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**Cost-effectiveness analysis for sector-wide priority  
setting in health**

**Kosten-effectiviteitsanalyses voor sectorale prioritering  
in gezondheid**

**Thesis**

to obtain the degree of Doctor from the  
Erasmus University Rotterdam  
by command of the  
Rector Magnificus

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*To Lois, Noémi and Gaël*

*Kepada oma Otji dengan oma Ena*



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# Chapter 1

## Introduction

Based on:  
Generalized cost-effectiveness analysis for priority setting in health.  
Hutubessy RCW, Baltussen RMPM, Tan Torres-Edejer T, Evans DB.  
Applied health economics and health policy (2002) 1(2), 89-95





## Introduction

Cost-effectiveness analysis (CEA) provides one means by which decision-makers may assess and potentially improve the performance of health systems. The process can help to ensure that resources devoted to health systems are achieving the maximum possible benefit in terms of outcomes that people value. Over the past three decades there has been an exponential growth in the number of economic appraisals performed in health. Following standard textbooks on economic evaluations, most of these CEA studies pursue an incremental approach which requires comparison of the additional costs of an intervention over current practice with additional health benefits [1,2]. Such an incremental approach, however, is unable to provide policy makers with all necessary information relating to decisions like: “Do the resources currently devoted to health achieve as much as they could?”, or “How best to use additional resources if they become available?”.

This thesis proposes a broader sectoral approach via the application of a generalized CEA framework which also allows examination of existing inefficiencies in the health system – that is, the wide variations in CE ratios observed among interventions that are currently in use suggest there is considerable room to improve efficiency by moving from inefficient interventions currently in use to efficient interventions that are under-utilised [3]. In developing countries in particular reallocation of scarce financial resources is most important [4]. The generalized CEA framework compares interventions to a common counterfactual or to a situation of ‘doing nothing’. This may allow both existing and new interventions to be analysed and will also allow cost-effectiveness results to be more generalizable across settings. The proposed framework focuses on the general use of cost-effectiveness information to inform health policy debates without being completely contextualized. Traditional incremental analysis however, remains a necessary and complementary method to generalized CEA.

This introductory chapter presents some evidence of existing inefficiencies in health care both at the macro and micro level indicating the need for a reallocation of health resources. In addition, it discusses some sectoral cost-effectiveness attempts in the past dealing with allocative efficiency problems, including the problems encountered in their analysis. In a subsequent section the generalized cost-effectiveness framework will be proposed and how it should be used for priority setting in health.

## Existing inefficiencies in health care systems

Both at the macro and the micro-level there is ample evidence on existing inefficiencies in health care. On the macro level health systems have multiple goals, yet their defining objective is to improve health. Despite this common aim, health systems with very similar levels of health expenditure per capita can show wide variations in population health outcomes.

The *World Health Report 2000* published a first attempt to measure attainment of the proposed health systems goals by 191 countries and considered how well countries

were performing given the resources available [5]. Evans and colleagues [5,6] showed that countries like Sri Lanka and China, which are believed to have been efficient in producing health, perform less than countries at similar levels of development. Furthermore, the authors concluded that efficiency is positively correlated with health expenditure per capita, especially at low expenditure levels and that performance sharply increases with expenditure up to about I\$80 per capita a year<sup>1</sup>. These findings can in part be explained by variation in non-health systems factors, such as the level of education of the population. However, a further part can be explained by the fact that some systems devote resources to expensive interventions with small effects on population health, while at the same time low cost interventions which would result in relatively large health improvements are not fully implemented or even ignored.

At the micro level Tengs [7] and Murray and colleagues [8] argued that health both in the United States and sub-Saharan Africa could be greatly improved by reallocating available resources from interventions that are not cost effective to those that are more cost-effective but not fully implemented. For the case of the United States it was estimated that a set of 185 currently publicly-funded interventions costs about US\$214.4 billion, for an estimated saving of 592,000 years of life. Re-allocating those funds to the most cost-effective interventions could save an additional 638,000 life years if all potential beneficiaries were reached [7].

## Sectoral CEA

One approach which has been developed to facilitate policy-makers in decisions to reallocate resources is the construction of a 'league table' that rank-orders interventions by their cost-effectiveness ratios (cost per QALY). Many published 'league tables' have been criticised for including only few interventions [9-11], or only including interventions within one disease area. For example, recently Pinkerton and colleagues [12] constructed 'league tables' to compare interventions to prevent sexual transmission of HIV. Only rarely has the 'league table' approach been applied in an explicit broader sectoral perspective, in which CE-studies are compared on a wide range of health interventions in a single research effort with an explicit budget level [13]. Exceptions are the work of Oregon Health Services [14], the Harvard Life Saving Project [15] and World Bank Health Sector Priorities Review (HSPR) [16]. What these studies have in common is their aim to allocate health care resources across many interventions and population groups to generate the highest possible overall level of population health in a single exercise. Each study will be described in more detail hereafter.

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<sup>1</sup> International dollars, exchanged from domestic currency using purchasing power parities rather than official exchange rates.

## ***World Bank HSPR project***

The most comprehensive sectoral CEA example on a global level is the World Bank HSPR. In 1987, as recognition mounted of the importance of the HIV epidemic, many groups called upon the health sector of the World Bank to make HIV control their number one priority in health. This provoked a debate on substantive priorities for action in the health sector. The World Bank initiated the HSPR to address this problem. A list of more than twenty important conditions or clusters of conditions was drawn up. The main results of the HSPR are estimates of the long-run average cost-effectiveness of a set of interventions.

Overall, the study showed that categorical assessments such as “primary health care is cost-effective and hospital care is cost-ineffective” are too simplistic: each intervention needs to be evaluated and one cannot guess cost-effectiveness on the basis of an intervention being curative or preventive or delivered at a given level of the health system. But one of the key findings was that many of the interventions currently undertaken are very expensive ways of improving health, while many of the low cost ways of improving health are not fully funded. This implies there is considerable room to improve allocative efficiency, even if technical efficiency is also low. The World Development Report 1993 [17] introduced a global ‘league table’ of priority of health interventions, cardinally ranked by health gain per dollar spent in order to improve efficiency of public health expenditure. Based on this global ‘league table’ the World Bank proposed a minimum package of basic public and curative health interventions.

## ***Oregon Health Plan***

The Oregon Health Plan (OHP) has been widely heralded as an important innovation in American medical care policy. Oregon’s pioneering model of prioritizing funding for health care through systematically ranking services has drawn an extraordinary amount of national and international attention. The rationing of services rested on an elaborate technical analysis, one that merged cost-effectiveness analysis and medical outcomes research with public participation in policy-making decisions.

A Health Services Commission was organized to compile clinical information from physicians, treatment costs and benefit data, and community values from the public. This Commission reduced over 10,000 services to a prioritized list that initially rank 709 condition and treatment pairs.

The net effect has been to exclude a limited number of services such as medical management of back pain, but to expand coverage of Medicaid to more people without increasing the budget. The Oregon Health Plan has sparked significant controversy in the US concerning the role of the state in controlling the set of available services in the health sector.

## ***The Harvard Life Saving Project***

A project at the Harvard Center for Risk Analysis was undertaken to review the published literature on the cost-effectiveness of interventions that reduce mortality [15,18]. It was based on published papers, with minor amendments for differences in methods, and does not include non-fatal health outcomes. As with the HSPR, the study shows a substantial range of cost-effectiveness ratios across interventions that are currently undertaken in the USA. The Harvard Life-Saving Project estimated that this type of reallocation for primary prevention interventions in the USA would save an additional 600.000 years of life annually for the same level of investment. Tengs [18] has subsequently shown that reallocating resources from those that are cost-ineffective to those that are cost-effective in the US could save a very considerable number of years of life.

## **Requirements for sectoral CEA**

The sectoral CEA studies presented in the previous section have demonstrated major inefficiencies in the current allocation of resources, implying that countries could make significant gains in population health by shifting resources from high-costs, low-effect interventions currently in use, to low cost, high-effect interventions that are not used, or under-utilised. However, it is not always clear how to interpret the results from current CE studies to the aim of sectoral analysis. Some of the difficulties encountered with the use of current CE studies for sectoral analysis will be presented hereafter. These problems (or requirements) should be evaluated for any CE study to be useful to the allocation of resources across a broad range of interventions.

Firstly, current CE studies are typically based on the incremental or 'intervention-mix-constrained' CEA approach which is appropriate in settings where policy makers are constrained not only by the availability of resources but also by the current level of care for the condition under discussion. However, in the longer run where policy is *not* constrained by the current mix of interventions, incremental analysis does not provide best guidance to policy makers. It ignores the question of whether current interventions themselves are cost-effective. Yet, there is considerable evidence that some interventions currently undertaken are not cost-effective.

Secondly, this form of incremental analysis has limited use to decision makers in settings other than the one in which a study is undertaken. The starting points for an incremental analysis varies across settings (according to the current state of infrastructure and the current mix of interventions), while the additional health effects achieved from a given increase in resource use is dependent on what is currently done. This makes it very difficult to generalize CEA results.

Thirdly, as has been pointed out in CE literature the comparison of CE results becomes problematic when studies are based on varying costing methods and if economic evaluations are undertaken at different points in time [2,19,20]. For the sake of sectoral analysis, standardised methods must be used consistently across individual CEA studies to ensure external validity [21,22].

Fourthly, the World Bank [17] estimated that a minimum package of basic public and curative health interventions, each of which was considered to be cost-effective in its own right, would cost US \$12. Yet this package was unaffordable in many of the poorest countries where health expenditure per capita was as low as US \$2 [23,24]. The usefulness of such a general statement might be questioned and a regional or national league table might be more useful. As a minimum, CE studies should identify the full resource implications of implementing intervention identified to be cost-effective, a practice that is slowly beginning to occur in literature [23,25-30]. To take the case of malaria: at low levels of health expenditure in a country with a high burden of the disease, case management and prophylaxis for pregnant women would be very cost-effective and affordable. Only with more resources available might impregnated mosquito nets also be implemented [31].

Fifthly, current CE studies do typically not consider synergistic effects between interventions. In reality interventions interact on the costs and effectiveness or health systems side. For example, passive case detection and treatment with directly observed short course therapy (DOTS) interact on both costs and effectiveness with BCG vaccination. If BCG is delivered, the number of cases of tuberculosis that will occur will decline so that the variable cost component of the treatment programme will decline. Likewise, 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 [3].

Sixthly, changing strategies from cost-ineffective to cost-effective interventions will incur transaction costs which are typically not taken into account in current CE studies. That is, what the health system is currently doing or trying to do with its existing infrastructure be easily re-directed. For example, in their Health Resource Allocation Model (HRAM) the authors point out that the presence of existing capital investments such as staff, buildings and other infrastructure play a major role in budget allocation processes [32]. Another example is that the cost and effectiveness of delivering anti-malarials closer to households will depend critically on whether a network of village workers currently exists [28] or on the current and past environmental management of malaria control [33]. The evidence on transaction costs in the health care sector is scarce. Examples can be found in health care reform initiatives in the United States [34], United Kingdom [35] and New Zealand [36].

Finally, current CE studies typically only handle uncertainty around cost-effectiveness ratios (CER) at the individual study level or do not take uncertainty into account at all. When uncertainty ranges around CERs of different interventions overlap the question is how decision-makers should interpret this information when allocating resource across a large number of interventions. For example, the WDR 1993 only reported point estimates of the CERs. The 'league tables' proposed in these sectoral studies do not provide information about uncertainty to a decision-maker who is risk averse. In particular, this may be troublesome when a fixed budget applies as there may also be considerable uncertainty about the actual costs of a programme.

## Generalized CEA framework

The above discussed requirements for sectoral CEA in health care are closely related to the use of 'league tables' in general. Many commentators have cautioned against the unthinking use of 'league tables' because of non-comparability of methods, inappropriate comparators, and non-generalisability of results [9,11,37]. Most of the issues raised are addressed within the newly developed WHO generalized CEA approach [3]. Most importantly in the context of sectoral allocative efficiency issues, this new approach overcomes constraints imposed by incremental mix constrained analysis: it allows existing and new interventions to be analysed at the same time. Previous sectoral analyses have been restricted to assessing the efficiency of adding a single new intervention to the existing set, or replacing one existing intervention with an alternative. The generalized approach is of considerable policy importance. Because the analysis is not constrained by what is already being done, policy-makers now have a tool to revisit and possibly revise past choices made, and they will have a rational basis if they decide to reallocate resources from less to more cost-effective interventions. This form of sectoral analysis estimates the impact of health care interventions compared to a situation of 'doing nothing' i.e. without constraints of current mix of intervention. Furthermore, the use of a common methodology enhances comparability between disease areas and transferability of findings across countries. Bearing in mind that obtaining evidence on context specific cost-effectiveness information is intensive, time consuming and costly, the issue of generalizability of information is important, in particular for low- and middle income countries.

The interactions between interventions, in terms of both costs and effectiveness, are a major focus within the Generalized CEA approach. As explained earlier in the tuberculosis example in the previous section, interventions that are likely to be delivered together in a way that reduces the unit costs are analysed singly or together, and likewise on the effectiveness side: interventions in which the effectiveness is likely to be altered if delivered with another intervention are also analysed singly and together. This approach approximates more closely the practical situation faced by policy-makers.

This thesis also introduces stochastic 'league tables' to inform decision makers about the probability that a specific intervention would be included in the optimal mix of interventions for various levels of resource availability, taking into the uncertainty around cost and effectiveness of different interventions simultaneously [38]. This would overcome the requirements outlined earlier on uncertainty of the existing sectoral league tables. This information helps decision makers decide on the relative attractiveness of different mixes of interventions given the resources available. Moreover, stochastic 'league tables' inform policy makers about the total budget impact of an intervention. More recently similar attempts to incorporate affordability thresholds and uncertainty around CE results have been proposed by other authors [39-41].

## Sectoral CEA and priority setting

For sector-wide priority setting, cost-effectiveness information should be collected in a way which will allow policy-makers to address the policy questions raised earlier in the introduction of this chapter: "Do the resources currently devoted to health achieve as

much as they could?" and "How best to use additional resources if they become available?" It has been shown that sectoral CE exercises in the past have their limitations e.g. they do not allow to assess the current mix of interventions in place, are setting specific, and based on incremental CE information with inconsistent methodologies and typically inappropriate comparators. Generalised CEA permits both questions raised on technical and allocative efficiency at sectoral level to be answered and deals with them simultaneously.

Since the generalised CEA approach focuses on the general assessment of the costs and health benefits of different interventions in the absence of various highly variable local decision constraints the only remaining constraint using a general league table for priority setting is the availability of resources. It will give policy-makers indications of how to plan and organize their health system from a long-term perspective.

Yet, other information than cost-effectiveness 'league tables' is also important: evidence about major causes of ill-health and death; responsiveness of the system to people's non-health needs; inequalities in health outcomes, responsiveness and in the way households contribute financially to the system [42]. The debates on the use of CE information from the Oregon experience clearly showed that political, ethical, or social issues can easily take precedence over economic criteria [43,44]. More generally, in order to choose the appropriate mix of interventions, cost-effectiveness information is only one of a set of criteria that a health system may be asked to respect; it ought to protect people from financial risk, to be consistent with the goal of fair financial contribution; it should strive for both horizontal and vertical equity; and, it should spend public funds in favour of the poor [45]. In addition, what makes it particularly difficult to set priorities among interventions is that these different criteria are not always compatible. In particular, efficiency and equity can easily conflict, because the costs of treating a given health problem differ among individuals, or because the severity of a disease bears little relation to the effectiveness of interventions against it or to their costs. The application of GCEA is one way to ensure that sound evidence on cost and effects is used in the sector wide policymaking process.

## Outline of the thesis

This thesis consists of a number of studies that describe and analyse different aspects of sectoral cost-effectiveness analysis. The need for sectoral CEA is presented in this first introductory chapter and chapter two while some basic methodological issues on the broader use of sectoral CEA in practice will be proposed in the subsequent two chapters. Applications of this broader type of CEA at country level using diabetes and stroke will be presented in chapter five and six. A regional application of sectoral CEA, which focuses on the reducing the risk factors of cardiovascular diseases, will be illustrated in chapter seven. The main conclusion of this thesis is that for sector wide priority setting a broader type of economic evaluation, i.e. that of generalized CEA is required complemented with the traditional incremental approach.

Chapter 2 presents some critical issues on economic evaluation in health care. Some methodological issues and shortcomings of traditional economic evaluations will be given and illustrated with communicable diseases particularly in developing countries.



Chapter 3 will give the minimum requirements and steps to be undertaken on both the costs and effect sides when performing generalized CEA. As the 'counterfactual' is one of the key-elements of generalized CEA much emphasis will be given on how to obtain and determine the costs and effects under the 'counterfactual' scenario.

Chapter 4 introduces the concept of stochastic league tables as a means to communicate uncertainty around cost-effectiveness ratios to policy makers to be used in a budgetary context.

Chapter 5 presents one of the two firstly introduced attempts of generalized CEA at national level. In this chapter the Dutch guidelines for intensive control and treatment of complications in type 2 diabetes will be evaluated. In addition common grounds and differences of the stochastic league table technique and other methods of presenting uncertainty around cost-effectiveness ratios to decision-makers will be discussed.

Chapter 6 shows the second application of generalized CEA in the Netherlands. Here the lifetime effects and medical costs of interventions for average stroke patients will be evaluated. For both chapter five and six the results with uncertainty will be presented by means of stochastic league tables.

Chapter 7 illustrates a first ever regional analysis of generalized CEA. Costs and effects are reported of selected interventions to reduce the risk associated with elevated levels of cholesterol and blood pressure in areas of the world with different epidemiological profiles.

Chapter 8 gives an illustration of other issues in addition to the efficiency criterium important in the sector-wide priority setting process, based on the experience of the introduction of "big ticket" technologies in a number of developing country settings in Asia. The study describes and explains the diffusion and utilization pattern of costly technologies like magnetic resonance imaging (MRI) in several Asian settings.

Finally, chapter 9 presents a summary of the previous chapters and discusses the existing issues of generalized CEA and areas of future research.

## Chapter 2

# **Critical issues in the economic evaluation of interventions against communicable diseases**

Reprinted from:

Critical issues in the economic evaluation of interventions against communicable diseases.

Hutubessy RCW, Bendib LM, Evans DB.

*Acta Tropica* 78 (2001) 191-206.



## Introduction

Economic evaluation is a tool to help priority setting. It compares the consequences of an intervention with the costs and guides policy makers wishing to maximise the benefits produced by the scarce resources available to them. Interest in the economic evaluation of health interventions has increased substantially recently. The number of published studies was reported to have increased from 78 in 1979 to over 260 in 1990 [46] and to almost 500 in 1996 [47].

We searched the published English language literature for the period 1990-April 2000 inclusive using several medical subheading (MeSH) terms and text searches to identify articles in Medline and HealthStar (see Table 2.1). We also searched the World Health Organization's regional index medicus databases as well as hand searching the reference lists of published reviews. Our search revealed 1,058 publications classified as cost-benefit analysis (CBA) over the last 10 years and another 4,974 (an average of 497 per year) on cost-effectiveness analysis (CEA) (here defined broadly to include cost-utility analysis (CUA)). Even though some of these papers were not genuine economic appraisals - i.e. some considered either costs or outcomes without explicit comparison of costs and consequences - the trend is exponential.

Table 2.1. Systematic search on different types of economic evaluations

Systematic search <sup>a</sup>	Number of studies
Economic evaluations <sup>b</sup>	12,275
Cost-Benefit Analysis <sup>c</sup>	1,058
- including Willingness To Pay or Contingent Valuation <sup>d</sup>	96
Willingness To Pay or Contingent Valuation <sup>e</sup>	267
Cost-Effectiveness Analysis <sup>f</sup>	4,974

a. Based on MEDLINE (1990-April 2000) and HealthSTAR (1992- April 2000) using Internet Grateful Med (IGM). In addition, we searched the World Health Organization's regional index medicus databases as well as hand searching the reference lists of published reviews.

b. As a proxy "Cost and Cost Analysis" as MeSH term was used.

c. As a proxy "Cost-Benefit Analysis" as MeSH term was used.

d. A combination of the following key-words was used: ("Cost-Benefit analysis" as MeSH term) AND ("Willingness To Pay" OR "Contingent Valuation").

e. A combination of the following key-words was used: "Willingness To Pay" OR "Contingent Valuation".

f. A combination of the following key-words was used: ("cost utility") OR ("year" of life") AND ("cost") OR ("life-year") AND ("cost") OR ("well year") AND ("cost") OR ("healthy year") AND ("cost").

After losing popularity for more than two decades CBA has reappeared in the health literature, particularly over the last 3-4 years with the rediscovery of willingness to pay (WTP) and contingent valuation as a way of measuring benefits [48-51]. However, the published literature does not yet include many applications to communicable diseases or to the major health problems of developing countries.

Many of the published papers on CEA were theoretical and most applied studies focused on developed countries (see *Table 2.2*). We defined communicable diseases as the 14 categories of infectious and parasitic diseases for which estimates of burden were made by Murray & Lopez [52]. Only 127 publications, an average of 13 per year, considered communicable diseases control directly related to poorer countries (defined as any country not classified by the World Bank as Established Market Economies).

There have been a number of reviews of this literature from the perspective of the control of particular diseases – e.g. Hepatitis B, HIV, various types of immunisation programmes [53-60] and it is not feasible to review the results disease by disease here. In addition, two recent studies have reviewed economic evaluations of tropical and communicable diseases comprehensively, evaluating them against technical criteria for economic evaluation laid down in standard textbooks of economic evaluations [21,61]. The purpose of our paper is different. We focus on key issues raised by this literature which prevent decision-makers using the results of this literature to the maximum potential. We focus particularly on issues that make the results of studies generalizable across settings – or “external validity” questions as defined by Walker and Fox-Rush [21]. The objective is, of course, to help use resources better to reduce the burden of communicable diseases.

**Table 2.2.** Cost-effectiveness studies published by communicable diseases<sup>a</sup> from 1990 to April 2000 and the global estimates of the burden of disease of communicable diseases in 1999<sup>b</sup>.

Infectious and parasitic diseases	Number of studies by disease				Global DALYs lost to communicable diseases	
	World wide		Poorer countries <sup>c</sup>			
	Number	%	Number	%	DALYs lost (x1,000)	%
TB	23	7.7	12	8.9	33 198	9.5
STD (syphilis, chlamydia, gonorrhoea, excluding HIV)	10	3.4	3	2.2	19 331	5.5
HIV	110	37.0	22	16.3	88 709	25.3
Diarrhoeal diseases	8	2.7	3	2.2	71 807	20.5
Childhood-cluster diseases (pertussis, poliomyelitis, diphtheria, measles, tetanus)	17	5.7	11	8.1	54 593	15.6
Bacterial meningitis	6	2.0	3	2.2	9 686	2.8
Hepatitis B and hepatitis C	46	15.5	4	3.0	2 623	0.7
Malaria	28	9.4	28	20.7	44 996	12.8
Tropical-cluster diseases (trypanosomiasis, Chagas disease, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis)	33	11.1	33	24.4	12 965	3.7
Leprosy	5	1.7	5	3.7	476	0.1
Dengue	0	0.0	0	0.0	465	0.1
Japanese encephalitis	1	0.3	1	0.7	1 046	0.3
Trachoma	1	0.3	1	0.7	1 239	0.4
Intestinal nematode infections (ascariasis, trichuriasis, ancylostomiasis, necatoriasis)	9	3.0	9	6.7	2 652	0.8
Others	-	-	-	-	7 153	2.0
Total	297	100	135	100	350 939	100

a. Communicable diseases reported here correspond to 14 categories of infectious and parasitic diseases reported in Global Burden of Disease Study.[52]

b. Source: World Health Report 2000.[5]

c. All countries not defined by the World Bank as Established Market Economies

The paper is organised around four critical themes. The first is the need to focus on allocative efficiency which requires provision of information in a standardized way on the costs and consequences of a wide range of interventions. The second concerns methodological improvements which would allow results to be more generalizable than

they currently are. The third focuses on problems of measuring long term effects of interventions, while the final concern centres on the need to consider explicitly the question of affordability. The literature outlined above is used to illustrate the arguments, but our purpose is not to summarise on a disease by disease basis, not to exhaustively evaluate this literature against set technical criteria in the manner of Walker and Fox- Rushby [21,61].

