs and effectiveness determinants are adjusted is unlikely to be useful.

The strategy for the development of this idea will be to define a limited set of average health system and epidemiological contexts within which null set comparisons are likely to be informative. Many groupings of countries or communities could be developed, on the basis of income per capita, region, public/private splits in health care finance or provision, burden of disease, etc. This will be one major challenge for the development of this approach.

The benefits of analysing the costs and health benefits of interventions with respect to the null set for a group of related interventions appears to be greater but the technical challenge of estimating the conditions in the null set counterfactual need to be addressed. In theory, in ICM-CEA, costs and benefits of each intervention are evaluated with respect to the current mix of interventions but many studies are based on retrospective analysis where the intervention cost and benefits are evaluated with respect to a past mix of interventions not necessarily the current mix [134,135]. Likewise, estimates of benefits of interventions that involve a time lag between purchase and benefit, such as hepatitis B immunization, are based on relatively implausible assumptions that the current mix of interventions will apply in the

future [136–139]. A symptom of this problem is demonstrated by the standard practice in ICM-CEA of estimating the benefits of life saving interventions using period life tables when in fact the cohort life expectancy at each age would be a more accurate (but more difficult to estimate) estimate of the years of life gained. Historically, cohort life expectancy has been 10–20 years higher at birth than period life expectancy [140] so that this is not a minor bias.

Estimating the null set conditions for a group of related interventions will require the development of natural history models. Some have already been developed and some have been used in cost-effectiveness studies [137,141–149]. De Koning *et al.* [150,151] have developed a natural history model for breast cancer in the Netherlands as part of an in-depth analysis of intervention options for breast cancer. To implement this generalized approach to CEA, clear guidelines and standards on the development of natural history models will need to be developed as a priority.

DISCUSSION

Broader use of cost-effectiveness studies to analyse the allocative efficiency of health systems and recommend resource allocations has led to a number of challenges. It appears that the field can develop in two distinct directions, towards increasingly contextualized analyses or towards more generalized assessments. Cost-effectiveness studies and the sectoral application of CEA to a wide range of interventions can become increasingly context specific; at the individual study level by incorporating directly other social concerns, such as distributional weights or a priority to treating the sick, and at the sectoral level by developing complex resource allocation models that capture the full range of resource, ethical and political constraints facing decision-makers. We fear that this direction will lead ultimately to less use of cost-effectiveness information in health policy dialogue. Highly contextualized analyses must by definition be undertaken in each context, the cost and time involved as well as the inevitable complexity of the resource allocation models will limit their practical use.

The other direction for sectoral cost-effectiveness, the direction that we are suggesting, is to focus on the general assessment of the costs and health benefits of different interventions in the absence of various highly variable local decision constraints. A general league table of the cost-effectiveness of interventions for a group of populations with comparable health systems and epidemiological profiles can make the most powerful component of CEA readily available to inform health policy debates. Judgements on the relative cost-effectiveness of interventions such as DOTS for tuberculosis is highly cost-effective and liver transplants for alcoholic cirrhosis are highly cost-ineffective, can have wide ranging influence—as one input to an informed policy debate they can enhance the allocative efficiency of many health systems. Information on generalized cost-effectiveness can be used alongside consideration of the effect of different resource allocations on other important social goals, such as equity. Because we believe this is the most constructive use of cost-effectiveness information, we would like to open for debate the proposal to modify standard cost-effectiveness methods. The modifications proposed, to remove the current intervention mix decision constraint, will expose current allocative inefficiencies to analysis and at the same time enhance the transferability of results from one population to another.

For many narrower applications of CEA, such as the appraisal of new drugs in a specific country, the currently practised ICM-CEA remains the most appropriate method. Nevertheless, even in these circumstances it would be useful for authors to also estimate the costs and health benefits of interventions with respect to the null set. This would substantially improve the world's body of knowledge on the cost-effectiveness of different interventions. In this way, each new study would add to our collective knowledge of the relative costs and effectiveness of different interventions.