## **A focus on allocative efficiency**

The primary reason for undertaking an economic appraisal is to provide information to decision-makers to help ensure that scarce resources are used to maximise one or more objectives. In sectors other than health, the objective function has been assumed to be the level of income or consumption, so CBA has been the most common technique. It relates the benefits of an intervention, measured in terms of the increased income or consumption, to the costs. Where the sum of the discounted benefits exceed the sum of the discounted costs, the project is deemed to be worth undertaking. However, health outcomes are difficult to measure in monetary units and attempts to do so raise ethical concerns [62,63]. Moreover, health is something that improves well-being independently from its admitted impact on income-earning potential, so health should be valued for its own sake. Partly for these reasons, CBA has not been used extensively in health but the recent revival based on the use of WTP in North America and Europe [64-67] is beginning to seep into the literature on communicable diseases [68,69].

The approach needs to be treated with care [50,63]. For example, valuations obtained from WTP are positively correlated with wealth and income so give preference to interventions favouring the rich. In addition, the technique assumes that health resources should be allocated according to people's willingness to pay for personal health benefits. This ignores altruism and does not allow for externalities or social preferences different to individual preferences. For a more complete discussion of the strengths and weaknesses of CBA based on WTP see [64,70-74]. Because of the dominance of CEA in the literature on communicable diseases, the remainder of this paper focuses on CEA.

Health outcomes in CEA are measured in physical units – either intermediate outcome indicators such as the number of children fully immunised in vaccination programmes [60], or final outcome indicators such as the number of years of life saved in providing antiretroviral drugs to pregnant HIV-infected women [75]. A special form is known as cost-utility analysis where the impact on both morbidity and mortality are combined in a generic measure of health such as the quality adjusted life year gained (QALY) or the disability adjusted life year averted (DALY). QALYs, for example, have been used as the measure of effectiveness for different strategies to control meningitis epidemics and schistosomiasis [76-78]. DALYs have been used to measure the impact of malaria control strategies and interventions designed to reduce HIV transmission to children [23,28].

Over the last 10 years, the most common focus for applied studies on communicable diseases in developed countries has been HIV/AIDS and hepatitis while for developing countries the focus has been on tropical diseases, malaria and HIV/AIDS (see Table 2).

Table 2 also suggests that researchers and research funders have not used the burden of disease as the sole rationale for selecting their research topics. There have been relatively few studies on diarrhoeal diseases and the vaccine preventable diseases compared to their burdens in terms of DALYs lost, perhaps because it has been widely accepted for the last decade at least that interventions against these diseases were cost-effective. On the other hand, there have been proportionally more studies on malaria, helminths and the tropical cluster than suggested by their relative contributions to ill health. This probably relates to the initiatives taken by the Special Programme for Research and Training in Tropical Diseases (TDR) to stimulate research in these areas.

In this literature, two types of questions relating to the use of scarce resources have been posed. The first involves comparison of different ways of doing the same thing. For example in reducing the burden of schistosomiasis in school-age children, the costs and health effects of chemotherapy delivered through schools were compared with chemotherapy integrated into the routine activities of the primary health care system [79]. This type of analysis concerns technical efficiency, asking which option is the most efficient use of resources to meet a particular health problem.

The second is to determine if a single intervention is worth doing at all, or which of a group of competing interventions should be given priority. This focuses on allocative efficiency - the distribution of scarce resources among different programmes or interventions to achieve the maximum possible socially desired outcome, in this case health level. Only rarely has the overall sectoral approach been taken explicitly in cost-effectiveness (CE) studies comparing a wide range of health interventions - exceptions are the work of the Oregon Health Services [14,80], the Harvard Life Saving Project [7,15,81] and the World Bank Health Sector Priorities Review [16,17]. Of these, only the World Bank made international comparisons. All studies show major inefficiencies in the current allocation of resources, implying that countries could make significant gains in population health by shifting resources from high-cost, low-effect interventions currently in use, to low-cost, high-effect interventions that are not used, or under-utilised. For example, the Harvard Life-Saving Study estimated that this type of reallocation for primary prevention interventions in the United States would save an additional 600,000 years of life annually for the same level of investment [18].

In fact, a large proportion of the studies that focus on single interventions do not address technical efficiency at all and seek to determine if the intervention represents an efficient use of resources. This requires comparing the costs and effectiveness of the intervention under study with other possible ways of using those resources (e.g. with other interventions), or with some cut-off value of cost per unit of outcome derived by considering what would be achieved by other interventions. For example, a cost-effectiveness ratio below US\$ 50 per DALY has been used as a cut-off point in some studies in developing countries [23,82], on the basis of the range of CE ratios observed in the Health Sector Priority Review [16].

This explicit or implicit use of "league tables" has been criticised [9] but cannot be avoided. In fact, even studies which purport to be about technical efficiency, comparing different ways of doing the same thing, cannot avoid important questions about allocative efficiency. For example, in a study on anthelmintic treatment with levamisole in Nigeria, mass treatment offered to all inhabitants in a village was less costly and more



effective than the selective approach of treating the most heavily infected inhabitants. The authors argued that the former was technically more efficient and should be given preference[83]. This result is rare. In most comparisons, one option will be more effective and more costly than others. The question then becomes whether it is worth spending the extra resources to get the additional benefits, and this can only be answered by asking what else can be done with those scarce resources – or using an implicit or explicit league table.

In fact, even where one option is both more effective and less costly than the alternatives - i.e. it "dominates" the alternatives - recourse to a league table is necessary. In the helminth example, while the results showed that mass treatment was more technically efficient than selective treatment, they did not help a policy maker decide if anthelmintic treatment should be given preference over other types of health interventions. This could only be done by considering what else could be done with the resources needed for helminth treatment.

Accordingly, we argue that broad comparisons with other ways of using scarce resources to improve health, requiring information on the costs and effectiveness of alternative options, is inevitable in CEA and even studies which purport to be concerned with technical efficiency raise allocative efficiency questions. Some form of league table analysis is inevitable when using CEA.

## **Methodological issues to allow results to be generalised**

If it is accepted that comparison of a wide range of interventions is inevitable, standardised methods must be used consistently across CEA studies to ensure external validity [21]. In practice published studies have differed significantly in the way they have calculated costs and health effects [84], and these methodological differences can lead to wide variations in estimates of CE ratios [16,53,58-60]. One result has been an increase in the number of methodology guides for CEA, with at least 30 published in the last decade - most recently [2,85-100]. In addition, a number of academic journals have issued methodological instructions for articles submitted for publication [90,101,102].

Rather than listing all sources of disagreement and confusion, we focus on the question of generalisability of results. No country has been or will be able to do all the studies necessary to give it a complete idea of which interventions are efficient and which are inefficient uses of its scarce health resources. There are simply too many interventions and not enough analysts. Decision-makers need to be able to have access to results from other settings which are also likely to be applicable to their own environments [21,103-106]. So the focus of this section will be on critical methodological issues that allow CEA results to be generalised from one place to another.

### ***Traditional incremental and generalised cost-effectiveness analysis.***

Textbooks recommend that incremental analysis is the theoretically correct form of CEA – requiring comparison of the additional costs of an intervention over current practice

with the additional health benefits [1,2,107]. Although this is appropriate in certain settings it does not fulfil all necessary requirements for sectoral priority setting. Firstly, incremental analysis, even of a simple study of a new technology versus current practice, will always require comparison with a range of other options, as stated earlier. Where new technologies have higher costs but produce higher health outcomes, for example, the question becomes whether these additional resources could produce more health benefits used somewhere entirely different – requiring explicit or implicit comparison with other ways of using the scarce resources.

Secondly, incremental analysis does not allow examination of whether current practice is efficient and should have been done in the first place. It simply asks if a small change improves efficiency. Yet the wide variations in CE ratios observed among interventions that are currently in use, discussed earlier, suggest there is considerable room to improve efficiency by moving from inefficient interventions currently in use to efficient interventions that are under-utilised. Related to this is the fact that where incremental analysis is undertaken with an inefficient intervention as the baseline, the result could well be to move further away from the optimal distribution of resources that would have resulted if the policy-maker had information on the efficiency of existing and new interventions at the same time [3].

To illustrate, a study on meningitis [76] compared new ways of dealing with the disease with the standard form of current care (mass vaccination during epidemics). Routine vaccination of five-year old children without mass vaccination during epidemics would be more costly, but would prevent more cases at a cost of an additional US\$ 50 per additional QALY saved. This number is difficult to interpret partly because there is no way of determining from this type of comparison whether the additional investment is worth undertaking. In addition, by framing the question in terms of the incremental analysis, it avoids the issue of whether current practice was worth doing in the first place. To answer these questions requires an assessment of a full portfolio of options – or a more generalised form of CEA [3].

Thirdly, incremental analysis is not generalizable across settings as it is specific to the starting point (i.e. current practice). For example, the CE of expanding coverage of immunisation programmes depends on the existing coverage rate, which varies across different regions and countries [54]. Moreover, the costs and effectiveness of delivering antimalarials closer to households will depend critically on whether a network of village health workers currently exists [28].

## ***Measuring effectiveness and costs***

CEA studies have often relied on process or intermediate rather than final outcome indicators. For example, the effectiveness of mass drug therapy for intestinal helminth infections has been measured in terms of the number of heavy infections, or the number of years of heavy infection prevented or cured [108]. Evaluations of vaccination programmes commonly report the number of children fully immunised as their indicator of success [60], while the number of impregnated bednets used, or the total number of people protected by nets, has been used for malaria prevention evaluations [109]. All

are assumed to be correlated with the final improvement in health that would result from the prevention or treatment of the disease in question. For technical efficiency purposes this is appropriate, but only where one of the options is both more effective and less costly than the other(s) and it is accepted that some type of intervention against that condition must take place. However, as stated earlier this is rare. The question whether it is worth paying the extra US\$ 7,000 to prevent an extra 1,123 children from being infected by switching from schistosomiasis mass treatment by a mobile team to reagent-strip testing by school teachers requires comparison with what could have been achieved by using the US\$ 7,000 somewhere else [79]. Comparing the protection of 1,123 children from schistosomiasis with children who would have been fully immunised if the resources had been allocated to the childhood immunisation programme is difficult.

This type of question, and the generalisability of results, requires the use of a final outcome indicator such as the DALY or QALY. This is not the place to discuss the relative merits of DALYs versus QALYs. Suffice it to say that final outcome indicators are required if policy makers are to gain maximum benefit from the economic evaluations that are undertaken.

Other questions important for generalisability relate to the source of estimates of costs and effects. Some CEA studies have used only one source - in their study on visceral leishmaniasis (VL) interventions in emergency settings the authors have only one source of effectiveness estimates [110]. Sometimes only one source is available. But where multiple sources exist, there is a consensus that all relevant sources should be considered to develop estimates of effectiveness. Systematic reviews and meta-analyses of outcomes are becoming more rigorous, as shown by the Cochrane meta-analysis of trials of impregnated mosquito nets in sub-Saharan Africa [111]. This allows CE studies to estimate lower and upper bounds of possible outcomes of interventions [28,112].

This trend is to be applauded. Major challenges remain, however. Most evidence on effectiveness is really closer to efficacy, coming from randomised studies. While this can be used as an upper limit of effectiveness, ways of generalising the results to allow for the fact that adherence (both provider and patient) in practice will be less than in controlled trials, that the quality of the support system may well be lower, and that the intervention is likely to be given to a wider or different group of patients or population than those in the trials, need to be found [113,114]. This is a major challenge for CEA.

Costs pose even more problems. Cost estimates for CEA are often taken from a single study with no attempt to review the possible range or uncertainty interval – with some notable exceptions [28]. Moreover, costs in the published literature are rarely reported in enough detail to allow readers to judge their validity, or to see how they might differ across settings. While this might well be a result of space limitations imposed by editors, the rigour with which effectiveness evidence is reviewed and reported does not as yet extend to publications on costs. Indeed, studies often report a single cost in terms of dollars, with no details of the physical inputs or their monetary values, making it difficult to reproduce the calculations; sometimes it is unclear what alternatives are being compared [105].

Generalisability requires reporting costs using the ingredients approach, where the physical inputs are reported separately from the prices. It also requires thorough review of the various sources and validity of cost estimates in the same way that is increasingly being applied to effectiveness reviews. It would be useful if editors of journals refuse to send papers for review unless the cost data behind the economic analysis was fully available to reviewers and based on the ingredients approach. As more journals begin to publish on the World Wide Web, they could also insist that authors agreed to publish the background costing spreadsheets on the web. Only then would reviewers and the reading public be in a position to judge the validity of the results. Only then would analysts in a different country to the one of the study be in a position to decide the extent to which the published cost data would be relevant to their settings.

There are many other small methodological differences between CEA studies – e.g. the choice of discount rate, whether or not to discount health benefits, and the treatment of indirect benefits (possible increases in economic production as a result of an intervention). Comparability requires standardisation, sometimes in an arbitrary way. To promote comparability, we will be releasing details of the assumptions for CEA to be supported by WHO in the near future. They build on the work of the published guidelines discussed earlier, as well as earlier work supported by WHO [89,95,100]. The difference is that the new guidelines are aimed specifically at the need to produce generalisable results.

Major features will be that CEA based on average costs (i.e. incremental analysis compared to the counterfactual) is more generalizable across settings than CEA based on incremental costs for independent interventions (although this will need to be combined with incremental analysis for mutually exclusive interventions -i.e. interventions, which cannot be undertaken at the same time). Costs should be reported using the ingredients approach, showing clearly how many resources are used by an intervention as well as the unit costs. Effectiveness of existing and new interventions should be evaluated in comparison with a “do nothing” option, again to allow transportability of results across settings. Finally, uncertainty intervals should be derived based on feasible assumptions about the range of possible costs and outcomes, using the best available evidence.

## **Long-term health effects.**

Many health benefits from interventions do not occur immediately. For example, the effects of preventing tuberculosis (TB) with BCG vaccination lasts approximately 15 years after immunisation [115,116]. Similarly, vaccinating children against hepatitis B will not result in lower rates of liver cancer and cirrhosis for approximately 45 years - although some of the other benefits would occur more rapidly [117,118].

This type of long-term effect is well accounted for in the literature where the costs and consequences of an intervention are traced over time and discounted back to their present values. The only controversy concerns the discount rate – what it should be,

whether health benefits should be discounted at all, and if so, whether they should be discounted at the same rate as costs [2,119,120].

Similarly, longer-term effects related to the impact of an intervention on the transmission of communicable diseases are increasingly being incorporated into studies of intervention effectiveness. For example, transmission models have been developed to examine the impact of different intervention strategies against tuberculosis [121,122], building on earlier work showing that an undiagnosed and untreated smear-positive source of tuberculosis infection would infect on average between ten and fourteen persons per year [123,124]. Similar models have been developed for other transmissible diseases such as HIV/AIDS [125,126]. Incorporating the total effects of treatment (or prevention) in terms of curing current cases as well as in preventing future cases greatly increases the observed cost-effectiveness of this type of intervention [115].

Other types of long-term effects have proved more difficult to include in CEA. The first involves conditions in children that might affect their ability to lead full lives in the future because of the impact of the disease on cognitive development or physical growth. For example, over a third of the world's population is infected with one or more species of parasitic worm, and in most communities these infections are most prevalent and intense in school-age children [127-131]. Intense infection with parasitic worms is associated with compromised physical growth, cognitive function and school performance, often interacting with the impact of micronutrient deficiency, anaemia and undernutrition [132]. Treatment of these infections in children has been shown to stimulate catch-up growth and enhance performance in some tests of cognitive function [127,129,133-136]. If these improvements are sustained, they should improve the individual's health and well being, broadly defined, over their entire lives.

For example, some types of employment opportunities in lower income economies depend on physical strength and endurance, so helminth treatment leading to long-term improvements in physical growth should result in lifetime benefits for infected children [137,138]. Similarly, there is a large literature showing a positive cross-sectional correlation between education and earnings, so if improvements in cognitive function lead to long-term increases in years of schooling, there would be substantial long-term benefits of to children of treatment during school age [139].

However, this type of effect has proved difficult to incorporate in cost-effectiveness studies for a number of reasons. Firstly, it is not yet clear if improvements in physical and cognitive development observed after short-term treatment result in bigger, more educated adults. Secondly, even if this information were available, it is not yet clear the extent to which people perceive physical size and educational attainment as factors directly influencing their quality of life (required to measure QALYs) or their levels of disability (required for DALYs).

The second long -term effect which has not yet received sufficient attention is the growth of resistance to pharmaceutical products and chemicals used to control disease vectors. Analytical methods must be developed to allow for the growth of resistance over time, and incorporate trade-offs between higher drug costs, immediate decreases in morbidity and mortality, and potential increases in resistance to replacement drugs that could lead to higher morbidity and mortality in the future [28,82].

One response to observed increases in resistance has been to suggest that use of the particular product, for example an antimalarial or antibiotic, should be tightly controlled [28]. While this would slow the spread of resistance, thereby reducing costs, it could well mean that fewer people would benefit from the intervention now, thereby costing lives. Selected work has been done to test ways of slowing the spread of resistance by encouraging greater adherence with recommended treatment doses [140], but most studies of interventions to control infectious diseases have not taken into account the impact of the interventions on resistance – they consider only the short-term effectiveness of the interventions [17,82,141].

Including the impact on resistance, and the possible trade off between saving lives now and keeping drugs available longer, is not easy because it is difficult to predict the future patterns of resistance. However, it is critical to a full understanding of the full impact of interventions against many communicable diseases. This has been illustrated recently in studies showing that the cost-effectiveness of malaria interventions varies significantly under different scenarios of the spread of resistance [28,141].

## **The affordability of cost-effective interventions**

A major problem in interpreting the results of individual CEA studies is that there will never be sufficient resources to do everything deemed to be cost-effective if each intervention is regarded in isolation. For example, the World Bank (1993) estimated that a minimum package of basic public and curative health interventions, each of which was considered to be cost-effective in its own right, would cost US\$ 12. Yet this package was unaffordable in many of the poorest countries where health expenditure per capita was as low as US\$ 2 [17,23].

Priority setting requires information on costs and effects but affordability is also critical. If a new intervention is deemed to be cost-effective, it can be undertaken only if the required resources are taken from some other use - either from other health interventions or from interventions that produce benefits outside the health sector. So, for example, Politi and colleagues estimated that switching from melarsoprol to eflornithine to treat late-stage African trypanosomiasis would cost an additional US\$ 207.7 for each additional DALY averted, and this appeared to be cost-effective in terms of the yardsticks used at that time. However, the switch would cost Uganda US\$ 284,899 per year [142]. Decision-makers could not make a decision on the basis of these numbers alone. Donors, for example, would require data on the cost-effectiveness of alternative health interventions they could fund with those resources, and governments with fixed health budgets would need to identify which interventions currently undertaken could be reduced or eliminated to fund the new trypanosomiasis treatment.

At a minimum, CE studies should identify the full resource implications of implementing the intervention they identify as cost-effective, a practice that is slowly beginning to occur in the literature [25,27-30]. But ideally, decision-makers need information on the CE of a wide range of competing interventions, both new and existing. This would not be so important if all interventions were infinitely divisible, i.e. if they could be undertaken at all possible rates of coverage. In such cases, decision-makers could simply start with

the most cost-effective, and work their way to the point at which their resources were exhausted, even if that meant implementing an intervention at less than full coverage.

However, many interventions are “indivisible” - they must be done at a certain level or not at all for technical or political reasons. For example, it would be unacceptable for a government to offer childhood immunisation to only 40% of the children who presented at a health centre, or malaria treatment only to urban residents. This means that CE studies, in addition to estimating standard CE ratios, should identify the coverage levels that are technically or politically feasible, and provide decision-makers with a full estimate of the resources required.

In fact, we do not believe that it is useful to use CE ratios in the formulaic way described above even if all interventions were fully divisible. Nor do we think it is useful to define rigid minimum packages based on CEA. This is partly because of the uncertainty surrounding some estimates of CE, and partly because improving the aggregate level of population health - the implicit objective of CEA - is only one of the goals that need to be considered when allocating resources[143]. We argue that decision-makers need access to “menus” identifying a range of interventions that are cost-effective, and those that are not, in their settings (and the likely uncertainty surrounding these estimates). This information would enter the policy debate locally, to be weighed alongside other goals and objectives of the health system, and other reasons for allocating scarce health resources in particular ways [5].

## Discussion.

The World Health Report entitled *Health Systems: Improving Performance* [5] suggested that the health systems of many countries were not performing as well as they could for the observed levels of health expenditures. Performance could be increased by eliminating waste (improving technical efficiency) and ensuring that priorities are set to ensure that scarce resources are used to provide the most cost-effective mix of interventions (improving technical efficiency). To do this requires information on the costs and effects of a wide range of interventions.

There has been a rapid increase in published studies seeking to provide this information over the last two decades, partly because of the recognition that societies cannot afford access to every intervention that has some chance of improving health. Although a majority of these studies have been performed in North America and Europe, increasing applications have been undertaken in developing countries focusing on communicable diseases. Some of the evidence is already useful for policy. For example, childhood immunisation interventions are very cost-effective at current coverage rates. Despite this, decision-makers are faced with many perplexing problems. For example, is it better to add new vaccines to existing schedules or try to expand the coverage of existing vaccines, if additional resources become available?

The concept of opportunity cost, or what else could be done with scarce resources, is paramount, and decision-makers require information on what could be achieved (i.e. the cost-effectiveness) of a wide range of interventions in their settings. Given that few

countries have the resources to undertake all the necessary analyses, it is important that studies in one setting are undertaken in a way that allows generalisability to other settings. Some of the most important challenges this poses for CEA have been identified in this chapter. Firstly, incremental analysis is appropriate to local decision making when policy-makers are constrained to keep the current interventions and can consider only marginal improvements. However, this form of analysis does not allow re-evaluation of the efficiency of existing interventions and is not transferable across settings. CEA based on average costs and effectiveness measured in comparison with a "do nothing" option is more transferable.

Secondly, data on costs and effectiveness are often not presented in useful ways. The challenge on the effectiveness side is to adjust the evidence from efficacy studies to identify effectiveness when applied to different patient or population groups, with local variations in adherence, coverage, and infrastructure. In terms of costs, it is important for studies to report the physical resources used in an intervention as well as unit costs, to allow analysts and decision-makers to evaluate the extent to which costs might vary across settings.

Thirdly, some long-term effects are still not well incorporated into CEA, especially those affecting child development and drug resistance. These questions are technically challenging and will require more concerted efforts over the next few years.

Finally, it is important for analysts to provide decision-makers with estimates of the resources that would be required to implement the intervention in their setting. We do not suggest that policy makers will set priorities solely on the basis of CEA even if studies were revised to incorporate the suggestions in this paper. Evidence on cost-effectiveness will be one input to the policy debate when setting priorities for the allocation of scarce resources. Policy makers will also be concerned with the impact of proposed investments on equity and responsiveness, for example see the World Health Report 2000 [5]. They would also need to consider possible transactions costs involved in moving from an existing mix of interventions to a more cost-effective mix. However, a change in the focus of CEA to incorporate the elements suggested in this review will make it easier for policy makers to incorporate the results of research into their decisions.





## **Chapter 3**

# **Sectoral cost-effectiveness analysis in practice**

Based on:

Generalized Cost-effectiveness analysis: A guide.

Tan Torrest-Edejer T, Baltussen RPMP, Adam T, Hutubessy RCW, Acharya A, Evans DB, Murray CJL.

World Health Organization, Global Programme on Evidence for Health Policy: Geneva.2003.



## Introduction

The objective of this chapter is to provide the reader with a clear understanding of the concepts, benefits and practical implications of sectoral CEA. Therefore, the focus of this chapter is on those methodological issues, which make sectoral CEA different from other forms of CEA, such as e.g. the definition of the counterfactual for analysis. By sectoral CEA we mean that all alternatives uses of resources for a number of distinct programme interventions are evaluated in a single exercise with an explicit budget constraint [13]. Sectoral CEA and other forms of CEA i.e. incremental CEA share many of the same methodological issues (such as the in- or exclusion of productivity costs, perspective, generic outcomes or not), or the same techniques (such as the methods for the allocation of overhead costs). Because these issues are related to both sectoral CEA and CEA in general, these are not discussed in detail in this chapter but the reader is referred to literature in some instances [1,2,19]. Although theoretical foundations are debated, little is done on actual methodological implications [7,144].

The WHO-CHOICE<sup>2</sup> initiative is a one of the few attempts to standardize sectoral analysis methods for priority setting in health by proposing the so-called 'generalised CEA'. Here, generalised is described as a form of sectoral analysis which aims to arrive at cost-effectiveness estimates that are in principle valid for other, comparable settings and serve as a basis for more specific incremental analyses.

The ideas and concepts presented in this chapter are derived from a theoretical paper by Murray and colleagues [3] and the practical guidelines of the WHO-CHOICE initiative on generalised CEA. These are designed to help the policy makers understand the benefits of this type of economic analysis [145]. This chapter critically reflect the basic features and ideas of generalised CEA as an example of one of the uses of sectoral CEA.

The chapter firstly discusses the concept of sectoral CEA. Next, the central element in the more general use of sectoral CEA, the definition of the counterfactual, i.e. the (hypothetical) situation reflecting the absence of health care against which interventions is evaluated. The implications of this concept on estimating effectiveness and costs of interventions are discussed in subsequent sections.

## Concepts of sectoral CEA

Sectoral CEA has been developed as a reaction to the broader research and policy question it poses compared to traditional approaches to CEA. Therefore, this section starts off outlining some of the uses of CEA, the requirements and policy context of non-sectoral methods, and directions for adjusting these methods including the reasons for the development of sectoral CEA in particular.

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<sup>2</sup> Choosing Interventions that are Cost-Effective project: see [www.who.int/evidence/cea](http://www.who.int/evidence/cea)

## *Uses of CEA*

The growing use of CEA to evaluate the efficiency of specific interventions is dominated by studies of prospective new interventions compared to existing practice [46,146]. 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 or with a fixed price cut-off point representing the assumed social willingness to pay for an additional unit of benefit. In many cases this type of analysis is performed in order to generate CE information for context or disease specific resource allocation decisions.

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 [147,148]. This is called sectoral CEA. This type of analysis does 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. Implicitly this type of analysis requires decisions on how many additional resources need to be transferred from another health intervention or from another sector. 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 [149], the World Bank Health Sector Priorities Review [16] and the Harvard Life Saving Project [15]. Of these, only the World Bank attempted to make international or global standardized comparisons of sectoral cost-effectiveness.

At the heart of this broadened policy use is the notion that health resources 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, moving resources from cost-ineffective interventions to cost-effective ones could enhance the allocative efficiency of the health sector. 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 [150,151].

As chapter 1 shows, current CEA practice 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 CEA 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. Moreover, 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 [9]. For most countries, but particularly for low and middle-income countries where the majority of the world's poor live, 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. Finally, the difficulties of generalising context-specific CEA studies have been institutionalised by the proliferation of multiple national or sub-national guidelines for CEA practice, all using slightly different methods [152]. To date, one single international standardized set of guidelines has not to date been developed.

## ***Two sectoral uses of cost-effectiveness analysis***

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<sup>3</sup> but the focus here 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 set of resource constraints (hereafter called a budget), a set of options for use in the budget, and a series of other (ethical or political) constraints. The set of constraints in this 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. 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 which 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.

The results of this type of analysis suggest replacing a less efficient intervention aimed at a particular condition by a more efficient alternative aimed at that condition, or if current practice involves doing nothing, it might suggest adding a new intervention. But it is not used to eliminate interventions against a particular condition that are not efficient. For this reason, this is referred to this standard practice as intervention mix constrained CEA or IMC-CEA – there is a constraint against eliminating interventions that are currently in place unless they are replaced by another intervention targeting the same disease or condition [3].

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, which contributes 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 at the international and national level. 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

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<sup>3</sup> For example, CEA may be employed by pharmaceutical firms to set price levels of pharmaceuticals.

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 conceptualise 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 starting point for evaluating the directions for enhancing allocative efficiency in a variety of settings.

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 generalised approach will enhance transferability and will make it possible to provide useful, timely and affordable information on the health generating characteristics of interventions. In some sense, there is a trade-off between making CEA information precise to a given context and the time and resources required for that contextualization. For policy-making, in practice, there seems to be a preference for the more general use of CEA or generalised CEA [153], which indicates the outcome of that trade-off. Here, results from incremental analysis are often used in a generalising way.

### *The development of the generalised CEA*

One of the requirements for the more general use of sectoral CEA is the need to identify current allocative inefficiencies as well as opportunities presented by new interventions. Generalised 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. Consequently modification of the standard IMC-CEA is required i.e. lifting the constraint on the existing mix of interventions to evaluate the cost-effectiveness of all options including currently funded interventions.

In brief this general use of sectoral CEA can be summarized in two propositions.

- 1) In theory, the costs and benefits of a set of related interventions should be evaluated with respect to the counterfactual of the related interventions i.e. a hypothetical reference situation in the absence of any intervention. This would provide 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 initially be presented in a single league table as the first step of policy analysis. Subsequently the decision would be made about the appropriate cut off point for classifying interventions as very cost-effective, very cost-ineffective and somewhere in between, as described earlier.

By analysing the costs and benefits of sets of related interventions with respect to the counterfactual of those interventions, the results are likely to be more transferable from

one population to another. 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. But one major factor limiting the relevance of IMC-CEA results in one population to another population, namely different current mixes of interventions, can be removed by using the more general use of sectoral CEA. To put it another way, the counterfactual 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 set. It will depend on the development of the health system and on the epidemiological pattern.

Although the generalised CEA approach could be useful to the identification of the efficient mix of interventions, IMC-CEA is still required, as an additional analysis once the efficient mix of interventions has been identified. Since both uses of sectoral CEA serve different policy questions within different decision making context, both types of analysis are complementary to each other. IMC-CEA is then used to provide information on how this efficient mix of interventions can best be achieved, starting from the current mix of interventions. In practice, this reallocation of resources entails a long process of taking away resources from the current mix of interventions (e.g. curative care) to allocate them to the efficient mix (e.g. preventive care), including many other shifts of resources in the real world. In this process of reallocation, IMC-CEA is instrumental to assess the most efficient way to move from the current mix of interventions to the most efficient mix of interventions. Since populations differ in their current mix of interventions, the most efficient pathway of achieving the efficient mix of interventions will also differ, and context specific IMC-CEA may be useful in this respect. In other words, where the generalised CEA is instrumental to define non-context specific efficient mixes of interventions as a long-term goal for decision makers, the actual optimal pathway towards this goal is context-specific and could be subjected to additional or complementary IMC-CEA.

## **Defining counterfactual situation of analysis**

### ***Interpreting the counterfactual***

The more general use of sectoral CEA requires the analyst to consider what would happen, starting from today, if all resources in the health sector could be reallocated. The counterfactual against which all interventions should be evaluated is what would happen if none of the current set of interventions were implemented in a particular disease area. The cost-effectiveness of all possible interventions – individually and in combination as shown above – are assessed in relation to this counterfactual. The next question is now to define ‘the absence of any interventions’. It is not possible to estimate the current levels of population health in every setting assuming that none of the existing or past interventions had ever been undertaken. It is possible to estimate what would happen if all existing or implemented interventions ceased forthwith – that is, what would happen if they were eliminated today.

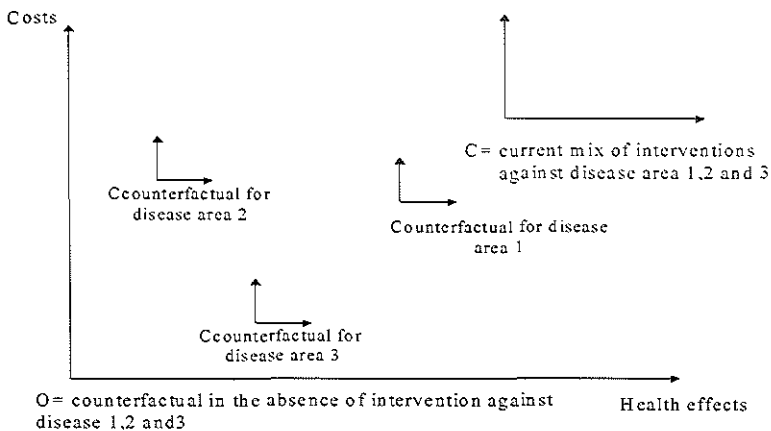
The counterfactual does not necessarily reflect an hypothetical equilibrium situation in which one observes a stable prevalence of disease as is often used in health modelling as a reference situation. Rather, if one for example supposes a sudden absence of



interventions (*'what would happen if all existing interventions were eliminated today'*), model hazard rates change and cause the modelled epidemiological situation to be out of balance: eventually, prevalence of disease will adapt to the counterfactual hazard rates and the equilibrium will be restored. However, the time lag involved will differ per disease- or intervention-cluster and may pass the time horizon of analysis. The counterfactual defined this way does not represent a single epidemiological situation, but merely a transition of the epidemiological profile of disease over time.

The definition of the counterfactual (over time) in terms of its epidemiological profile depends on a number of factors. Firstly, it depends on the past history of interventions within the group of interrelated interventions: e.g., in case many preventive interventions have been in place historically, current incidence of disease is relative low and the present epidemiological profile will be characterized by a relative low prevalence of disease. Since the present epidemiological profile is the starting point for the counterfactual, also the counterfactual (over time) will be characterized by a relative low prevalence of disease. Secondly, it depends on the development of infrastructure, which relates to factors within the health system such as the existing training level of health staff, but also to factors outside the health system such as roads and education that may affect the current epidemiological profile of a population. Since these factors may vary across populations, also the definition of counterfactuals may vary across population: in the ideal case, separate analyses should be done for every sub-population in a country. However, because of research-constraints, this is often not possible, and analysis is to be carried out for populations that are assumed to be relatively homogeneous.

In defining the counterfactual, it is not necessary to assume that no interventions at all exist. Since it is clear that the costs and health effects of many interventions are unaffected by the existence of others, a key issue is to define clusters of interventions which are interrelated either because they interact on either costs or effects or because



**Figure 3.1.** Condition specific counterfactuals on the cost-effectiveness plane

they are mutually exclusive. The counterfactual, therefore, can be defined as what would occur if a specific group of interrelated interventions were eliminated today. Given this definition of the counterfactual as that state in which groups of interrelated interventions no longer exist, different so-called 'condition-specific counterfactuals' can be defined within a generalised CEA framework. These counterfactuals are thus defined by the elimination of a specific group of interrelated interventions, while interventions in other groups of interrelated interventions continue to exist but are assumed to have no impact on incremental costs and health effects of the interventions under study and are only reflected in an unchanging residual mortality. Since different condition-specific counterfactuals are connected with each other through their excess mortality rate it is possible to determine the counterfactual situation in the absence of interventions.

Graphically, the condition-specific counterfactual of different group of interrelated interventions can be represented in the cost-effectiveness plane where C represents the current mix of interventions referring to all disease areas (in this example three disease areas), and O represents the counterfactual when all available groups of interrelated interventions were eliminated (*Figure 3.1*). The figure displays different hypothetical examples of condition-specific counterfactuals, their location in the cost-effectiveness plane depending on the absolute costs and health effects in the health system in the absence of the group of interrelated interventions in question. The cost-effectiveness of individual interventions within a certain intervention cluster is dependent on their location in relation to the condition-specific counterfactual. So, while the existence of other intervention clusters may affect the absolute location of the intervention on the cost-effectiveness plane, cost-effectiveness results are not affected since they are a function of incremental costs and incremental health effects in comparison to the origin of the condition-specific counterfactuals.

Again, the implicit assumption here is that the costs and effects of implementation of an intervention in one intervention cluster is independent of the existence of other intervention clusters. Whether this assumption holds depends on the rigor with which clusters of interventions have been defined. In case when clusters capture all possible interactions in costs and health effects of all interrelated interventions, costs and health effects of interventions with a certain cluster are not affected by the existence of other groups of interrelated interventions. If this would not be the case, not only total costs and effects of the intervention cluster under study would be affected by the existence of other cluster of interventions being in place (i.e. the location of the condition-specific counterfactual), but also the incremental costs and effects of the individual interventions under study (location in relation to the condition-specific counterfactual).

On a more practical level: in some disease areas, costs and health effects of a large number of interventions are (remotely) interrelated, and clear boundaries are not easy to be drawn. For example, costs and health effects of a cluster of interventions in diarrhoea control are interrelated with a large number of other interventions, such as vitamin A supplementation, oral dehydration supplementation (ORS) and breast-feeding. Whether the benefits evaluating diarrhoea control and breast-feeding in a single framework outweighs the extra analytical effort is a debatable decision and in practice is left to the discretion of the analyst. As another example, consider costs and health effects of a cluster of interventions in trachoma control. Except for small changes in residual mortality these interventions are likely to be unaffected by many clusters of

interventions in other disease areas (e.g. cardiovascular diseases) and therefore, the analysis of trachoma control in a condition-specific counterfactual framework seems warranted.

### ***Defining clusters of interventions and interactions***

Closely related to concept of (condition-specific) counterfactuals is the definition of a cluster of interventions. Groups of interventions that are interrelated should be evaluated together in one cluster, and there are two situations when this is the case.

Firstly, many interventions interact in terms of either costs or effects at the population level and interacting interventions are done in different combinations in different settings. In other words, the health impacts of undertaking two interventions together are not necessarily additive, nor are the costs of the joint implementation. To understand whether they are efficient uses of resources independently or in combination requires assessing their costs and health effects independently and in combination. Only by this approach, it is possible to account for interactions or non-linearities in costs and effects.

For example, the total costs and health effects of the introduction of bed-nets in malaria control is likely to be dependent on whether the population is receiving malaria prophylactics: this means that three interventions would be evaluated – bed-nets only, malaria prophylactics and bed-nets in combination with malaria prophylactics. By evaluating such interrelated interventions in a single cluster, interactions can be captured and a more realistic estimate of cost-effectiveness can be produced. Traditional incremental analysis focusing on the introduction of the bed-nets would emerge from this analysis.

Secondly, mutually exclusive options should be evaluated together, i.e. interventions that can by definition not be implemented simultaneously in the same population, for example, annual and biannual breast cancer screening of individuals. By defining such interventions as mutually exclusive, and by evaluating them in a single cluster, it is ensured that only one of the interventions may appear in an optimal mix of interventions.

Figure 3.2 illustrates interactions using hypothetical data for a cluster of interventions for tuberculosis: passive case detection and treatment with DOTS (A), BCG at 50% coverage (b1), BCG at 75% coverage (b2) and BCG at 100% coverage (b3). 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 (respectively ab1, ab2, ab3). 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.

The interaction of the benefits of the two programmes can be estimated, here using a multiplicative model. In *Figure 3.2* the cluster of interventions – including each individual intervention and the possible combinations – are depicted and can be used to develop a league table. The intervention with the smallest slope (BCG at 50% coverage – b1) is

the most efficient and should be done first if funds are available. The slope from b1 to any other point should then be assessed and the lowest slope chosen, and the process is repeated. This results in the following sequence of choices for this set of mutually exclusive interventions: BCG at 50% coverage (b1), BCG at 50% coverage combined with passive detection and treatment (ab1), BCG 75% with detection and treatment (ab2) and BCG 100% with detection and treatment (ab3). BCG at 75%, BCG at 100% and passive detection and treatment alone do not appear in the list as they are dominated by the other alternatives. The decision rules of generalised CEA therefore require all interventions and combinations to be evaluated compared to counterfactual or 'doing nothing', and then the incremental analyses built on top of the most cost-effective option.

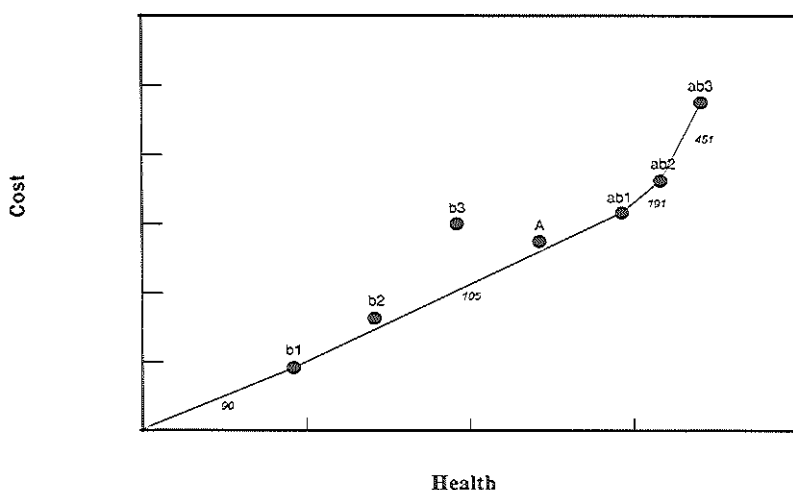


Figure 3.2. Costs and health benefits of interventions with cost and effectiveness interactions

In the literature on cost-effectiveness [154] 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.

## Assessing the effectiveness of interventions

This section examines issues related to the estimation of the denominator term in the cost-effectiveness ratio, which is the difference in effectiveness between an intervention and the counterfactual to which it is compared (the net effect). This section starts off by a discussion on how to estimate the counterfactual for analysis, which is one of the most important challenges in conducting sectoral and also CEA. This is followed by a discussion of the estimation of intervention effectiveness. The primary objective of this section is to review the process of estimating effectiveness specifically for generalised CEA, not effectiveness in CEA in general. Since the two share many of the same techniques, e.g., the reliance on models to combine data from various sources, these are not discussed in this section. In those instances, the reader is referred to other literature (e.g. [155]).

### *Estimating the counterfactual*

To be useful in CEA, the difference in effectiveness between the intervention and the counterfactual set requires a single numerical estimate, in terms of QALYs or DALYs. The difference is then considered as the intervention effectiveness. To actually estimate the counterfactual in terms of the number of QALYs or DALYs, a number of steps are

required. The first step involves the definition of the cluster of interrelated interventions to capture all relevant interactions between costs and effects of different interventions. In the second step, the impact of the hypothetical elimination of all interventions in this cluster needs to be assessed in terms of the epidemiological profile of the disease under study. This will be used as an input to the third step: the construction of a population model to estimate the impact of this epidemiological profile on the number of DALYs or QALYs at the population level. These steps are discussed in turn. Wherever the term counterfactual is used in this section, it refers to the condition-specific counterfactual, except where explicitly stated.

### ***Step one: Defining cluster of interrelated interventions***

As noted above, sectoral CEA requires the analyst to consider what would happen, starting from today, if all relevant interventions were eliminated. It was said that, in defining the counterfactual, it is not practical or necessary to assume that no interventions at all exist, and that the costs and health effects of many interventions are unaffected by the existence of others. The counterfactual, therefore, was defined as what would occur if a specific group of interrelated interventions were eliminated today. Given this definition of the counterfactual as that state in which groups of interrelated interventions no longer exist, different so-called 'condition-specific counterfactuals' can be defined within the generalised CEA framework.

### ***Step two: Defining the epidemiological profile of the counterfactual***

This section discusses how the counterfactual can be expressed in terms of its epidemiological profile. Starting point for defining the epidemiological profile of the counterfactual is often an existing epidemiological situation.

How the counterfactual is to be estimated in practice depends to a large extent on the nature of the intervention cluster under study. In case in this cluster, the current intervention mix comprises only preventive interventions, affecting disease incidence, then their hypothetical absence will only affect the incidence of disease and to some extent to disease survival (see chapter 7). In case the relevant intervention mix includes only curative interventions, then the counterfactual can be characterized by a change in the remission and/or case-fatality rate (see chapter 5 and 6). In some other instances, the hypothetical elimination of interventions may reflect in a change in the severity of the non-fatal health outcomes. However, in most intervention clusters, the hypothetical absence of interventions is reflected by a change in a number of hazard rates simultaneously. To adequately describe the counterfactual for an intervention cluster, they also need all to be quantified and modelled simultaneously. It is important to note that the counterfactual is defined as the absence of interventions over the life time horizon of the individuals in a population: this implies that also the counterfactual hazard rates need to be estimated for all ages, existing cohorts and the period under consideration.

In some instances, the counterfactual hazard rate may be easy to define. For example, in the case of cataract intervention cluster, the only interventions are of surgical nature. Since there is no natural remission from cataract, the hypothetical absence of these interventions implies a zero remission rate. However, for most intervention clusters, deriving the counterfactual hazard rates is more complicated. There are a number of

approaches to obtain the hazard rates<sup>4</sup> reflecting the absence of interventions, including the use of observed patient data, or using the method of back adjusting. Special attention should be paid to the quality of the counterfactual hazard rate estimates.

### *Using observed patient data*

*Natural history models.* Conceptually an attractive option is to acquire information on hazard rates in the absence of interventions is the use of natural history models. (LN: this is not the situation describe in the previous situation) Such models illustrate the progression of a disease in the absence of treatment. In theory this approach refers directly to the counterfactual, and has therefore much appeal. Natural history models can be based on data from various origins. Firstly, data may refer to deprived populations whose access to care is limited, e.g. the aboriginal population in Australia. In the absence of interventions, observed hazard rates could be interpreted as natural hazard rates. Secondly, considering population groups whose disease indicators reflect the absence of care in a particular area can mimic the natural history of disease. For example, the natural (or counterfactual) incidence rate of diabetes mellitus was assumed to be similar to badly regulated diabetes patients (i.e., with a minimum glycosylated haemoglobin (HbA1c) level of 10%). Thirdly, natural history models may be based on cohort studies, and it is this kind of models which can often be identified in the literature (e.g. [156-158]). Many of such models are derived from cohort studies where some intervention is already being applied. Analysts need to make sure that no intervention in the cluster under study was implemented.

*Trial data.* Another option is to use data collected in trials, such as randomised controlled trials (RCTs). RCTs randomly assign subjects to study arms to study the effectiveness of interventions: the randomisation enhances the comparability of the study and control groups and provides a more valid basis for inferring that the intervention actually caused the observed outcome. For the intended use of estimating counterfactual hazard rates, the control group data is of interest if this refers to a do-nothing scenario. The analyst needs to ensure that 'do-nothing' actually refers to the absence of any intervention, and does not imply the consumption of 'usual care'. In case the regimen in the control group was not 'do-nothing' but the administration of placebo's, analysts must in addition be aware of the placebo effect on the health outcome. A recent meta-analysis has shown a beneficial effects of placebo for trials with subjective outcomes, but none for trials with objective outcomes [159]. Analysts may choose to make adjustments to extract out the 'placebo effect'.