NOTES

a. The term allocative efficiency can be used in many ways. Here, we strictly use it to refer to whether resources are allocated across different health interventions (specific public health, curative, promotive, rehabilitative, or palliative interventions) so as to maximize population health status.
b. Some of the problems of international transferrability of results even for generalized CEA are discussed later in the paper.

c. Issues of divisibility of interventions are at the heart of many of the theoretical issues in CEA. For example, the definition of extended dominance [23,24,34] depends on the assumption of divisibility. In fact, divisibility of interventions is only required because of the problems of the choice of the last intervention with a hard budget constraint. If the most cost-effective intervention is indivisible and costs more than the available slack in the budget, then other interventions, including some that may be weakly dominated, may be in the optimal resource allocation. The issue of divisibility of interventions often plagues simple illustrations of optimal resource allocation across a small set of interventions [22,123,124,141,142]. For these graphical representations to provide clear and correct answers, it is necessary that each possible combination of cost and benefit that could be implemented be represented as a specified point. In reality, for most programmes, one cannot purchase any level of coverage for technical or political reasons. For example, in implementing short-course chemotherapy for smear-positive tuberculosis using passive case detection, by the nature of the case detection modality only one level of coverage can be achieved with that strategy. To change the coverage would require an explicit change in the case detection strategy, such as active screening or public awareness campaigns, which would have different costs and benefits and thus should be seen as another incompatible intervention. Alternatively, while it is theoretically possible to envisage a vaccination strategy that targets only a quarter or a half of the population, it would be impossible to implement for political reasons in most countries. In reality, there would be a few mutually exclusive combinations of costs and coverage for most programmes. The decision rules developed in this paper apply to this situation.
As has been argued above, faced with a budget constraint and a series of indivisible interventions, the health maximizing allocation of the budget is complicated by issues of slack—close to the budget constraint, it might not be possible to fully implement the preferred intervention. The examples in this paper have been designed to avoid these problems, but we do not believe that slack is a critical issue in any real allocation decision. First, the size of any slack *vis-à-vis* the total budget is likely to be very small [13]. Slack problems are exaggerated in the practical examples in the literature, where the number of interventions purchased is always small, which means that slack may be a large percent of the budget. In any real health system, slack related to the last intervention selected is likely to be very small. Second, in any real health system, budget constraints are never so firmly fixed that issues of slack become an issue in actual debates on resource allocation. In fact, we strongly believe that results of the type of CEA proposed in this paper should not be used with such precision.
A more important issue concerns the situation concerning the indivisibility of a capital investment, where the investment can be used for several patient or population groups, such as a hospital. Such problems can only be addressed with resource allocation models [13]. For example, Murray *et al.* [24] developed a resource allocation model in which expansion of capital infrastructure was evaluated as a separate type of intervention, which relaxed the physical infrastructure constraint in the resource allocation model.

d. A simpler approach to allocating resources across a set of interventions might be to rank all independent and mutually exclusive interventions by their average cost-effectiveness and then fund down the list of interventions until the budget is exhausted. In this example, for a budget of 170, the average cost-effectiveness rank list approach would choose intervention c4 producing 31 health units. This is substantially less than the health maximizing combination of c1 and b2 yielding 39 units. Average cost-effectiveness rank lists that ignore the issues related to mutually exclusive interventions will in general yield sub-optimal resource allocations.

e. This point has been made in various forms in the literature, e.g. see Drummond *et al.* [58].

f. We use the term 'fungible dollars' to describe the assumption that no constraints other than physical capital and the total budget are binding. The total budget can be moved between all inputs other than capital with no restrictions.

g. A challenge to our approach will be to separate out technical inefficiencies in production of a given intervention from the allocative efficiency questions described here. For example, it has also been shown that the physical quantities of resources used for a given intervention can vary from place to place according to practice patterns [152,153]. If by chance the cost-effectiveness of an intervention has been evaluated in a setting that is technically inefficient and another is evaluated in a setting that is technically efficient, conclusions on relative cost-effectiveness may be biased. The confounding effect of variation in technical efficiency across study locations for the development of generalized cost-effectiveness league tables needs to be minimized. At the same time, systematic regional variation in technical efficiency due to health system characteristics or epidemiological patterns should be incorporated into regional league tables of generalized cost-effectiveness.

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