*Observational study data.* In observational cohort studies, a defined population is followed over time to observe the rate of occurrence of the outcome according to treatment. To obtain counterfactual hazard rates, interest is in the outcomes for the subgroups not receiving the treatment. Again, these outcomes are only useful if this subgroup is not receiving any intervention at all (related to the intervention cluster), and not just abstain from the treatment of interest.

The chances of identifying counterfactual hazard rates using the above three approaches is limited in developed countries. Because of the wide availability of care,

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<sup>4</sup> Population models typically make use of instantaneous transition rate or hazard rate to express e.g. incidence or remission rates. This is a more accurate representation of transitions between health states than the use of proportions, often applied in decision-tree analysis (see Mandelblatt et al. in Gold et al. for more detail[2]).

ethics may prevent studies to provide study arms with no (or a placebo) treatment at all. This situation may be different in some developing countries: despite the presence of effective treatments elsewhere, these treatments may not yet have been considered as standard in the local context, and therefore no treatment or even placebo is provided in the comparison arm.

### ***Back adjusting***

Conceptually, eliminating the impact of interventions, i.e., by considering their coverage and their effectiveness can also assess the counterfactual hazard rates. This approach can be labelled 'back adjusting' since the analyst makes inferences on the current epidemiology, and calculates backward to estimate counterfactual hazard rates (note that the use of observed patient data to estimate counterfactual hazard rates is irrespective of current epidemiology) [145]. More specifically:

$$\text{counterfactual hazard rate} = [\text{current hazard rate} / (1 - (\text{interventions coverage} * \text{intervention effectiveness}))]$$

The approach assumes that the (i) mix of interventions currently being provided is known, including (ii) the coverage rates of the individual interventions, and (iii) their effectiveness. Especially the latter is a critical assumption since effectiveness of implemented interventions can obviously not be easily estimated, and may differ considerably from efficacy as measured in optimal circumstances. In practice, this approach uses efficacy estimates in or without a combination with crude coverage estimates. As will be discussed in chapter 8 of this thesis many other critical factors will come in when operationalising experimental effectiveness estimates into practice.

### ***General quality issues***

When using the above approaches, analysts need to be very careful by extrapolating identified counterfactual hazard rates to other contexts than the study contexts. For example, there may be important genetic or environmental differences in the natural history of a disease that may differ across populations. Especially in infectious diseases, the context of where the disease occurs can change transmission dynamics. Clearly, this will not apply to all diseases. Moreover, observed patient data may actually describe the natural course of the disease without treatment, but these studies may refer back to periods long ago. There may be concerns about extrapolation of such data to the present since the health outcomes may also be dependent on other confounding, health and non-health care, variables which change over time, e.g. educational or nutritional status. Therefore, although the use of observed patient data is conceptually very attractive, the analysts must take great care with their interpretation to derive the counterfactual for a particular intervention cluster. Similar arguments apply to the use of 'back-adjusting': analysts should ensure the representativeness of their effectiveness (or in many cases: efficacy) estimates beyond the actual study context.

A critical issue in defining the counterfactual is the internal consistency of the various counterfactual hazard rates. Internal consistency is warranted when all relevant hazard rates stem from the same epidemiological data set (e.g. from a single longitudinal study), but may be problematic if the rates are obtained from different studies. For example, natural remission may be estimated to be higher than natural incidence of disease if data come from different sources, which does not reflect an equilibrium situation, also not in



the long run, and can therefore be qualified as inconsistent. Software such as DisMod<sup>5</sup> has been developed to warrant consistency in epidemiological data as currently observed, and can also be used to maintain consistency in counterfactual hazard rates under the equilibrium assumption. Moreover, DisMod can be used to estimate missing hazard rates. However, its application is limited: in the counterfactual, prevalence of disease is considered as a dependent variable, which implies it cannot be used as benchmark for analysis.

Depending on the level of detail required and the nature of the disease, age- and sex-specific counterfactual hazard rates may need to be estimated. However, often, available only provides a single hazard rate because of the small sample size of the related study, and the analyst need to determine appropriate age and sex function for specific hazard rates. Again, DisMod can be of use, since it incorporates a number of such functions. Furthermore, independent of interventions, hazard rates may change over time reflecting a changing disease epidemiology. Analysts may wish to take such secondary trends into account.

As discussed, all the proposed methods have limitations and the approach to be chosen depends primary on the specific research which interventions to evaluate for whom, and on the availability of studies and their quality. It is clear that uncertainty analysis using different assumptions for the counterfactual set needs to be undertaken.

### ***Step three: Constructing a population model***

The third step to define the counterfactual is the construction of a population model to estimate the impact of the counterfactual hazard rates on the QALYs or DALYs at the population level. Note that the construction of a population model is equally important to the estimation of intervention effectiveness. A population model describes the health experience of a population conditional on a number of health states (such as healthy, death, ill) and events (or transitions between health states), such as incidence, remission and mortality, reflected in hazard rates. As a function of these hazard rates and the starting population distribution in the various health states, a population model describes population health in terms of QALYs or DALYs, over the lifetime of the individuals in the population. The analyst must define a population model that is able to incorporate all information necessary to adequately define the counterfactual (as aforementioned) and the evaluation of interventions (see next section). The interested reader is referred to Mandelblatt et al.(1996) [160] and Kuntz and Weinstein (2001) [155] for a detailed discussion of the use of models in CEA.

### ***Estimating the effectiveness of interventions***

Many methodological issues in the estimation of effectiveness of interventions, such as the use of systematic review studies or the application of models, has been described

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<sup>5</sup> The original version of Dismod (DisMod v1.0. President and Fellows of Harvard College. All rights reserved, 1994) is available from the WHO website at <http://www.who.int/whosis>, under Burden of Disease activities. Installation instructions are also provided on the website. Also available is DISMOD II, a new software system developed to provide a full graphical interface, database storage capabilities and substantially enhanced features and options. The usefulness and the limitation of this generic disease model that describes the relation between incidence, prevalence and mortality has critically been discussed in a paper by Kruijshaar et al. [361]

in detail elsewhere (e.g.[2] ). Of special interest to general use of sectoral CEA is that the effectiveness of interventions should be compared to the counterfactual, i.e. the absence of interventions. In that respect, the data sources for the estimation of effectiveness parameters are very much related to those suggested for use in defining the counterfactual.

The use of trial data is limited to the extent that the effectiveness of interventions has been derived in comparison to doing nothing, i.e. the absence of any intervention. This disqualifies the use of many (recent) studies that typically estimate the effectiveness of interventions in comparison to current practice. As said above, analysts may choose to make adjustments in case interventions has been compared to a placebo, in order to cancel out the placebo effect. Although the chances of identifying effectiveness studies – using the absence of interventions as comparator – may be low in developed countries, they may be higher in some developing countries: despite the presence of effective treatments elsewhere, these treatments may not yet have been considered as standard in the local context, and therefore no treatment or even placebo is provided in the comparison arm.

### ***Estimating costs***

This section discusses a number of methodological issues related to estimating costs in Generalised CEA. In applying sectoral CEA, groups of related interventions are analysed with respect to the 'counterfactual', i.e., the absence of interventions. This has implications for the inclusion of some cost items, i.e. existing infrastructure, and joint costs. Again, the focus of this section is only on those issues which are specific to general use of sectoral CEA: the reader is referred to other literature for discussion of issues in the measurement of costs which are relevant to any form of CEA.

#### ***Costs in the counterfactual***

In theory, the absence of any intervention would be reflected in zero costs. However, some costs can be assumed to be existing or ongoing and will continue at the same level regardless of the different mix of interventions that are delivered with other resources. Since sectoral CEA focuses on the redistribution of resources as allocated to interventions, such 'ongoing' costs do not need to be included. Two types of 'ongoing' costs can be identified.

The first type relates to the current level of education of health professionals. If the skills required to deliver an intervention are already available, training costs to develop those skills should not be included as part of the intervention costs. However, if those skills are not already available, such costs should be included.

The second type related to costs of central administration that are part of the overall planning and management of the health system and that are unrelated to the development and implementation of particular interventions should not be included. Some activities of a Ministry of Health, for example, would exist and have a certain staffing profile independent of any particular set of interventions that may be done in the country for the available resources.

### ***Intervention costs***

Once the counterfactual has been identified in generalised CEA, the next step is to consider what it would cost to introduce the intervention(s) under study. There are two specific issues to generalised CEA, i.e. the measurement of changes in infrastructure related to the implementation of an intervention, and the inclusion of interactions of costs in clusters of interventions (joint costs).

### ***Changes in infrastructure***

Intervention-mix-constrained CEA typically only considers the incremental costs of an intervention, i.e. marginal changes in resource use because of the implementation of an intervention within a certain disease or therapeutic area. Often, costs of a mere administrative nature are not included as these are not expected to change in case alternative interventions are introduced. generalised CEA needs to take a broader approach, and needs to capture all changes in resource use related to an intervention which are prone to change when resource are reallocated across disease areas.

### ***Joint costs***

The evaluation of cluster of interventions requires the evaluation of each intervention singly and in combination with other, related, interventions. This requires identifying all resources required to establish and run each intervention, including intervention-specific overheads. In practice, the simplest way to identify some of these overheads is to identify shared costs used by current interventions and using joint costing rules or some basis of allocation related to the usage of the overhead item [1].

### ***Cost-offsets***

Generalised CEA may identify savings resulting from the joint implementation of interventions. Interactions between interventions in terms of costs and outcomes are taken into account by defining combinations of mutually exclusive interventions as described above. So if coverage of BCG reduces the subsequent number of cases of TB requiring treatment, at least 3 mutually exclusive interventions would be defined at the population level – x% of children covered by BCG with no treatment of subsequent cases; treatment of all TB cases only; and x% coverage of BCG with treatment of subsequent cases.<sup>6</sup> If all were evaluated against the counterfactual, cost offsets directly linked to BCG immunization – i.e. savings in treatment costs due to fewer subsequent cases - would automatically be included.

## **Discussion**

The more general use of sectoral Cost-Effectiveness Analysis (CEA) is to be used as an input into resource allocation decisions concerning a wide spectrum of alternative

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<sup>6</sup> An infinite number of combinations could be defined by varying x. It is necessary to be pragmatic in practice and define a parsimonious set of combinations, by identifying critical levels of coverage at which the slope of the expansion path is likely to change – see Murray et al. 2000.

disease programmes. Current approaches to economic evaluation do not meet the requirements for generalised CEA because of two reasons. The first is that traditional analysis has focused on assessing new or additional interventions in comparison to current practice in that area. It is difficult to use this type of 'incremental' analysis to determine if the current mix of interventions represents an efficient use of resources. Secondly, for all but the richest countries, the cost and time required to evaluate the large number of interventions required to use CEA to identify opportunities to enhance efficiency are prohibitive. It is important to maximize the possibility of generalizing results from one setting to another. The approach of generalised CEA seek to provide analysts with a method of assessing whether the current mix of interventions is efficient as well as whether a proposed new technology or intervention is appropriate. It also seeks to maximize the generalizability of results across settings.

The more general use of sectoral CEA should be considered as complementary to existing approaches to CEA. This form of sectoral CEA proposes the evaluation of interventions to the counterfactual in the absence of existing interventions, thereby providing decision makers with information on what could be achieved if they could start again building up (subsets of) the health system, i.e., reallocate all health resources. This information is a prerequisite to the definition of an efficient mix of interventions, achievable in the long run. This specific feature - not addressed in traditional CEA, which typically evaluates interventions in comparison to the current mix of interventions - categorizes the more general use of sectoral CEA as a different, more fundamental, type of economic analysis. For many narrower applications of CEA, such as the appraisal of new drugs in a specific country, the currently practiced incremental CEA remains the most appropriate method although it should be realized that this does not inform decision makers on the best use of health resources in general.



## Chapter 4

### **Stochastic league tables: communicating cost-effectiveness results to decision makers**

Reprinted from:

Stochastic League Tables: communicating cost-effectiveness results to decision makers.

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## Introduction

Uncertainty in cost-effectiveness analysis (CEA) has received much attention in recent years, leading to the development of a range of approaches like non-parametric bootstrapping [161], the construction of confidence planes [162], mathematical techniques [163], probabilistic sensitivity analyses using Monte Carlo simulations [164], and the net health benefit approach [165]. These techniques all present study results in terms of some type of uncertainty interval. However, little or no attention is paid to the question of how decision-makers should interpret the results where uncertainty intervals overlap.

This absence of guidance to decision makers is exacerbated in sectoral CEA based on the implicit or explicit use of cost-effectiveness league tables [9,10]. Sectoral analysis requires that interventions be ranked on the basis of their cost-effectiveness ratios. In deterministic analysis, decision-makers are assumed to work down the list, starting with the most cost-effective, and to stop funding interventions when the resources run out. The addition of uncertainty to this analysis is more realistic, but uncertainty intervals of many of the ratios may overlap and the decision-maker is left with no guidance in the literature. It is simply assumed that no decision about which intervention is more efficient can be made. Yet, decision-makers must and do make decisions about which interventions to encourage even when uncertainty is high (e.g. with overlapping confidence intervals).

We propose a new approach to presenting decision-makers with the results of CEA including uncertainty through the construction of a 'stochastic league table'. This informs decision-makers about the probability that a specific intervention would be included in the optimal mix of interventions for various levels of resource availability, taking into account the uncertainty surrounding its total costs and effectiveness. Each intervention should be thought of as a national programme or policy, which can only be purchased at one point [3]. Although the argument is presented with reference to the generalized method for sectoral CEA which we recently proposed, allowing decision makers to assess the efficiency of the current mix of interventions as well as the relative attractiveness of changes to this mix should new resources become available [3], it is applicable to any form of sectoral analysis.

## The analytical framework

The construction of stochastic league tables requires four steps (a software program, Monte Carlo League (MCLeague) ®, has been developed to carry out this process)<sup>7</sup>. Firstly, using Monte Carlo simulations, random draws are taken from estimated distributions of total costs and effects for the interventions under study. These distributions are *a priori* defined by the analyst and may take different forms, for example normal, log-normal, and uniform distributions [164]. Table 4.1 presents the hypothetical costs and effect data first presented in Murray et al. [3]. To reflect uncertainty, costs are here assumed to be log normally distributed with standard deviation of 20 and effects are assumed to be normally distributed with standard deviation of 20. The covariance

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<sup>7</sup> The original version of MCLeague is available from the WHO website at <http://www.who.int/evidence/cea>.



is assumed to be zero. The conclusions are not dependent on these assumptions. Random draws are taken from these distributions for all interventions.

**Table 4.1.** Costs, effects and cost-effectiveness of three independent sets of mutually exclusive alternatives

Interventions	Total costs		Total effects		Cost-effectiveness*
	Mean	S.D.	Mean	S.D.	
A1	120	20	1	2	-
A2	140	20	5.5	2	25.4
A3	170	20	3	2	-
A4	190	20	7	2	33.3
B1	100	20	12	2	-
B2	120	20	17	2	7.1
B3	150	20	20	2	10.0
C1	50	20	22	2	2.3
C2	70	20	24.5	2	8.0
C3	120	20	29	2	11.1
C4	170	20	31	2	25.0

\* cost-effectiveness ratios after exclusion of dominated interventions

The second step is to determine the optimal mix of interventions for given levels of resource availability following the procedure for choosing between mutually exclusive and independent interventions outlined in Murray et al. [3]. The most efficient intervention in the set of mutually exclusive interventions is evaluated according to its average CE ratio (versus doing nothing), while the CE of others in the mutually exclusive set are evaluated incremental to the most efficient intervention.

Thirdly, this process is repeated a large number of times (here 10,000) to provide 10,000 estimates of the optimal mix of interventions. If P equals the number of times that an intervention is included in the optimal mix, P/10,000 is the probability that the intervention is included. Hence, P is the proportion of samples from the estimated distribution for which the intervention is estimated to be optimal based on the sample average and incremental cost-effectiveness ratios. In our example, for resources equal to 50, C1 is included 4,323 times, a 43% probability of being included (*Table 4.2*). P for C2 equals 1,406, a probability of inclusion of 14%. In the remaining cases (43% of all random draws), costs of each possible option overrun the available resources and no intervention can be funded fully. This explains why the probabilities do not add up to 100%.

The fourth step involves repeating this procedure for various levels of resource availability to reveal the 'resource expansion path', showing the probability that each intervention will be included at different levels of resource availability (*Table 4.2*). Decision makers can use this information to prioritize interventions should more

resources become available for health care. The probability that a more expensive alternative will be included increases with the level of resource availability. For example, the probability C2 is included increases from 14% to 50% when resources increase from 50 to 100. In our example, no intervention is included in the optimal mix with certainty – even at high levels of resource availability – because of the relative large standard deviations assumed for costs and effects.

The degree of uncertainty in costs and effects of an intervention can have a large impact on its probability of inclusion in the optimal mix. If we change the standard deviation of the cost distribution for intervention A2 from 20 to 70, its probability of inclusion at a level of resource availability of 300 increases from 5% to 22% (*Table 4.3*). This is because intervention costs now are sometimes very low thereby rendering the intervention relatively cost-effective (with resources  $\geq 600$ , its probability of inclusion decreases because it now has to compete with the more cost-effective interventions A3 and A4 which can be afforded). The general conclusion is that the higher the uncertainty in costs and effects, the more equal the probabilities of inclusion of interventions will be, other things equal. This is true both within the same mutual exclusive set as well as between independent sets of interventions.

In *Table 4.2*, the numbers in bold represent interventions that would be selected in a traditional league table based on the cost-effectiveness ratios calculated in *Table 4.1*. These interventions would also be chosen by the stochastic league table because of their higher probabilities of inclusion. However, the stochastic league table provides additional information to the decision maker. With resources of 200, a traditional league table would choose intervention C2 whereas our stochastic league table shows almost identical probabilities of inclusion of C1 and C2 in the optimal mix of interventions. This information provides decision makers with more information than simply presenting the confidence intervals for all CERs. For example, it allows decision makers to better evaluate the impact of trading off the efficiency goal against other objectives such as reducing health inequalities in their selection of interventions [42]. In general, the more interventions (belonging to the same mutually exclusive set) differ regarding their probabilities of inclusion in the optimal mix, the more efficiency decision makers give up if they choose to over-ride the results in favor of other goals in their choice of interventions – the stochastic league table in our example informs decision makers that they are not likely to lose much in terms of efficiency if they decide to select C1 rather than C2 for equity reasons. This important information is not revealed in deterministic league tables or in the traditional approach to uncertainty in CEA.

**Table 4.2.** Stochastic league table presenting the probability of inclusion (%) of three independent sets of mutual exclusive interventions in the optimal mix of interventions at different levels of resource availability\*

Intervention	Resource availability							
	50	100	150	200	300	400	600	800
A1	0	0	0	0	1	2	0	0
A2	0	0	1	1	5	25	28	29
A3	0	0	0	0	0	1	4	4
A4	0	0	0	0	0	11	67	67
B1	0	3	14	11	2	0	0	0
B2	0	1	18	35	26	21	15	15
B3	0	0	4	36	72	78	85	85
C1	43	40	30	36	8	3	0	0
C2	14	47	25	37	17	10	0	0
C3	0	13	38	16	45	33	24	23
C4	0	0	8	11	31	54	76	76

\* numbers in bold represent interventions that would be listed in a traditional league table.

**Table 4.3.** As Table 4.2, with standard deviation for costs of intervention A2 increased from 20 to 70

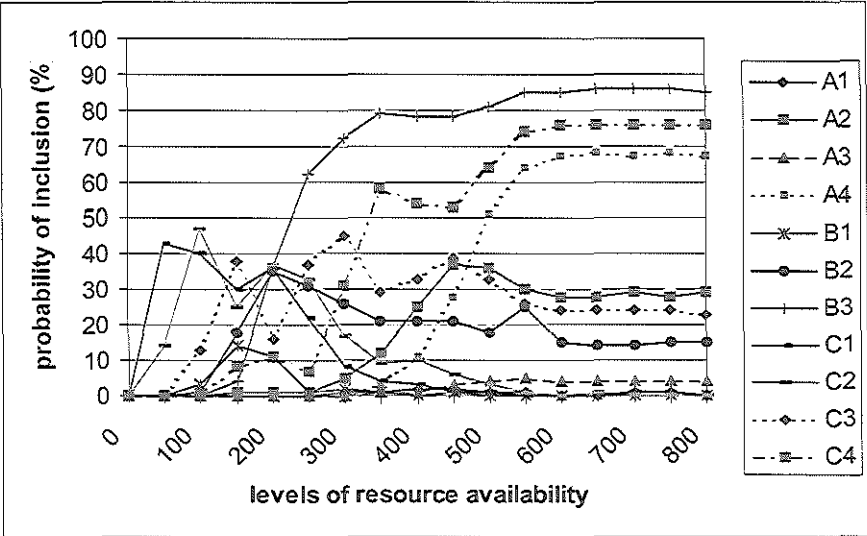
Intervention	Resource availability							
	50	100	150	200	300	400	600	800
A1	0	0	0	0	1	2	1	1
A2	7	9	14	12	22	37	28	28
A3	0	0	0	0	0	1	5	4
A4	0	0	0	0	1	9	67	67
B1	0	3	15	10	1	1	0	0
B2	0	1	19	35	28	18	15	14
B3	0	0	3	37	71	81	85	86
C1	43	40	30	39	11	3	0	0
C2	15	47	30	33	17	7	1	1
C3	0	13	34	17	45	30	23	24
C4	0	0	6	11	28	60	77	75

\* numbers in bold represent interventions that would be listed in a traditional league table.

Another advantage concerns the information provided in the expansion path, illustrated in *Table 4.2*. With resources of 200, there is little to choose between B2 and B3 but preference would be given to B2. However, if the decision maker felt that additional resources would become available in the near future, and that the costs of switching from B2 to B3 might be substantial, it would be sensible for them to choose B3. Again, this type of information is not provided in the standard approach to uncertainty.

Stochastic league tables may also show that interventions that would otherwise have been ruled out by dominance in traditional league tables might well be included in some draws. In our example, intervention B1 will never be eligible for selection in a deterministic league table because it is (weakly) dominated by B2. However, taking into account uncertainty the stochastic league table (*Table 4.2*) shows that B1 has a low but non-zero probability of being included in the optimal mix. Whether decision makers will actually select such interventions depends on the probability of inclusion compared to other mutually exclusive alternatives, and the trade-off between efficiency and other objectives of health systems.

*Figure 4.1* depicts an alternative way of visualizing the information of *Table 4.2*. The vertical axis shows the probability of being chosen at the level of resource availability on the horizontal axis. The logic is the same as that described for the interpretation of the tables.



**Figure 4.1.** Probability of inclusion (%) of three independent sets of mutually exclusive interventions

## Discussion

The stochastic league table developed in this paper is a new way of presenting uncertainty around costs and effects to decision makers. It provides additional information beyond that offered by the traditional treatment of uncertainty in CEA, presenting the probability that each intervention is included in the optimal mix for given levels of resource availability. The most likely optimal mix will be the one that contributes the most to maximizing population health for that level of resources. Decision makers can then decide the extent to which they should trade off gains in efficiency for gains in other goals of the health system.

Stochastic league tables are conceptually different from the recently suggested portfolio approach, borrowed from financial economics and characterizing health care resources allocation as a risky investment problem [166]. This approach provides the optimal intervention mix given decision-makers' explicit preferences concerning risk and return. Our stochastic league table provides the probability of an intervention being chosen in the optimal mix, given uncertainty. Risk-neutral decision makers would choose the most likely combination of interventions.

A drawback to our framework (and to the portfolio approach for that matter) is that distributions of costs and effects are assumed to be independent e.g. no joint distributions are defined. Moreover, the definition of the distributions is left to the analyst, who may have very little information about the actual distribution, but whose choice is likely to have a large effects on the results. It is technically possible to include covariance between costs and outcomes in the analysis, but this requires more information about covariances than is usually available. Alternatively, where empirical data on patient' costs and effects are available, our framework could employ the technique of non-parametric bootstrapping in which samples are drawn with replacement from the original data. This approach has the advantage that it does not rely on parametric assumptions concerning the underlying distribution and that covariances between costs and effects can be easily incorporated [1]. The development of stochastic league tables is an important step forward in the interpretation of uncertainty at the decision making level.

## Chapter 5

### **Stochastic league tables: a sectoral application to diabetes interventions**

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Stochastic league tables of diabetes treatment.  
Hutubessy RCW, Niessen LW, Dijkstra LF, Casparie AF, Rutten FF.  
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## Introduction

Recently, the technique of stochastic league tables (SLT) has been introduced [38,167] and discussed [168,169] as a method for presenting uncertainty around costs and effects in sectoral priority setting. To date, the method has not been tested with a real-world example. This paper will present an application of the SLT-approach based on results on the cost-effectiveness of treatment based on Dutch guidelines for diabetes mellitus (DM) type 2 patients in primary and in secondary care [170].

Building on earlier discussions [168,169], this chapter reviews the concept of SLT and discusses its use for decision-making in cost-effectiveness analysis (CEA). Furthermore similarities and differences with other methods i.e. cost-effectiveness acceptability (CEAcc) curves will be presented. The chapter argues that current methods of presenting uncertainty in cost-effectiveness ratios (CERs) - which are used in incremental CEA - have limited use for sectoral priority setting. In contrast with CEAcc, the SLT approach considers multiple interventions and affordability issues. It addresses the reality that health systems are resource constrained and that decision-makers have budgets constraints [3].

The next section summarizes the deterministic results for sectoral costs-effectiveness results of DM type 2 interventions in primary and secondary care in the Netherlands. The following sections focus on how to communicate and analyse uncertainty around cost-effectiveness estimates for decision makers. Our basic technique for uncertainty analysis is the Monte Carlo (MC) sampling method. Based on the same MC simulation data, section three will review the use of cost-effectiveness acceptability curves involving two sets of multiple and mutually exclusive DM interventions. Section four will present the use of the SLT approach and how it can be applied to more than two sets of DM interventions. The final section offers a discussion of issues raised in this chapter.

## Cost-effectiveness of diabetes treatment

Cost-effectiveness analyses of diabetes guidelines are relevant for both clinical practice and health policy. Long-term clinical follow-up studies demonstrate that intensive control of blood glucose is effective in reducing the risk of severe complications of diabetes [171]. Health economic studies show that intensive treatment have the potential to lower health care costs, especially through lowering the frequency of institutional episodes [172]. Such studies typically report the costs and effects of an intervention given an existing level of control and treatment and hence are context-specific. It is of interest for health policy to have more general information on allocation options in diabetes care given the various options for prevention and treatment of complications [173,174]. One study has considered the efficiency of current interventions [3,38]. There a low diabetes control level of 10% glycosylated haemoglobin (HbA1c) was taken as the reference level of care. The DM model used was based on Eastman et al. [175] and has been described [170].

We have collected data on current care and also used data on guidelines from two experimental settings [176,177]. For both current and guidelines care, we give the details on the input values for the effectiveness and costs for two sets of eight possible



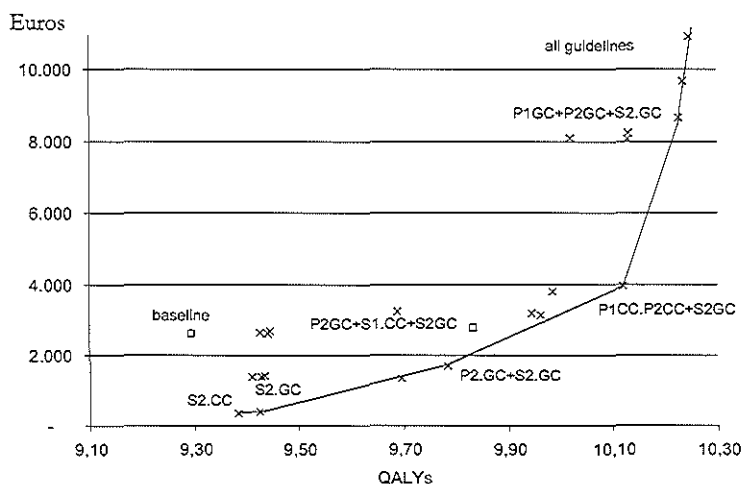
intervention mixes each. One set includes all possible mutually exclusive intervention mixes for primary care (P) and the other includes all possible mutually exclusive mixes for secondary care (S). We present effects and costs of the eight single interventions and eight combinations for control and preventive treatment of eye, renal and lower extremity complications (P1+P2 and S1+S2 respectively). This leads to results for sixteen intervention mixes as listed in *Table 5.1*.

**Table 5.1** Possible diabetes intervention mixes and codes.

Primary care (P)				Secondary care (S)			
Control (1)		Treatment of DM complications (2)		Control (1)		Treatment of DM complications (2)	
Current Care (CC)	Guidelines Care (GC)	Current Care (CC)	Guidelines Care (GC)	Current Care (CC)	Guidelines Care (GC)	Current Care (CC)	Guidelines Care (GC)
Current DM control P1.CC	Intensive DM control P1.GC	Current treatment of complications P2.CC	Guidelines treatment of complications P2.GC	Current DM control S1.CC	Intensive DM control S1.GC	Current treatment of complications S2.CC	Guidelines treatment of complications S2.GC

*Figure 5.1.* and *Table 5.2* present the computed QALYs lived and the discounted additional lifetime costs per average diabetes patient for the 16 possible combinations of the four intervention mixes (P.CC, P.GC, S.CC, and S.GC). The calculated baseline life expectancy is 9.29 QALYs (SD=5.3). This standard deviation compares well with observed figures for the unadjusted life expectancy [178]. The higher costs of guideline control (*Table 5.2*) and the treatment costs of complications are partially offset by reductions in costs of severe complications, especially by savings on care for severe renal and lower extremity complications. All primary care interventions together according to guidelines (P1.GC+P2.GC) show the highest health yield for a single intervention set: about 0.8 QALY per average lifetime. As a single intervention, eye screening and laser coagulation (not listed in the *Table 5.2*) fall within the same range of cost-effectiveness. The cost-effectiveness ratios for current treatment for renal and lower extremity complications (not listed in *Table 5.2*), as single interventions, are much less cost-effective.

Based on the point estimates as illustrated in *Figure 5.1* the two guidelines intervention mixes for prevention and treatment of complications (P2.GC and S2.GC) are dominant compared to the current care of complications (P2.CC and S2.CC). Guidelines treatment of complications (P2.GC and S2.GC) is cost-effective for three reasons: the intervention costs are low, the effects are immediate in a large majority of patients, and the indicated patient subgroup is relatively small. In diabetes control, annual costs are higher, health gains occur later in life, and many patients need to be treated to prevent relatively few, severe and costly complications. Therefore, current control is less cost-effective than preventive treatment of complications.



'P'= primary care; 'S'= secondary care; '1'=diabetes control; '2'=care of complications; 'CC'= current care; 'GC'= guideline care.

**Figure 5.1** The cost-effectiveness plane: QALYs lived and lifetime medical cost (3% discounted) for each intervention mix, the baseline value and combinations of P and S mixes.

**Table 5.2.** QALYs lived and medical costs (1996€) per average remaining diabetic lifetime for the two independent sets P and S of intervention mixes, ordered by QALYs lived.

Intervention mixes		Model outputs		Cost-effectiveness results
No	Single set mixes	QALYs gained	Lifetime costs	Point estimate CER
0	Baseline care	9.294	2,626	reference
1	S2.CC	9.384	349	most dominant
2	S1.CC	9.410	1,403	dominant
3	S2.GC	9.424	411	dominant
4	S1.GC+S2.CC	9.425	2,642	123
5	S1.CC+S2.CC	9.427	1,384	dominant
6	S1.CC+S2.GC	9.433	1,427	dominant
7	S1.GC	9.442	2,637	76
8	S1.GC+S2.GC	9.446	2,699	485
9	P2.CC	9.689	3,247	1,575
10	P2.GC	9.695	1,355	dominant
11	P1.CC	9.945	3,189	866
12	P1.CC+P2.CC	9.963	3,141	771
13	P1.CC+P2.GC	9.986	3,811	1,714
14	P1.GC+P2.CC	10.020	8,099	7,543
15	P1.GC	10.128	8,078	6,543
16	P1.GC+P2.GC	10.130	8,238	6,716

In last column are the CERs relevant to the expansion path based on the point estimates. Here, in each step, the preceding optimum mix is the reference intervention.

Baseline care = care exclusively for severe complications (see Table 5.1); CER = cost-effectiveness ratio; P= primary care; S= secondary care; 1 =diabetes control; 2 =care of complications; CC = current care; GC = guideline care.

Table 5.2 and Figure 5.1 indicate only one possible optimal resource expansion option i.e. how to prioritise implementation of efficient diabetes care starting from a baseline level. Here, one would start by choosing the most cost-effective option at the lowest budget needed, followed by the next cost-effective option until resources are exhausted [148]. For the sets of mutually exclusive interventions (P and S) the order would be to start with the guidelines treatment for complications, next to add primary control, and last to implement intensive secondary control interventions. The optimal expansion path for all combinations of all possible P and S mixes starts with S2.CC. This is the most efficient and least expensive option i.e. gives most savings, compared to baseline level (Table 5.3). The specific implementation steps would be to improve this to S2.GC, add P2.GC, add P1.CC, improve this to P2.GC, and, last, to include the remaining S2.GC option. Many more expansion paths are possible if one takes into account uncertainties e.g. standard deviations of health effects and lifetime costs. This is dealt with in the next two sections.

## Cost-effectiveness acceptability curves

Uncertainty in CEA models has traditionally been analysed using univariate and multivariate analysis [179]. Various methods for estimating confidence intervals around CERs have been presented in literature [179,180]. However, several authors [165,179,181] outlined major limitations of using ratio statistics in CEA. The use of ratio statistics in cost-effectiveness analysis has some technical difficulties when the joint distribution of incremental costs and incremental effectiveness extends over more than one quadrant of the CE plane. Since the iCER is a discontinuous function of the mean difference in effectiveness, it is an ill-defined parameter and has no meaning without further information about the joint distribution of incremental cost and effectiveness on the CE plane. The statistical intractability of the iCER has led to two important and related developments [179]: the use of the net-benefit (NB) statistic and the presentation of uncertainty in CEA using cost-effectiveness acceptability curves (CEAcc) [182]. We first will discuss the case of decision involving two interventions following the framework proposed by Fenwick and colleagues [39] before we review the case of multiple interventions.

**Decisions involving two interventions.** For decision making involving two interventions, the analysis can be undertaken using incremental net benefits (INB). The intervention of interest is deemed to be optimal compared to another intervention for any particular iteration (e.g. from a Monte Carlo iteration) when the INB is *positive*. Hence, the technique involves determining the proportion of iterations in which the intervention of interest has positive INB, for each externally set willingness to pay,  $\lambda$ . To provide a graphical representation of the probability that a particular intervention is optimal, over a range of values of  $\lambda$ , cost-effectiveness acceptability (CEAcc) curves have been proposed [179].

Our DM case traditionally is to be analysed by comparing two mutually exclusive options of primary or secondary care treatments [182]. For instance, in primary care intensive control would be compared to current control of DM type 2 patients (P1GC versus P1CC) or guidelines treatment of DM complications for secondary care patients would be compared to current treatment of DM complications (S2GC versus S2CC). Figure 5.2a depicts the incremental CEAcc curves for primary care current (P1CC) and intensive DM control (P1GC). The probability in terms of percentages that an intervention is optimal is measured on the vertical axis. The horizontal axis measures the monetary value ( $\lambda$ ) that the decision-maker puts upon the health effects generated and can be derived explicitly as the maximum price that society is willing-to-pay for health benefits or implicitly as the shadow price of health benefits. Typically this standard way of presenting uncertainty surrounding CE results is only focusing at one patient group (primary or secondary) involving two interventions at the same time. As Fenwick et al. [39] have suggested the switch point on the CEAcc frontier (see Figure 5.2b), where the a priori decision changes from one intervention to the other, corresponds to the base iCER for the decision. Since the underlying distribution of INB in our DM example is symmetric, the switch point occurs at a probability equal to 50%.

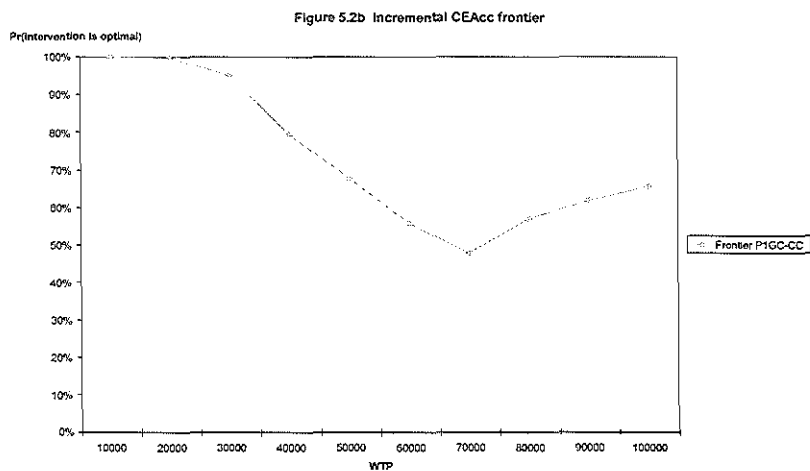
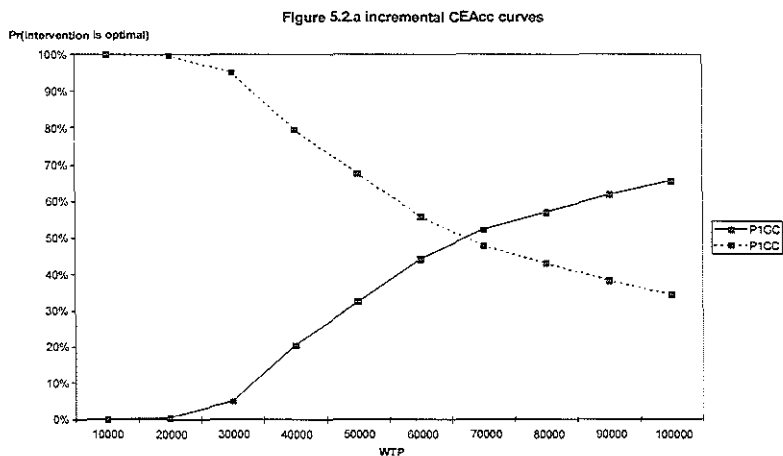
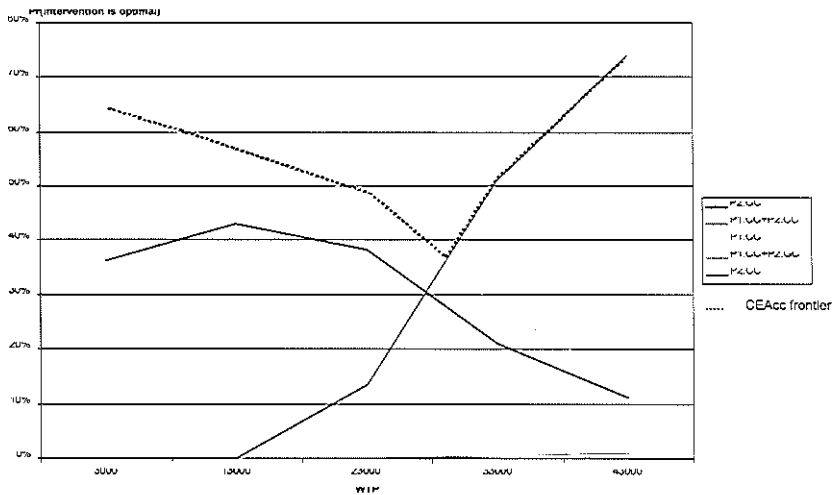


Figure 5.2 Incremental CEA acceptability curves and frontiers

**Decisions involving multiple interventions.** Originally CEAcc curves were introduced to represent the uncertainty concerning the CEA of health care interventions in the context of decisions involving two mutually exclusive interventions [182,182]. In order to deal with decisions involving more than two interventions Fenwick and colleagues [39] proposed the use of multi-intervention CEAcc curves. Following their method we employed the probabilistic DM model analyses to generate a distribution of costs and effectiveness for each intervention [170]. Based on these estimates we produced net benefit (NB) distributions for each intervention and each level of  $\lambda$ . In a multiple intervention decision making context, the CEAcc curve for each intervention can be established by calculating the proportion of iterations where the intervention is optimal (i.e. when it is associated with the *maximum* NB for a variety of values of  $\lambda$ ). Repeating this process for each intervention and simultaneously graphing the CEAcc curves provides a family of CEAcc curves, one for each intervention.

Based on the earlier defined sets of diabetes interventions in *Table 5.1* our next analysis considers a set of mutually exclusive interventions for primary care DM control and treatment of complications: current DM control (P1CC); current complications care (P2CC); the combination of P1CC and P2CC; guidelines care for DM control (P1GC) and both guidelines combined (P1GC and P2GC). Figure 5.3 depicts the CEAcc curves for these five selected diabetes interventions considered at primary level. The dashed line enveloping the individual intervention CEAcc curves represents the CEAcc frontier that is defined as the range of  $\lambda$  over which each intervention constitutes the *a priori* act [39].



**Figure 5.3** CEAcc curves for primary care diabetes interventions

## Stochastic league tables

The incremental CEAcc curves in *Figure 5.2.* are within the context of decisions involving two interventions. They are constrained by the current set of interventions and hence this type of uncertainty analysis is focused on incremental changes in costs and effectiveness. In addition opportunity costs of effectiveness gained are considered at the margin. However, at sectoral level, decision makers face uncertainty surrounding *a priori* decisions involving multiple interventions across disease areas and across patient groups.

The paper by Hutubessy et al. [38] suggested the SLT technique for decision-makers to employ in determining the optimal mix of interventions originally for sectoral cost-effectiveness analysis. By sectoral analysis we mean that all alternative uses of resources are evaluated in a single exercise, with an explicit resource constraint [3,13,183]. In summary the technique requires the adoption of Monte Carlo<sup>8</sup> simulation analysis to identify the probability that a certain program will be included in the optimal mix and expansion path given the uncertainty around the program's expected costs and benefits. The construction of SLTs requires four steps. Firstly, using Monte Carlo simulations, random draws are taken from estimated *a priori* distributions of total costs and effects for the intervention under study. The second step is to determine the optimal mix of interventions given levels of resource availability following the procedure for choosing between mutually exclusive and independent interventions outlined in Murray [3]. Thirdly, this process is repeated a large number of times (e.g. 1000) to provide the same number of estimates of the optimal mix of interventions along the expansion path. Important to note in this third step is that probabilities of inclusion of interventions depend on each other because both costs and effects are sampled simultaneously for different interventions and combination of interventions – potentially within and across independent sets, and across disease areas – within a single replication. The fourth step involves repeating this procedure for various levels of resource availability to reveal the 'resource expansion path' showing the probability of that each intervention will be included at different levels of resource availability.

An important step in the construction of SLTs is the determination of the optimal mix of interventions given levels of resources availability following the decision rules and procedure for choosing between mutually exclusive and independent interventions as explained by Murray et al. [3]. Independent programmes can be implemented either singly or jointly – for instance glucose control for primary care and secondary care DM patients can be implemented either singly or jointly. Mutually exclusive interventions involve the same group of patients and, therefore, one or the other must chosen. DM patients either receive guidelines care or current care, but not both [3,184]. At sectoral level the distinction between independent and mutually exclusive programmes is important: the most efficient intervention in the set of mutually exclusive interventions is evaluated according to its average cost-effectiveness ratio, while the cost-effectiveness of others in the mutually exclusive set are evaluated incremental to the most efficient intervention [3]. Not only at the sectoral level but also at clinical level incremental

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<sup>8</sup> In order to enable us to make a comparison between SLTs and CEAcc we used the same Monte Carlo simulation data of the cost-effective results of diabetes care using the MCLeague software © which is available on the web ([www.who.int/evidence/cea](http://www.who.int/evidence/cea)).

analysis of intensifying a particular intervention, in the case of mutually exclusive programmes, is a practical method of obtaining an estimate of the marginal cost-effectiveness, which is equal to the slope of the expansion path (i.e. the cost-effectiveness frontier) [184].

Our DM example first illustrates the SLT technique for decisions involving a single independent set of interventions (primary care interventions only). Next, to illustrate the potential use of SLT technique for sectoral CEA we present the case of decisions involving two independent sets of interventions in two distinct groups (primary and secondary care interventions).

**Decisions involving one independent set of interventions.** Using MCLeague software we employed Monte Carlo simulations on the cost and effectiveness estimates of five primary care DM interventions presented in the previous section. We made the conventional assumption that costs have a lognormal distribution and health benefits have a normal distribution and that there is no correlation between costs and effectiveness in each Monte Carlo replicate [184]. In all iterations we computed the optimal expansion path in an application of the MCLeague approach, described earlier [38]. *Figure 5.4* depicts the resulting stochastic league table diagram. The horizontal axes represents different levels of available resources and the vertical axis provides the probability that an intervention will be chosen in the optimal mix.

The results of the SLT diagram as presented in *Figure 5.4* are very similar to the multi-intervention acceptability curves in *Figure 5.3*. However, the procedure of determining the optimal intervention for any particular iteration is different. Whereas the optimum in CEAcc is based on maximum NB using an externally set limit  $\lambda$ , the SLT-approach uses a linear programming i.e. maximising health given a level of available resources. It should be noted that because of small differences in intervention effect size across the different interventions the level of resources availability and WTP as depicted on the horizontal axis in both figures are almost identical.

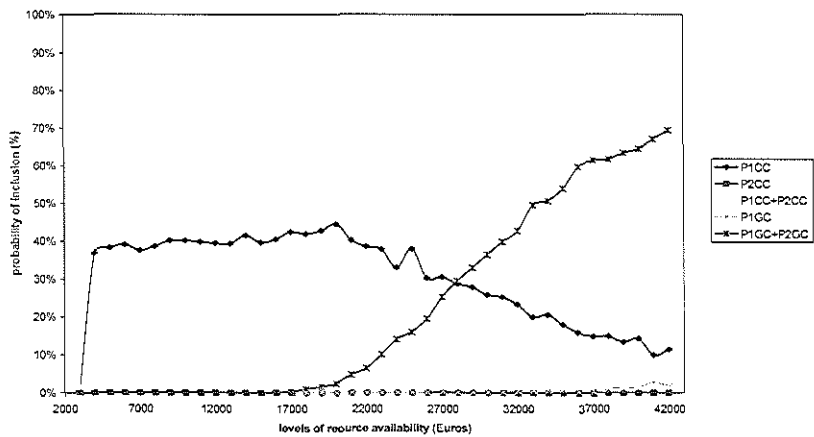


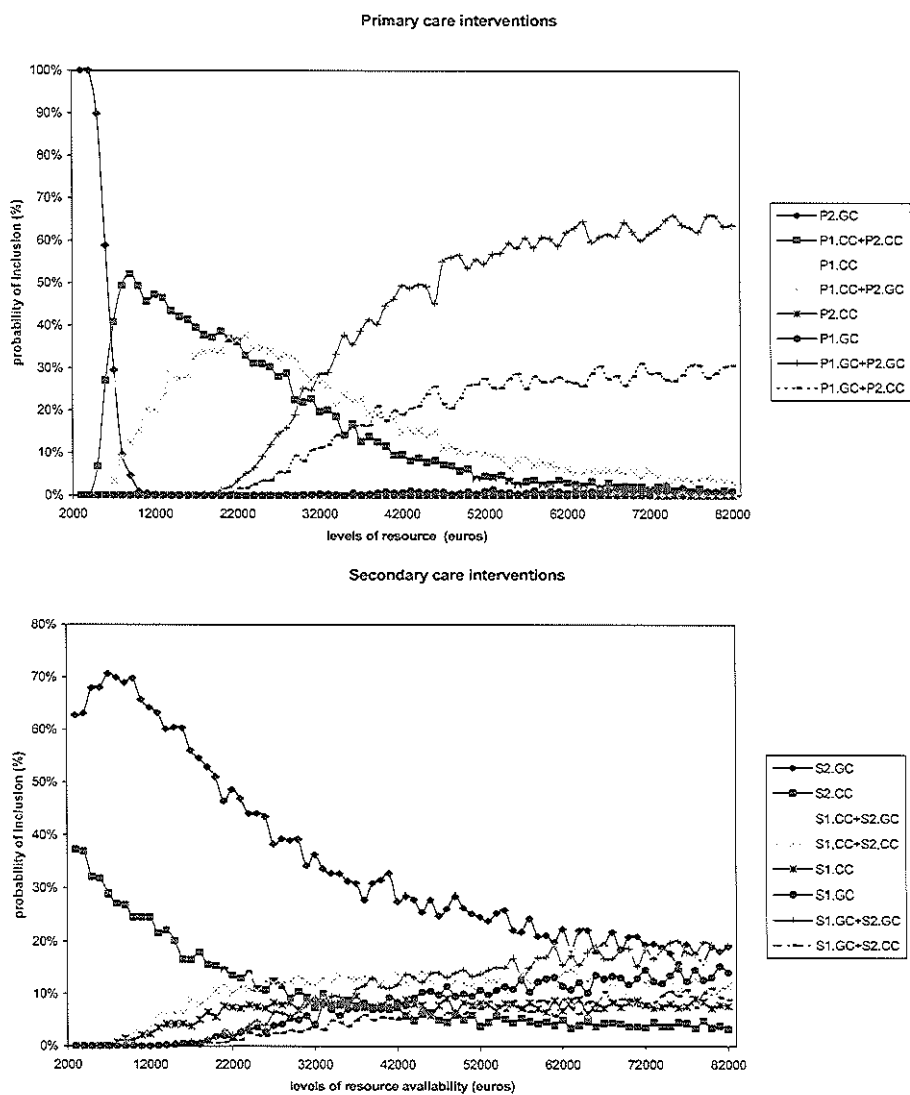
Figure 5.4 STL curves for 5 primary care diabetes interventions



**Decisions involving two independent sets of interventions.** One of the features of the SLT-approach is that it accounts for dependency of uncertainties between interventions and, instead of indicating the only optimal choice, it allows for combinations of packages for independent groups depending on the uncertainty levels. For our sectoral analysis we consider the two sets of interventions for primary and secondary care together but independently. This implies that one can implement one set without influencing the outcomes and /or costs for the other group of patients. Within each independent set only one intervention (or none) of all mutually exclusive options is selected. Depending on the resources available, one intervention from each set can be included at the same time. Taking all random simulations together one can calculate the number of times that a specific intervention would be included in the optimal mix of interventions at each level of resource availability.

Figure 5.5 shows the probability of inclusion in the optimum set for each intervention mix by available level of resource availability for the two combined groups (P and S). The computations include only the uncertainties in effectiveness and costs of the interventions (Table 5.1). We considered only the uncertainty in effectiveness and costs and not the uncertainties in the risk of dying and getting complications. The standard deviation in e.g. life expectancy is 6-8 years. Inclusion of the latter uncertainties is not standard and leads at the higher budget ranges to indifferent choices. As the number of interventions under consideration increases in the sectoral context the CEAcc frontier is useful as a graphical tool [39]. By extension, a stochastic league frontier, the switch point on the individual stochastic league curves where the *a priori* decision changes between two interventions, can be drawn for the two combined independent sets. Figure 5.6 depicts two STL frontiers for the decision involving all 16 primary and secondary care DM interventions together.

At the lowest budget level (< 2,000 euros), our analysis shows that the optimum mix is S2.CC for only a very short budget range. At this range is better to implement S2.GC. The size of the patient involved subgroups is small and costs are low. As shown in Figure 6.5 at somewhat higher budget levels (>2,000 euros), the optimal mix also includes the guidelines regarding complications for the small primary care group (P2.GC). Next, at slightly higher budgets, P1.CC+P2.CC is the better option. However, at the mid-range levels the adoption of primary guideline care of complications (P1.CC+P2.GC) is more likely to be efficient, in combination with guidelines care of the high-risk secondary care patients. The Figures 5.5 and 5.6 show a clear pattern at the highest budget levels commonly available in developed country: the inclusion of intensive diabetes control (P1.GC and S1.GC) is the best option, both as single options or combined with the guidelines for complications. The addition of these latter guidelines (P2.GC and S2.GC) leads to similar probabilities, as these two latter strategies need a lower budget per average lifetime. The pattern for secondary care patients is less certain than for primary care. One notable finding is that the current primary care options for complications should not be included at all (< 10%).



**Figure 5.5.** Probability of inclusion (%) in the optimum package for all diabetes intervention mixes, by available annual budget (1996€).

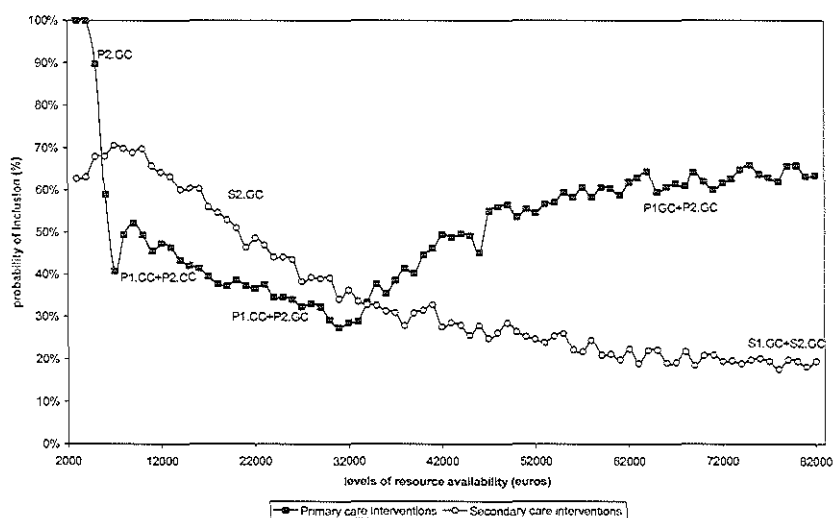


Figure 5.6 Stochastic league frontier for 2 independent sets of DM interventions

## Discussion

Using a multiple interventions decision-making example, we first presented the use of standard acceptability curves in an incremental analysis. Next, we presented two alternative approaches in this chapter to communicate uncertainty surrounding CE results to decision-makers. Although the development of both methods originates from two different points of departures i.e. based on two distinctive optimization procedures, our analysis has shown that both frameworks are very similar and supplement the use of single acceptability curves.

The first analysis for multiple interventions is an extension of the INB based approach applied to more than two interventions as introduced by Fenwick and colleagues [39]. The second approach, the stochastic league table technique as presented by Hutubessy et al. [38], is introduced in the context of communicating uncertainty around CE estimates to decision makers at the sectoral level. Both methods recognize the interdependence in the probability of inclusion in the optimal service provision of multiple interventions. As a result both methods allow decision-makers to better evaluate the impact of trading off the efficiency goal against other objectives such as reducing health inequalities in their selection of interventions.

The probabilistic analyses in our example show the advantages of the SLT-approach. First, we showed that diabetes care guidelines are cost-effective in reducing severe and expensive complications. This reconfirms the results of other studies [172,185]. In addition, in the SLT results give additional insights. First, our study results show that implementation of the guidelines for complications both in primary and secondary care reduces the current inefficiencies in diabetes care. Next, they show that in case of low available resources, a combination with moderate diabetes control (P1.CC) and care of complications in a high risk group is a good option. Last, they show that, when including uncertainties, the mixes that include guideline treatment of complications continue to be a likely optimum choice. At high resource levels, all primary and secondary care guidelines are relevant. The interventions in secondary care are cost saving compared to baseline; those for primary control cost about 6000-7000 Euro per QALY gained.

The question has been on how one can handle uncertainty in CEA results so that it presents these results in such a way to best inform decision-makers? The answer to this question depends on the realm of the decision-making problem. In a context-defined analysis the incremental CEAcc curve approach based on the INB framework is a possible way to graphically represent uncertainty concerning the CEA involving two interventions. Typically the INB technique is only focusing at one patient group (here, primary or secondary care patients) involving two interventions at the same time whereby it is assumed that policymakers make decisions at the margin. Although the incremental CEAcc curves shown in our study are general (in the sense that reference is made to a baseline and interventions are assessed in combination) such CEAcc still only allow of a 'binary' comparison. Hence, this incremental based uncertainty method only considers the outer envelope curve (or CEAcc frontier [39]) of the CEAcc when considering multiple interventions.

The crucial difference is that the NB approach makes use of cost-effectiveness thresholds whereas SLT approach start from a given resource constraint in the decision making process. For pragmatic reasons we believe that the latter framework is a more useful way of communicating uncertainty around CEA results of a portfolio of interventions. Firstly, the use of a budget constraint in the optimization procedure seems to be more relevant from the policy perspective than the application of a shadow price. Using thresholds in the decision-making process the NB framework and hence the multi-intervention CEAcc curves approach ignores opportunity costs of interventions chosen. That is, the fact to recognize that as new interventions are funded, other interventions have to be cancelled in order to avoid an ever growing health budget [186]. Furthermore, in reality  $\lambda$  is subjective, not known or not accepted. In health economics literature several ranges of budget thresholds have been proposed [180,187-191]. The NB approach rather forces the policy maker to make value judgements about  $\lambda$  based on the range of  $\lambda$  for which an intervention is cost-effective with specific probability. In addition to the use of such thresholds, no explicit consideration is given to the fact that health systems are resource constrained and that decision-makers hold budgets, which presumably must be balanced [41]. To deal with decision-makers budget constraint, Sendi et al. [186] have proposed so-called affordability curves. However it is not made clear how to apply the affordability approach to sectoral analysis i.e. assessing uncertainty for multiple sets of mutually exclusive interventions given levels of resource availability in one exercise.

Secondly, when the number of interventions to be evaluated becomes large the grouping of interventions in independent and mutually exclusive sets is more practical. As has been illustrated by our DM example the costs and health benefits of a set of related interventions are evaluated, singly and in combination, with respect to a reference situation where those interventions are not implemented. Within each patient group, interventions are evaluated singly and in combination, and the most efficient combination for a given resource constraint is identified. Efficient combinations are then compared across mutually exclusive groups in a single league table, ranked according to the cost per unit of health gain achieved. Subsequently, threshold values can be decided for classifying interventions into, say, those that are very cost-effective, those that are cost-ineffective and those in between. We believe that it is only by this broader approach to uncertainty analysis that questions on the broad allocation of resources can be adequately addressed.

Like in most economic appraisals sectoral CEA involve the use of modelling techniques to synthesis data from various sources to produce the cost-effectiveness results of interest. In the absence of parameter data in CEA models Briggs [184] suggests that decision-analytic-type modelling is inherently Bayesian in perspective. For parameters of a CE model that could, in principle, be estimated from observed data, consideration should be given to the prior distribution of these parameters to reflect uncertainty. Where possible, this should be based on the available data for studies, supplemented, where necessary, by expert opinion. The specified prior distributions should relate to second-order uncertainty rather than the variability in parameter values. In addition, care should be taken to ensure that prior distributions chosen are consistent with any logical bounds on the parameter values [184]. The 'confidence profile' technique introduced by Eddy et al [192,193] might be a useful approach to synthesising data based on empirical Bayes methods.

## Conclusion

Stochastic league tables deals both with decisions made on the margin and resource allocation problems at sectoral level given a fixed budget. Compared to the NB approach it is therefore a more useful and complete way of communicating uncertainty of sectoral CEA results to decision-makers.

Our example study on diabetes has shown that in case of low resource availability (< €300 per lifetime), none of the intervention mixes is a relevant policy option. Highly likely optimal strategies in resource-poor countries are the implementation of guidelines treatment of high risk groups and primary control. At budget over €12,000 per lifetime, one can afford the implementation of all interventions, although at the individual level uncertainties are high.

Our study shows the most likely cost-effective options based on data from semi-experimental settings. Policy makers often face the choice to implement programmes at larger scales based on experimental findings. The implementation results, however depend very much on the compliance within strategies followed [194]. Simply distribution of guidelines seldom leads to (cost-) effective implementation [195,196]. These uncertainties could be included in the SLT analysis.

There are also diminishing returns in intensive diabetes control. Further selection of high-risk subgroups (age, sex, risk factor status, and HbA1c level) , may lead to the identification of more specific, targeted and cost-effective implementation strategies that can be evaluated in similar SLT analyses.



## **Chapter 6**

### **Sectoral health effects and medical costs of stroke interventions in the Netherlands**

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Generalised life time costs and effects of stroke interventions.  
Niessen LW, Hutubessy RCW, Dippel DW, Kwakkel G, Limburg M.  
Submitted for publication





## Introduction

Stroke is a major cause of disability and death in aging populations, leading to high health care costs [52,197,198]. In some countries in the late stage of the health transition, secular decline in stroke mortality appears to level off [199-203]. Given this possible compression of stroke mortality, it is a present challenge to reduce stroke disability [204,205]. Consequently, reduction of severe stroke disability may lead to a reduction of health care costs [206].

During the past decade, promising therapeutic options in stroke care have appeared. Consensus guidelines are already recommending widespread implementation [207-209]. Yet, there are debates. There is one on the effectiveness, feasibility and pre-requisites for thrombolysis to treat patients within three hours after the onset of stroke [210-213]. Others are on the health effects and requirements of stroke units [214]. Options in secondary prevention are increasing and might compete in effectiveness with acetylsalicylic acid [215-217].

Demographic changes will lead to even higher numbers of stroke patients and the new medical technologies are leading to a higher demand for stroke resources. The premise of economic analyses is that, for any given level of resources available, one wishes to maximise the total aggregate health at the population level [148,218,219]. In another more standardised approach, the World Health Organisation proposes to compare health effects and costs of optional intervention mixes against a baseline disease level. Generalised comparisons of interventions provide evidence on population benefits in relation to associated costs and may lead to more informed priority setting, also in allocating for stroke care [3,38].

We describe the occurrence of stroke and related costs of care from a, population-based, health care perspective. Next, we analyse changes in stroke survival and medical costs under combinations of three interventions: trombolytic therapy, acute stroke units, and secondary stroke prevention. We do this in a consistent way for the three interventions, with the remaining life span of the average stroke patient as time horizon.

## Model description and scenario data

### *Multi-state stroke model*

We applied a multi-state life table model that has been used to describe the epidemiology of stroke in the Dutch population by age and sex [205]. Several papers have described this methodology [205,206,220]. The life table describes the disease history of stroke. It computes survival and death of patients by three linked stroke disability states: no disability, minor disability (Rankin scale score  $< 3$ ) and major disability (Rankin scale score  $\geq 3$ ) [205]. It does so according by age and sex. They may

enter one of the three states after a transient ischemic attack (TIA), leading to no disability, or a stroke, leading to a minor or major disability. Death risks in all states include death from stroke, cardiovascular disease, and all other diseases. It calculates all surviving patients in each stroke disability state, in time steps of half a year, until all patients have died. Patients may change health states after the first event. The table comprises risk of disability after one month, recovery from major disability at six months and risks of recurrent events and severe disability during the first year and during all other years.

For our analyses, we multiply the patient numbers for each disability state by quality-of-life weights for minor and major stroke. Added up, this yields the total of quality-adjusted life years (QALYs) lived by all three types of stroke patients. We also multiply these patient numbers with the medical cost estimates for each state for each half a year after stroke. The cost estimates are the product of health care utilization data per patient per state for each per year, and full costs per unit per health care service. This leads to an estimate of the average life time costs per patient.

We re-calculated the health effects and costs attributable to the stroke interventions by adapting the stroke table risks for mortality, disability, recovery, and recurrence accordingly and adding the intervention costs. The life table recalculates the survival of patients and the number of years lived in each state and the total stroke costs. The difference with the baseline computation generates the changes in quality-adjusted years and in costs for each stroke state and for the average stroke patient.

To validate the life table for the baseline situation we have compared model-generated age and sex-specific figures on stroke events and mortality to the national empirical figures on acute hospital admissions and stroke mortality for the year 1985 [205]. We also validated computed major stroke prevalence against data from the national nursing home registry of the same period.

***Input data on effectiveness of interventions*** In consensus meetings, we have selected effectiveness data from published meta-analyses (Table 6.1) [221]. We have added values from studies that allowed us to make an estimate of the effectiveness of the intervention in common practice i.e. beyond a randomized trial setting. We used the reported confidence intervals to estimate the probability distributions of the intervention effect, assuming a normal distribution [162,222].

For thrombolysis, until now, only recombinant tissue plasminogen activator (r-TPA) is shown to be effective [212]. Given within three hours after stroke it improves the outcome of acute stroke after three months [210-212]. This is also the case in non-experimental settings [223]. In a meta-analysis, we pooled the data of the three randomized studies. In the control group of 284 patients 52 died, among the 294 patients in the r-TPA group 50 patients died. In the r-TPA group 184 patients had a Rankin score < 4; in the control group only 154 patients had this score [174]. The small number of patients treated leads to an odds ratio for reducing the number of patients with a Rankin score  $\geq 3$  with a large confidence interval. We assumed that 10% of patients are eligible for thrombolysis, although the literature reports figures between 5-8%.

**Table 6.1.** Pooled odds ratios from meta-analyses by stroke intervention and stroke survival variable.

Intervention option and survival variable	Odds ratio (95% confidence interval)	Sources
Trombolysis		
Residual major disability at three months	0.68 (0.46-1.00)	[211,212]
Stroke unit care		
Acute case-fatality	0.87 (0.79-0.96)	[224]
Residual disability at 24 weeks	0.79 (0.56-1.10)	[225]
Secondary prevention		
Risk of recurrent stroke		
ASA <sup>†</sup> versus placebo	0.77 (0.61-0.96)	[215]
ASA + dipyridamol versus placebo	0.62 (0.45-0.70)	[216]
ASA + dipyridamol versus ASA	0.84 (0.64-0.96)	[217]
Risk of cardiovascular death		
ASA versus placebo	0.88 (0.64-1.21)	[215]
ASA + dipyridamol versus placebo	0.79 (0.49-1.21)	[216]
ASA + dipyridamol versus ASA	0.99 (0.86-1.65)	[217]

<sup>†</sup> ASA: Acetylsalicylic acid.

Stroke units lead to an improvement in stroke survival and stroke disability [214,224,226]. Two long-term follow-up studies show persistent improvements of stroke survival and disability level [213,226]. Our stroke unit care scenario includes reductions in acute fatality and in risk of a permanent severe disability, assuming a lifelong effect. In addition, we included more intensive nursing and rehabilitation in the acute stage, a length of hospital stay of 14 days and intensive rehabilitation until six months after onset [225].

Medical secondary prevention after stroke leads to reductions of both recurrent stroke and of cardiovascular mortality after a first TIA or first stroke [215,216,227,228]. We did not include disability or costs resulting from cardiovascular events. The effects of secondary prevention decrease during the years after the first stroke, possibly due to mortality selection or lack of patient compliance [215,216,227,228]. In our model, we incorporated the costs and effects of prevention during the five years after the initial stroke.

**Input data on cost estimates** Table 6.2 gives an overview of data used, published in our cost study [229]. The data include all medical costs after a first stroke related to hospital treatment, institutionalisation, rehabilitation, primary care, and home care. As the model distinguished two stroke states, we differentiated the cost data by these categories. For hospital settings, this is already known but not for the follow-up period.

The same study, however, collected data on the distribution of surviving patients after a first stroke among nursing homes, rehabilitation centres, and their own homes, during a five-year follow-up. We re-analysed the data set to find a rate of institutionalisation, by initial stroke severity and by period after a first stroke [230,231]. Almost no patients with a minor stroke stayed in an institution. After six months 29.1% (95% CI: 25.1-33.2) of the men with a major stroke stayed in an institution and 38.8% of the women (95% CI: 34.9-42.9). After that period institutionalisation stabilized among both men (16.5%; 95% CI: 12.6-20.4) and women (26.9%; 95% CI: 22.3-31.5). Some additional estimates of the additional costs of stroke units and intensive physiotherapy needed to be collected in a separate costing study on the Rotterdam Stroke Services [232]. Other outpatient cost estimates for medical treatment are based on official reimbursement rates (*Table 6.2*).

**Table 6.2.** Institutionalisation and costs of stroke care according to type of Intervention, hospital type and period after stroke onset.

Cost item	Academic hospital	General hospital
	Euro per day	
<i>Institutional costs</i>		
Hospital admission after minor stroke	264	196
after major stroke	310	224
after fatal stroke	426	252
Home care first six months	19	
after six months	4.5	
Nursing home admission	114	
Additional costs of hospital interventions		
R-TPA treatment *	2,385 (1,789-2,981)	
Stroke Unit * †	61 (44-78)	42 (32-53)
Intensive rehabilitation †	10	
	Euro per month	
<i>Additional costs of extramural interventions</i>		
Intensive physiotherapy or occupational therapy †	78	
ASA powder, 38 mg; tablets 100 mg ‡	7.0	
Dipyridamol Retard caps, 400 mg ‡	17	
Dipyridamol + Acetylsalicylic acid, 325 mg ‡	12	
Pharmacy prescription charge §	4	
General physician prescription charge #	2.7	

\* Costs of procedures and medication (uncertainty range  $\pm$  25%) [232]; Sources: † Rotterdam Stroke Service study; ‡ Insurance Council; § Royal Dutch Society of Pharmacists; # Dutch Society of Family Physicians. ASA= Acetylsalicylic acid

Input data on utility weighing for stroke disability We have applied utility weight distributions for minor and major stroke disability as defined by the Rankin scale [205,233]. For this, we used the EuroQol scale, shown valid in stroke patients [234]. We have assessed the disability status of 129 stroke patients (mean age 69 years) in two Rotterdam hospitals using both the Rankin scale and the five-dimensional EuroQol scale. The follow-up lasted up to six months after hospital admission. The total number of measurement pairs was 248. The measurements correlated well and are consistent during the time after stroke. Using the individual EuroQol scores, we calculated the average utility value and the average Rankin score for both minor and major stroke disabilities. The point utility value for minor stroke disability is 0.72 (SD=0.23) and for major stroke 0.47 (SD=0.31). For our analyses, accounting for uncertainty, we used the distribution of utility values from the original EuroQol data set given the two observed point utility weight score [234,235].

### ***Stochastic league table methodology***

Our analysis compares the relative efficiency of each intervention sets. Given a budget level, it selects the most cost-effective option first. If there is budget left for more options, it chooses the next cost-effective options, etc, until the budget is exhausted. To allow for this, we first computed lifetime health effects and costs for the baseline and seven intervention sets for stroke at 60, 70 and 80 years of age, by sex. Combinations of the three interventions define the sets. Each of the sets includes all possible (seven), mutual exclusive, mixes of intervention options, and the baseline scenario (*Table 6.3*). To account for uncertainties in estimated effects and cost, we included all uncertainty ranges in the input values for effectiveness, costs, and utilities. (*Tables 6.1-3* and Input data sections) The normal distributions have been truncated and entered in a random sampling procedure, using @Risk-Excel-software.

Next, the outcome distributions for QALYs and costs, generated in the multi-state life table, have been used in the stochastic league table approach. Their point estimates and standard deviations define these distributions (*Table 6.3*). The league table technique applies also random sampling (up to 10,000 iterations) to draw from generated distributions. Here, we made the, common, assumption that costs have a lognormal distribution and health benefits have a normal distribution. We use a software program called MCLeague, described in chapter 4 [38]. Using the results of each draw from the outcome distributions, it computes the cost-effectiveness of the intervention mix options in each set, compared to baseline. Next, it decides which combinations of mixes are to be included in the optimum package, given a budget ceiling. We treat the six sets of interventions as independent. This supposes that one can implement one without influencing the outcomes and /or costs for the other group of patients [3]. This means that, if additional packages are possible, given the budget available, these are included too. The league table presents the results of our comparative CEA. It indicates the probability that a specific intervention would be included in the optimal mix of interventions given a particular level of resource availability.

## Results

Table 6.3 shows the calculated lifetime costs and QALYs lived by intervention mix as point estimates. As the standard deviations vary little between intervention mixes, we only have listed the average standard deviations in the Table 6.3. This is to simplify the presentation. In our uncertainty computations, we use the individual estimates. Outcomes by age and sex vary up to 2.7-3.7 times the number of QALYs lived and up to 1.4-2.0 times the lowest lifetime costs. At age 60, the average stroke patient gains a maximum of 0.5 QALYs per lifetime from all combined interventions (Figure 6.1). Differences in health gain between the sexes are due to differences in absolute cardiovascular risks and remaining life expectancies. The table shows that all mixes lead either to cost savings or to low additional costs as compared to baseline and, hence, lead to more efficient stroke.

Trombolysis is indicated in only a small group of patients. It adds the lowest number of QALYs: about 0.1 per average stroke lifetime. Secondary prevention is about twice as effective, preventing both strokes after transient attacks and recurrent minor strokes, still a minority of the stroke population. Stroke units, as a single intervention package, or in combinations, yield about four times as many QALYs per lifetime.

Cost differences between major and minor stroke patients (not shown) vary between 2.5 and 2.9 for men and for women between 3.8 and 4.2 [232]. These differences are largest at younger ages as patients survive for a longer period. Our results compare with previously estimated Dutch average for all strokes [229]. Institutionalization dominates lifetime costs [229,230]. For comparison, in the United States the average lifetime costs of stroke are €49.000 for ischemic strokes at 65 years of age and €26.000 at 85 years, for men. For women this is €52.000 and €26.000 [236].

Changes in costs and effects are small in comparison to the computed uncertainty ranges (Table 6.3). The next section deals with selecting the optimum stroke package, given these uncertainties.

### *Stochastic league tables for stroke care*

Figure 6.1 shows the same point estimates in a so-called cost-effectiveness plane, by intervention mix. For each mix, both average health gain and average costs are higher in younger age groups and are higher among the women. Figure 6.1 clearly shows that stroke units give more benefit at slightly higher costs. It is most effective at younger ages. Here, cost per QALY gained is lowest for the mix including stroke units and secondary prevention: for men about €55.000 and for women €73.000. The plane demonstrates that trombolysis leads to relatively little average benefit at high average cost (the cost of institutionalisation of those not indicated for treatment). The same holds for secondary prevention as a single intervention. Here, cost-effectiveness ratios are over €100.000 per QALY gained. Their combination leads to as much health gain as stroke unit care at older ages.

Trombolysis and stroke units give immediate health benefits to the patient. When the age of stroke onset rises, there are fewer years without disability to gain and, consequently, cost-effectiveness of these treatments decreases with age. Optimum packages at lower budget levels would exclude these interventions at older ages.

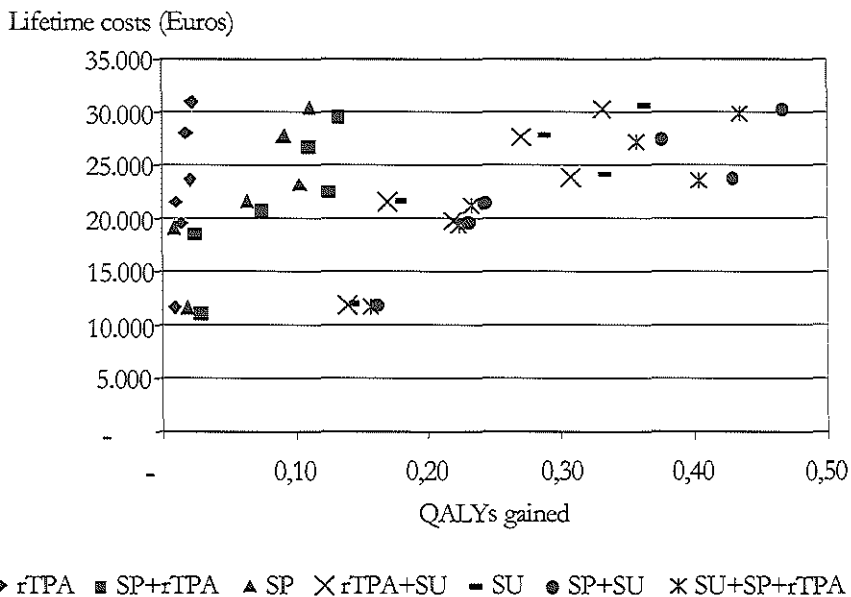
**Table 6.3.** Lifetime mean quality-adjusted life years lived and medical costs after a first stroke by stroke intervention mix.. Bottom row: standard deviations.

stroke interventions mixes	age of stroke onset											
	60 years				70 years				80 years			
	Men		women		men		Women		men		women	
	QALYs	Costs	QALYs	Costs	QALYs	Costs	QALYs	Costs	QALYs	Costs	QALYs	Costs
Baseline	5.33	23.528	6.17	30.704	2.30	19.370	3.97	27.958	1.45	11.648	2.32	21.722
SP	5.43	23.169	6.28	30.338	2.31	19.080	4.07	27.625	1.47	11.514	2.39	21.512
SP+rTPA	5.45	22.510	6.30	29.548	2.33	18.446	4.08	26.800	1.48	11.059	2.40	20.758
RTPA	5.35	23.604	6.19	30.829	2.32	19.376	3.99	27.996	1.46	11.631	2.34	21.438
RTPA+SU	5.63	23.849	6.50	30.212	2.52	19.673	4.24	27.489	1.58	11.863	2.49	21.401
SU	5.66	24.067	6.53	30.598	2.53	19.861	4.26	27.854	1.59	11.976	2.50	21.683
SP+SU	5.76	23.636	6.64	30.169	2.53	19.499	4.35	27.447	1.61	11.799	2.57	21.413
SU+SP+rTPA	5.73	23.419	6.60	29.789	2.53	19.313	4.33	27.086	1.60	11.686	2.56	21.133
average SD	0.96	1.049	1.11	1.612	0.43	865	0.73	1.503	0.27	494	0.43	1.128

'SP'= Secondary Prevention; 'rTPA' = trombolysis; 'SU'= Stroke unit care; 'SD'= standard deviation. Costs are in 1996Euros. Discount rate for costs 3%.

Secondary prevention has delayed effects and yields more health benefits at higher ages, as the risks of recurrent stroke are higher. Hence, also due to its low costs, its cost-effectiveness increases with age and leads to cost savings. Here, optimum packages at low budget would exclude younger ages.





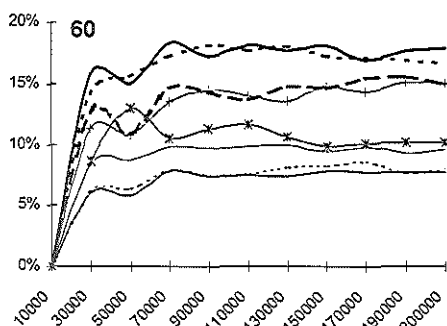
SP= Secondary Prevention; 'rTPA' = trombolysis; 'SU'= Stroke unit care; 'SD'= standard deviation. Discount rate costs 3%.

**Figure 6.1.** Lifetime health gain and total medical costs as compared to baseline by intervention mix (by age and sex; same markers; see *Table 6.3.* for values).

*Figure 6.2* gives the probability of each intervention mix to be included in the optimum stroke package by age and sex, using the stochastic life table approach. At the higher budget range (€150.000), interventions at all age and sex groups are relevant. Here, also the less cost-effective options can be included and the probabilities for each option, in each set, stabilise. At the high budget level, one can observe that any intervention mix that includes stroke units is most likely the optimum choice. Adding trombolysis or secondary prevention, actually, would not make a big difference, given uncertainties. At lower budget levels, younger age groups are, indeed, included in the optimum stroke package. One can also observe an interaction effect between trombolysis and stroke unit care: the combined effect is less than the added effect of the two options. If patients improve more because of one intervention, on average, there is less to gain from the second.

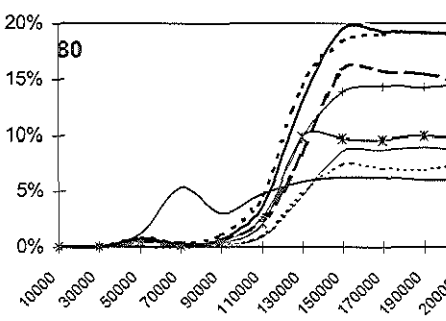
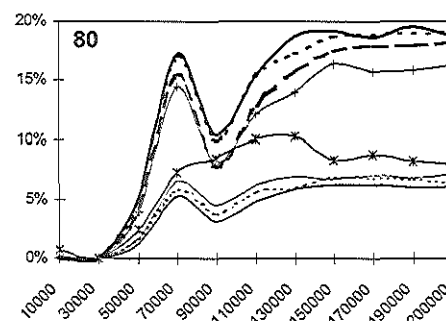
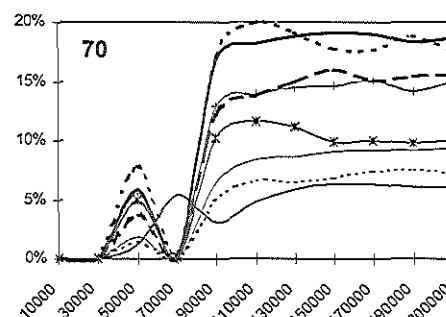
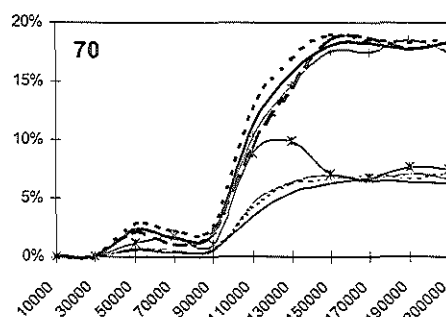
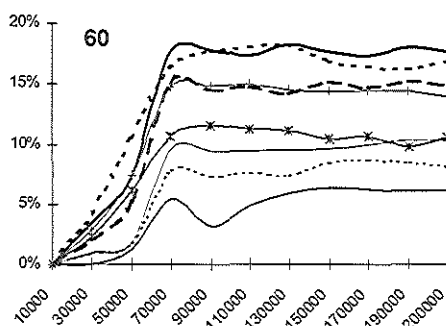
probability

men



probability

women



— Baseline      — SP      ..... rTPA  
 - - - SU      - x - SU+rTPA      — SP+SU  
 - + - rTPA+SU      . . . . . SP+rTPA+SU

budget level (Euros)

'SP'= Secondary Prevention; 'rTPA' = trombolysis; 'SU'= Stroke unit care.

**Figure 6.2.** Probability to be the optimal mix for the various stroke intervention options by available budget level. Stochastic league table analysis for different sex and age groups (MCLeague, [38]).

## Discussion

We conclude that stroke units and medical therapies after stroke are cost saving or are cost-effective as compared to a non-intervention situation. The medical therapies are effective for small patients groups only. Costs per QALY gained are higher in stroke units than for medical therapies, yet stroke units yield higher population benefits. The organization of specialized stroke unit care deserves more priority than until now is given. Our conclusion stands, even considering all relevant uncertainties.

The introduction of a stroke unit is a complex intervention. Most effectiveness research from Europe shows an improvement in stroke survival and handicap, and institutionalisation rate [213,214,237]. This improvement does not depend on age [238,239]. The few existing long-term follow-up studies after stroke unit care show a persistent improvement of stroke survival and disability [213,226]. In the United States, little evaluation research is available.[209,240,241]. This has been less systematic [242] - and clinical trials show a large design effect [243]. Stroke unit care deserves to be a priority also in this country [244].

One other relevant intervention, primary prevention of the major risk factor, hypertension, might yield more effective and even more cost-effective results, especially when co-existing risk factors like diabetes are treated as well. We did not include treatment of hypertension in our analysis, as there is a lack of consistent data.

### *Costs of stroke*

In comparison to previous studies [229,236] we have shown that lifetime costs of stroke by age of onset and sex differ according to initial severity. In cost-effectiveness calculations of stroke interventions, one has to account for these differences.

The results of our study and a previous one for the Dutch situation are consistent. Our league table estimates are rather robust to changes in probability of nursing home admissions. For comparison, in the United States the average lifetime costs of stroke are €49.000 for ischemic strokes at 65 years of age and €26.000 at 85 years, for men. For women this is €52.000 and €26.000 [236]. The average direct costs for a Medicare stroke patient lies in the similar range of magnitude as ours. We contribute this consistency to similar distributions of patients by sex and by residence. In Rochester among 218 patients admitted to nursing homes for the first time, 24% had been admitted for 91-365 days and 21% for 1-5 years after the stroke, as measured in residence days [245]. In the UK, after a 4.9 years follow-up, the distribution of patients is comparable with 29% of the survivors severely or moderately disabled, 37% were mildly disabled, and 34% were functionally independent [246].

For the same reason, including productivity costs to communities would not influence the relative cost-effectiveness values. On the other hand, early discharge from stroke units with professional support might increase the burden for kith and kin [231]. We did not use a human capital approach [236] which leads to, in our opinion, unrealistically high indirect cost estimates.

## ***Cost-effectiveness methodology***

Cost-effectiveness analyses of single stroke interventions are common and increasing. Outcomes are difficult to compare because of lack of standardisation and different referent populations. The population perspective and the use of a baseline make our approach consistent and allows for comparisons of different stroke interventions in different subgroups.

We compare the interventions against a baseline situation and choose the year 1985 as our reference situation. The assumption is that the studied interventions have become, or will become fully, effective in the Netherlands after this year. This is probably true for the medical therapies. Specialised stroke care probably started, gradually and earlier on a unknown scale. In our calculations, however, we consider the additional effort to be made [221]. For other countries, health gains as well as the additional costs of stroke units will most likely be bigger.

We used public utility values for minor and major disabilities. In another study, many patients at risk for stroke considered major stroke worse than death, i.e. a utility value lower than 0 [247]. The average utility value for major stroke in this study was 0.23 with a large spread of values. The utilities depended on how one rates one's presence status and how one rates living with severe disability. At older ages, utility values influence cost-effectiveness results more than at younger ages. As stroke units become less cost-effective with at older ages, it becomes important to consider patients' preferences [233]. In our analysis, lower utility values for major stroke would influence all our results in the same way and would not alter our conclusions.

## ***Conclusion***

We have compared the (combined) effects of three types of treatment after stroke on lifetime stroke disability and lifetime costs of stroke. The selected treatments reduce disability, and may be cost saving or cost-effective for the analysed patient groups. Uncertainties in our outcomes exist on intervention effectiveness and costs, institutionalisation rate, indirect costs and disability weighing. They affect the analyses in the same way and do not affect the population benefit ranking of the interventions. Our main conclusion - intensive care for stroke patients deserves priority - remains valid in spite of the large number of inherent uncertainties that we have shown.



## Chapter 7

### **Sectoral health effects and costs of cardiovascular risk interventions: blood pressure and cholesterol - a regional and global analysis**

Based on:

Effectiveness and costs of interventions to lower systolic bloodpressure and cholesterol: a global and regional analysis on reduction of cardiovascular disease risk

Murray CJL, Lauer JA, Hutubessy RCW, Niessen LW, Tomijima N, Rodgers A, Lawes CMM, Evans DB.  
The Lancet (2003) 361: 717-25



## Introduction

Cardiovascular disease (CVD) is a major cause of global disease burden. It accounts for 20.3% of DALYs lost in developed countries, and already causes 8.1% of DALYs lost in developing countries. The World Health Report 2002 quantified the major contribution of tobacco, alcohol, high blood pressure, high cholesterol, low fruit and vegetable intake, physical inactivity and high body mass index to the global burden of disease and the burden of CVD in particular [248,249].

Improved data on the levels of exposure and reassessments of the magnitude of the hazards has led to the recognition that high blood pressure and high cholesterol have much higher impacts on population health than previously thought [52]. Approximately two thirds of stroke and almost half of IHD can be attributed to blood pressure levels above 115mmHg. Total cholesterol over 3.8mmol/l accounted for approximately 18% of stroke and 55% of IHD. The joint effects of blood pressure and cholesterol would, of course, be less than additive because of the multi-causality of cardiovascular disease and the joint action of these two risk factors [249]. This regional analysis has also shown that high blood pressure and high cholesterol are major risks to health in all regions of the world, not just high-income countries.

Given the burden of disease caused by high blood pressure and high cholesterol, it is important to evaluate the costs and effects of the available intervention strategies to reduce these risks. These strategies should, however, be seen in the context of more comprehensive approaches to the control of CVD that focus on a number of inter-related risks to health including levels of blood pressure and cholesterol, tobacco consumption, body mass index, physical activity, diet and diabetes [250,251] In this chapter, we take advantage of the development of standardized methods and companion tools for the evaluation of costs, effects and cost-effectiveness of different interventions within and across regions [3,38,145,167,252-255] These methods and tools mean that results of intervention analyses can be compared more meaningfully across interventions and across locations.

Evaluation of the costs and effects of the major intervention strategies for reducing the burden attributable to blood pressure and cholesterol must address two key debates. First, what are the relative roles of non-personal health services such as mass media messages to change diet or legislation to reduce the salt content of processed foods, and personal health services such as the pharmacological management of cholesterol and hypertension?[250,251,256] Second, should management of blood pressure and cholesterol be based on thresholds for each risk factor seen in isolation, such as treating for a systolic blood pressure over 160mmHg, or should management be based on the absolute risk of cardiovascular disease for a given individual taking into account all their known determinants of risk?[257] In this chapter we analyse the population health effects and costs of non-personal health measures, treatment of individual risk factors and treatment based on various levels of absolute risk [258-260]



## Methods

### *Interventions*

Seventeen non-personal and personal health service interventions or combinations have been included in this analysis – summary details are provided in *Table 7.1*. Non-personal health interventions included health education through the mass media focusing on blood pressure, cholesterol and body mass, and either legislation or voluntary agreements on salt content to ensure appropriate labelling and stepwise reductions of the salt content of processed foods. Personal health service interventions included detecting and treating people with elevated levels of cholesterol for two thresholds; treating individuals with elevated systolic blood pressure again using two thresholds; treating individuals for both elevated cholesterol and elevated systolic blood pressure; and treating individuals based on their absolute risk of a cardiovascular event in the next 10 years (called the “absolute risk” approach [261]) using four different absolute risk thresholds. Risk levels are defined by fitting mean risk factor values to observed baseline risk levels. Estimates of the relative risk of modelled risk factors on cardiovascular events are used to predict the absolute risk of individuals with elevated levels of risk factors. Individuals with an absolute risk of cardiovascular disease greater than the threshold all receive a beta-blocker, diuretic, statin, and aspirin.

**Table 7.1. Interventions evaluated**

Intervention	Description
<b><u>Non-Personal Interventions (N):</u></b>	
Salt reduction through voluntary agreements with industry (N1).	Co-operation between government and the food industry for stepwise reduction of salt in processed foods and labelling.
Population wide salt reduction – legislation (N2).	Legislation to reduce salt content in processed foods and appropriate labeling.
Health education through mass media (N3).	Health education through broadcast and print media focusing on body mass index, cholesterol
Combined intervention of N2 and N3 (N4).	Combination of N2 and N3
<b><u>Personal Interventions (P):</u></b>	
Individual-based hypertension treatment and education (P1 and P2)	Treatment of people with systolic blood pressure (BP) above 160mmHg (P1) or above 140mmHg (P2) on a standard regimen of beta-blocker and diuretic.
Individual treatment for high cholesterol and education (P3 and P4).	Treatment with statins for people with total cholesterol levels above 240 mg/dl (6.2 mmol/L) (P3) and above 220 mg/dl (5.7 mmol/L) (P4).
Individual treatment and health education for systolic blood pressure and cholesterol (P5).	The combination of P2 and P3, with treatment thresholds of 140mmHg systolic BP and 240 mg/dl (6.2 mmol/L) for total cholesterol.
Absolute risk approach (P6 to P9).	<p>People with an estimated combined risk of a cardiovascular event (acute myocardial infarction; angina pectoris; congestive heart failure; first-ever fatal stroke; long-term stroke survivors) over the next decade above a given threshold are treated for multiple risk factors – with statin, diuretic, beta blocker and aspirin - regardless of their observed levels on individual risk factors. Four different thresholds were evaluated – 35% (P6), 25% (P7), 15% (P8) and 5% (P9).</p> <p>The definition of a cardiovascular event differs across studies, so the results reported here might not be strictly comparable with those of similar studies[262]</p>
<b><u>Combined Personal and Non-Personal Interventions (C):</u></b>	
Building the absolute risk approach at the four thresholds on to the combined non-personal health intervention (C1 to C4).	The combination of N4 with P6 to P9.

## ***Regions***

It would be desirable to evaluate all possible combinations of interventions in every country of the world – and for some of the larger countries, to evaluate these combinations at a sub-national level. No country has yet been able to do this, and many countries do not have the technical capacity to evaluate even a few of them. At the other extreme, global estimates are of little use to any specific country. The World Health Organization, through its CHOICE project, provides information on costs and health effects at a sub-regional level, with the different parts of the world divided by geographic proximity and epidemiology. This allows interventions to be placed into broad categories, such as very cost-effective, cost-effective and cost-ineffective, revealing the extent to which strategies to reduce risks to health should differ across different settings.

In addition, CHOICE provides results in such a way that analysts from countries within a region can adapt them to their settings if they wish. The costs, effects and cost-effectiveness of each of the 17 interventions have been evaluated for 14 epidemiological sub-regions of the world. These sub-regions are defined and described in *Annex 7.1*. The results from three of them are discussed in detail - SearD (in south-east Asia with high rates of adult and child mortality); AmrB (in Latin America with low adult and child mortality); and EurA (in Europe with very low adult and child mortality).

## ***Intervention Effects***

Effect sizes used in the analysis are based on systematic reviews of randomized trials where possible, or meta-analysis as shown in *Annexes 7.2-7.5*. From the evidence of large cohort studies in diverse populations the joint effects between interventions were assumed to be multiplicative [263-265].

Population health effects due to the interventions are modelled by stochastically simulating age-, sex-, and sub region-specific populations with the observed baseline levels of cardiovascular risk and the observed distribution of risk factors (systolic blood pressure, cholesterol, body mass index, and prevalence of long-term smokers) in those regions [266,267]. Interventions cover either the entire population (non-personal interventions) or sub populations meeting specific characteristics (personal interventions), such as having 10-year risk of a cardiovascular event, or having systolic blood pressure, over a certain threshold. Population level cardiovascular risk (incidence) is recalculated after applying the effectiveness of the intervention and the effect size of the implied change in risk factor levels to the population receiving the intervention.

To translate age and sex specific changes in the risk of cardiovascular disease events into changes in population health quantified using DALYs, a standard multi-state modelling tool, PopMod, was used [145]. In this model, health effects are estimated by tracing what would happen to each age/sex cohort of a given population over 100 years, with and without each intervention. PopMod is a four-state population model simulating the evolution of a population partitioned into four distinct health states – people who have the condition under study, have some other comorbid condition, have both conditions, and have none of the above (but are susceptible). Births and deaths are also included. The states can be considered either as simple states or as aggregates of other substates. Transition rates, such as incidence, remission, and mortality, govern movements between states.

The model is described by a system of ordinary differential equations with each population age and sex group modelled individually as a separate differential system.[268] The model shows the time evolution of the size of the population age and sex groups, through the four health states and death, in yearly steps. With the appropriate health state valuations, standard life-table measures as well as a variety of summary measures of population health can be derived. Monte-Carlo analysis of uncertainty in transition rates is possible. The side effect relating to the consequences of bleeding associated with the use of aspirin was included. The entire population is subjected to background mortality and morbidity, which is assumed to be independent of the cardiovascular disease states explicitly modelled.

In some cases, mostly in more developed countries, information on intervention effects was available for only one or two settings. The association of blood pressure and cholesterol, however, are remarkably similar in size and shape across Asia, Europe and North America [263,269,270]. We could not obtain evidence about how adherence vary across settings, so no variation was included. Nevertheless, policy-makers must still make decisions about how to use their scarce resources. One approach would be to simply to say that there is no evidence. The approach taken here is to provide the best available evidence, even if this means extrapolating from one setting to another. This approach carries additional uncertainty, especially in the case of behavioural interventions, and this should be considered when interpreting the subsequent results.

## Costs

Costs include *programme-level costs* associated with running the intervention (such as administration, training and media), and *patient-level costs* (such as primary care visits, diagnostic tests and medicines). For this analysis, potential cost-savings related to the prevention of CVD events have not been incorporated because the major interest is in identifying the costs of improving population health by preventing CVD events. Costs have been based on a standardized ingredients approach that has been developed by the World Health Organization to facilitate costing of interventions [145,252-254] The units of physical inputs required were assessed and multiplied by the unit price for each input. For programme costs the quantities of the required inputs (such as labour, vehicles, office space) were identified from the literature with additional details provided by programme staff in various parts of the world. The quantity of patient-level resource inputs required for a given health intervention e.g. hospital inpatient days, outpatient visits, medications, laboratory tests etc., were identified in a similar manner. Reporting costs using the ingredients approach is an important part of making the results transparent to policy-makers as well as providing a way for analysts to adapt the results to their own settings if they wish.

Unit costs of programme-level and patient-level resource inputs, such as the salaries of central administrators, the capital costs of vehicles, offices and furniture, or the cost per outpatient visit, were obtained from a review of the literature and supplemented by primary data from programme staff in several countries. Costs of drugs were based on the price of off-patent drugs from the lowest cost vendor of high-quality drugs.

Information on the costs and effectiveness of interventions that are undertaken inefficiently is of little value to decision makers. For that reason we assume capacity

utilization of 80% in most settings – e.g. that health personnel are fully occupied for 80% of their time. The results identify, therefore, the set of interventions that, if done relatively efficiently, would be cost-effective in the different settings.

Costs are reported in International Dollars to facilitate more meaningful comparisons across regions. An international dollar has the same purchasing power as the U.S. dollar has in the United States. Costs in local currency units are converted to international dollars using purchasing power parity (PPP) exchange rates rather than official exchange rates. A PPP exchange rate is the number of units of a country's currency required to buy the same amounts of goods and services in the domestic market as a U.S. dollar would buy in the United States. An international dollar is, therefore, a hypothetical currency that is used as a means of translating and comparing costs from one country taking into account differences in purchasing power. The base year is 2000. Details of the assumptions are found in *Annex 7.2*.

### ***Cost-Effectiveness***

Average cost-effectiveness ratios are calculated for each intervention by combining the information on the total costs with information on the total health effects in terms of DALYs averted. All costs and effects are discounted at 3% consistent with the Disease Control Priority Review [16], the first large scale attempt to compare the cost-effectiveness of interventions across diseases, and the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine [2].

Using a standard approach, we have identified the set of interventions a region should purchase to maximize health gain for different budget levels. The order in which interventions would be purchased is called an expansion path and is based on the incremental costs and benefits of each intervention compared to the last intervention purchased.

The Commission on Macroeconomics and Health recently defined interventions that have a cost-effectiveness ratio of less than three times Gross Domestic Product (GDP) per capita as cost-effective [271]. Based on this, three broad categories are defined here. Interventions that gain each year of healthy life (e.g. DALY averted) at a cost less than GDP per capita are defined as very cost-effective. Those averting each DALY at a cost between one and three times GDP per capita are cost-effective, and the remainder are not cost-effective.

The results of cost-effectiveness analysis should not be used formulaically – starting with the intervention with the lowest cost-effectiveness ratio, choosing the next most attractive intervention, and continuing until all resources have been used [3]. The uncertainty surrounding estimates is generally too great to support this approach and, moreover, there are other goals of health policy in addition to improving population health. The tool is most powerful when it is used to classify interventions into broad categories such as those used in this paper. This provides decision-makers with information on which interventions are low cost ways of improving population health, and which improve health at a much higher cost. This information enters the policy debate to be weighed against the impact of the interventions on other goals of health policy.

## ***Sensitivity Analysis and Stochastic League Tables***

Probabilistic multivariate sensitivity analysis was undertaken to assess the impact of uncertainty in the assumptions on the baselines levels of risks and effect sizes on the cost-effectiveness ratios. Effect size of changes in risk factors and population risk factor distributions are modelled as random variables so as to obtain mean estimates of incidence after intervention. Draws were made from limits developed from the literature review (*Annex 7.2 and 7.3*) producing upper and lower confidence bounds on the mean incidence. This also includes the effects on costs because different numbers of people will be covered by an intervention under the different scenarios. At the same time, the price of medicines – the key cost driver – was allowed to vary from half to double the base estimate.

Similar to the other applications in this thesis the league table technique was used. Here random sampling (up to 10,000 iterations) draws were taken from generated truncated distributions which were based on the results of the probabilistic multivariate sensitivity analysis (upper and lower confidence bounds of effectiveness and prices of medicine) as described above. Here, we made the assumption that costs have and health benefits have a normal distribution. We use a software program called MCLeague®, described in chapter 4 [38].

## **Results**

*Table 7.2* provides the total annualized costs, total annual health effect in terms of DALYs averted and the average cost-effectiveness ratio for each of the 17 interventions in three sub-regions with differing levels of adult and child mortality and different patterns of risks to health, EurA, AmrB, and SearD. The health benefits of all interventions follow an approximately bell-shaped curve when plotted against age. Depending on the intervention and the region, the curve reaches its maximum at around 60 years of age, with about half of the total intervention benefit occurring at younger ages, and about half at older ages. This is shown for AmrB in *Figure 7.1*.

All 17 interventions in all three regions are cost-effective according to the Commission on Macroeconomics and Health criterion. In all regions, the four non-personal interventions have cost-effectiveness ratios that are lower than personal health service interventions.

When considered individually, non-personal health interventions to reduce blood pressure and cholesterol are very cost-effective. Measures to reduce salt intake are potentially very cost-effective, with legislation being more cost-effective than voluntary agreements under the assumption that it would lead to the larger reduction in dietary salt intake. The impact of non-personal health service strategies to reduce cholesterol compared to salt reduction strategies depends on the distribution of risk factors in the region – it has a slightly lower impact on population health than legislation to reduce salt in EurA and AmrB, and a substantially higher impact in SearD.

Perhaps surprisingly, personal health service strategies have a much greater potential to reduce the burden of disease even though they are slightly less cost-effective than the population-wide strategies. Treatment of systolic blood pressure above 160mmHg falls into the very cost-effective category in all regions. Statins are now available off-patent at very low cost and their use for people with total cholesterol levels above 240 mg/dl (6.2 mmol/L) is also very cost-effective in all regions.

Table 7.2. Annual costs, effects, and cost-effectiveness of interventions

Intervention*	AmrB			EurA			SearD		
	Costs (\$ x 10 <sup>6</sup> )	DALYs (x 10 <sup>5</sup> )	Cost/ DALY (\$)	Costs (\$ x 10 <sup>6</sup> )	DALYs (x 10 <sup>5</sup> )	Cost/ DALY (\$)	Costs (\$ x 10 <sup>6</sup> )	DALYs (x 10 <sup>5</sup> )	Cost/ DALY (\$)
<b>Non-Personal (N)</b>									
N1: voluntary salt red.	82	3	244	297	7	438	199	5	373
N2: legislated salt red.	82	6	127	297	13	227	199	10	193
N3: mass media	81	6	136	202	12	165	204	14	143
N4: N2 and N3	163	12	135	499	24	205	403	24	168
<b>Personal (P)</b>									
P1: BP at 160	3,122	38	811	14,777	73	2,033	1,570	44	357
P2: BP at 140 mmHg	8,806	47	1,863	37,385	82	4,536	6,399	71	904
P3: cholesterol at 240	2,426	28	865	19,187	65	2,967	2,537	54	468
P4: cholesterol at 220	4,397	33	1,326	27,142	69	3,933	4,835	69	705
P5: P2 with P3	11,232	61	1,832	56,572	110	5,161	8,936	107	838
P6: Absolute risk 35%	1,335	51	259	11,555	87	1,324	1,650	74	224
P7: Absolute risk 25%	2,059	56	366	16,015	95	1,685	2,888	88	327
P8: Absolute risk 15%	3,352	62	542	22,226	104	2,147	5,078	106	477
P9: Absolute risk at 5%	6,456	69	931	35,750	114	3,144	10,183	133	768
<b>Combined Interv. (C)</b>									
C1: N4 then P6	1,365	54	252	11,045	91	1,209	1,829	82	222
C2: N4 then P7	2,056	58	352	15,474	99	1,570	2,994	95	314
C3: N4 then P8	3,332	64	523	21,612	106	2,031	5,149	112	459
C4: N4 then P9	6,394	71	903	35,095	116	3,023	10,173	137	745

\*See Table 1 for descriptions of interventions

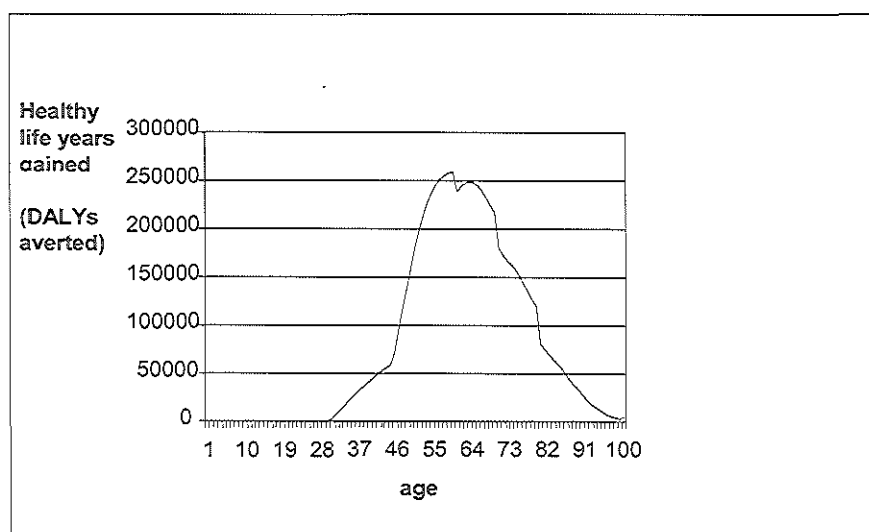


Figure 7.1. Total intervention benefit by age, AmrB

However, a comparison of their cost-effectiveness ratios with those of the absolute risk approach shows that treatment based on measured levels of blood pressure or cholesterol alone would not be the preferred option on cost-effectiveness grounds. The absolute risk approach at a threshold of 35% is always more cost-effective than treatment based on the measured level of either systolic blood pressure or cholesterol. It would avert an additional 65 million DALYs on top of the 21 million DALYs averted by the two non-personal interventions evaluated here.

As the absolute risk threshold is lowered, the health benefits increase but so do the costs – it gets more and more expensive to obtain each additional unit of health benefit. The exact point at which policy makers might choose to set the threshold will vary by setting and will take into account many factors in addition to cost-effectiveness, but it is very cost-effective to reduce the threshold even below 15% in the three regions under consideration, even taking into account the consequences of bleeding associated with the additional use of aspirin.

The cost-effectiveness ratios of the individual interventions do not tell the whole story. *Figure 7.2(a-c)* plot the annual cost and DALYs averted for each of the 17 interventions in the three regions. The slope of the line connecting the origin to each point is the cost-effectiveness ratio. The steeper the slope the more expensive the intervention is per DALY averted. These figures can also help visualize the incremental cost and incremental health gain of moving from one intervention strategy to another. From the perspective of how best to maximize population health for the available resources, the optimal overall strategy is a combination of the population-wide and individual-based interventions. The solid lines joining the most cost-effective points in *Figures 7.2(a-c)* show the optimal choice from a cost-effectiveness perspective. These “expansion paths” join the interventions that would be selected for increasing levels of resource availability. The slopes between them represent the “incremental cost-effectiveness ratio” – or the additional costs required to avert each additional DALY by moving from the lower to the higher cost intervention. The incremental costs, effects and cost-effectiveness ratios of points on the expansion path are reported in *Table 7.3*. If resources are extremely scarce, the non-personal interventions would be chosen first.

In all three regions, the expansion path is similar. In settings of extreme resource constraints, one of the non-personal interventions to reduce salt and/or cholesterol would be purchased first. Decision-makers who want to maximize health gain for available resources would next move to a combined strategy of legislated salt reductions in processed foods with mass media campaigns, and then add the absolute risk approach to managing blood pressure and cholesterol. Depending on the resources available, the absolute risk threshold for a cardiovascular event that would trigger intervention with beta blockers, diuretics, statins and aspirin would be lowered. While the total costs, total effects and cost-effectiveness ratios vary considerably across regions, the sequence of intervention strategies that would be purchased is similar.



**Table 7.3.** Annual incremental costs, effects, and cost-effectiveness of interventions

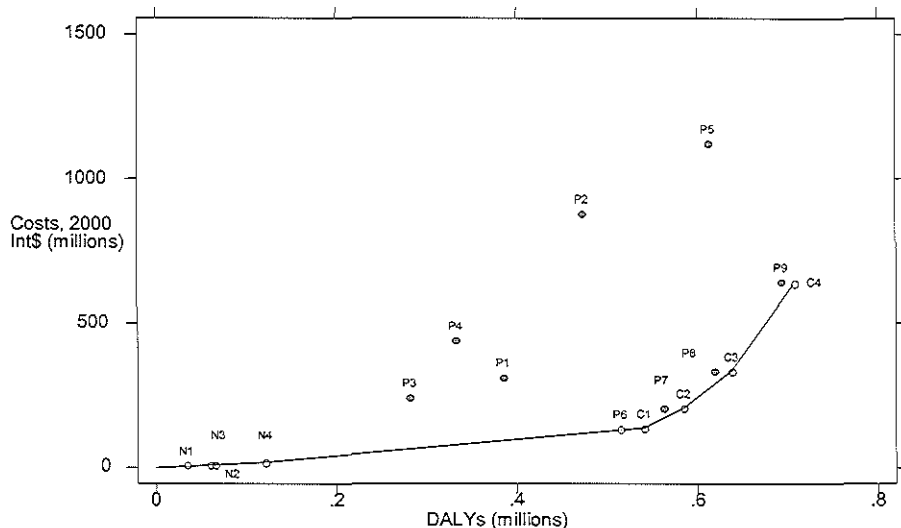
Intervention*	AmrB			EurA			SearD		
	Costs (\$x10 <sup>6</sup> )	DALYs (x10 <sup>3</sup> )	Cost/DALY (\$)	Costs (\$x10 <sup>6</sup> )	DALYs (x10 <sup>3</sup> )	(x Cost/DALY \$)	Costs (\$x10 <sup>6</sup> )	DALYs (x10 <sup>3</sup> )	Cost/DALY (\$)
<i>Non-Personal (N)</i>									
N2: legislated salt red.	82	7	127						
N3: mass media				202	12	165	204	14	143
N2 to N4 (combined N2,N3)	81	6	145						
N3 to N4				297	12	246	199	10	205
<i>Combined Interv. (C)</i>									
N4 to C1 (N4 plus P6)	1,201	42	286	10,546	67	1,573	1,426	58	244
C1 to C2 (N4 plus P7)	692	4	1,598	4,428	7	6,164	1,166	13	898
C2 to C3 (N4 plus P8)	1,276	5	2,392	6,138	8	7,812	2,155	17	1,289
C3 to C4 (N4 plus P9)	7,899	7	4,320	13,484	3	13,923	5,023	6	2,058

\*See Table 7.1 for descriptions of interventions

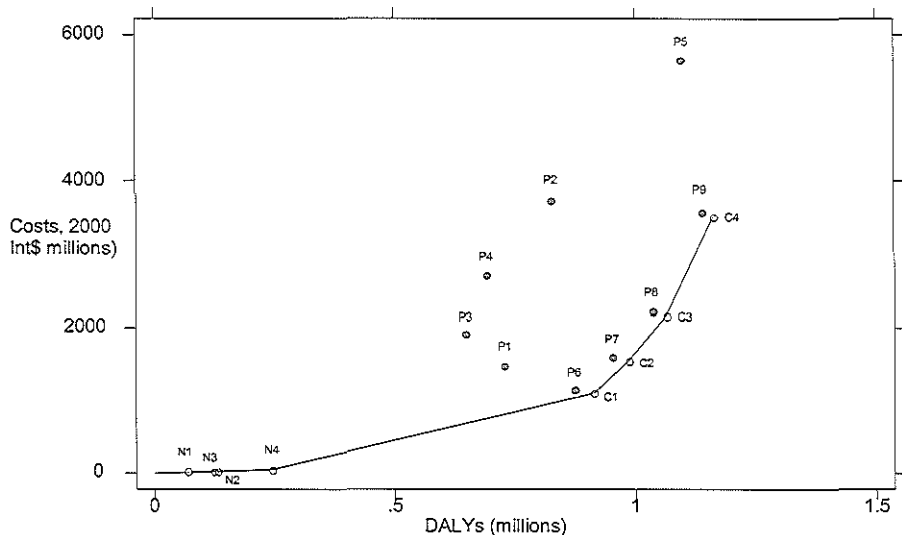
Figure 7.2(a-c) also show that the total effect on the burden of disease through the management of absolute risk is substantial. Population-level reduction in cardiovascular disease events of more than 50% is possible. Even in the less developed regions of AmrB and SearD, the absolute magnitude of the changes in the burden of CVD are impressive.

The multivariate uncertainty analysis illustrates that the cost-effectiveness ratios vary – depending on the region, they can be up to 83% higher on average or 53% lower. This variation, though apparently substantial, does not put any of the interventions classified as very cost-effective into a less desirable category. In addition, the essential features of the expansion paths in the three regions do not change with the changes in assumptions even if the slopes of the segments change somewhat. The order in which the two non-personal health interventions (salt reduction in processed foods and the mass media approach to reducing cholesterol) would be introduced might change, but in all cases one would be chosen as the most desirable option, then the second would be added, before the first personal intervention is considered. In addition, the absolute risk approach is more cost-effective than treating people based on either blood pressure or cholesterol alone in all cases.

**Figure 7.2a. Annual Costs and Effectiveness of CVD risk factor interventions, AmrB**



**Figure 7.2b. Annual Costs and Effectiveness of CVD risk factor interventions, EurA**



**Personal Interventions (P)**

- P1 – treatment of hypertension at 160 mmHg
- P2 – treatment at 140 mmHg
- P3 – treatment of cholesterol at 6.2 mmol/L
- P4 – treatment of cholesterol at 5.7 mmol/L
- P5 – combination of P1 and P3
- P6 – absolute risk approach, 35% threshold
- P7 – absolute risk approach, 25% threshold
- P8 – absolute risk approach, 15% threshold
- P9 – absolute risk approach, 5% threshold

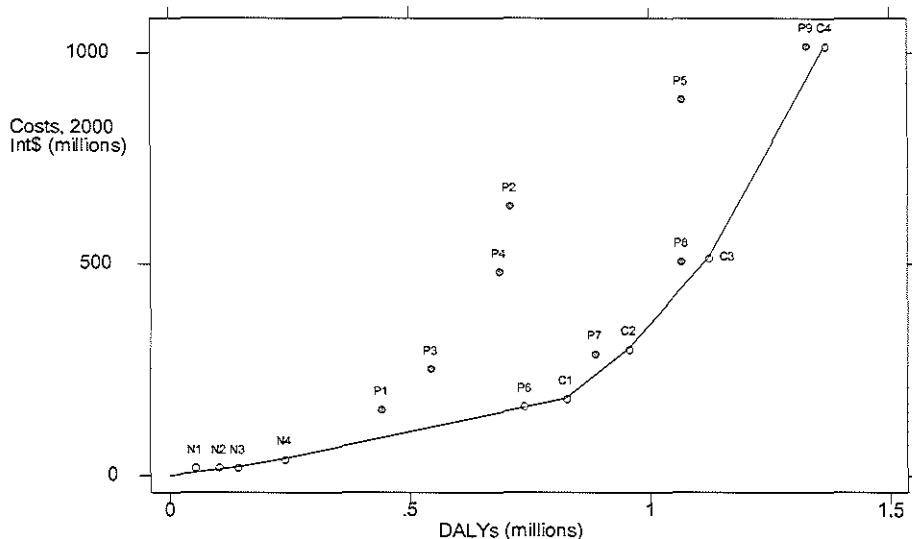
**Non-personal Interventions (N)**

- N1 – voluntary salt reduction
- N2 – legislated salt reduction
- N3 – mass media targeting cholesterol
- N4 – combination of P2 and P3

**Combined Personal and Non-Personal Interventions (C)**

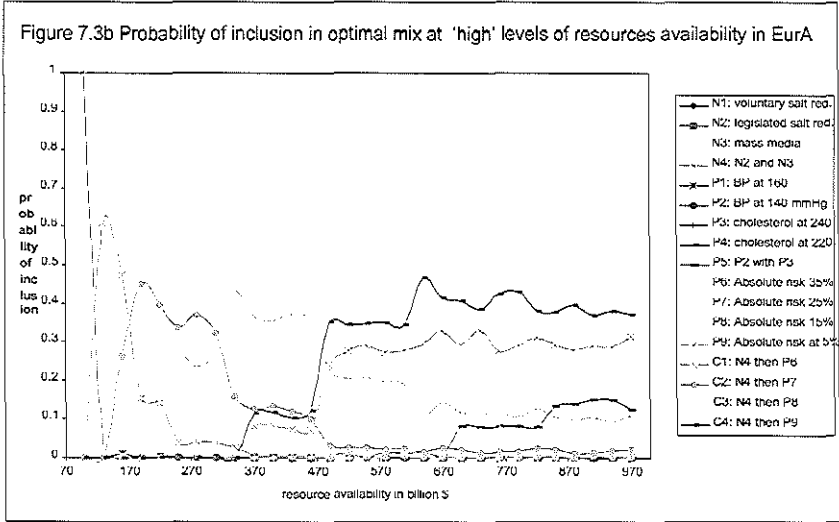
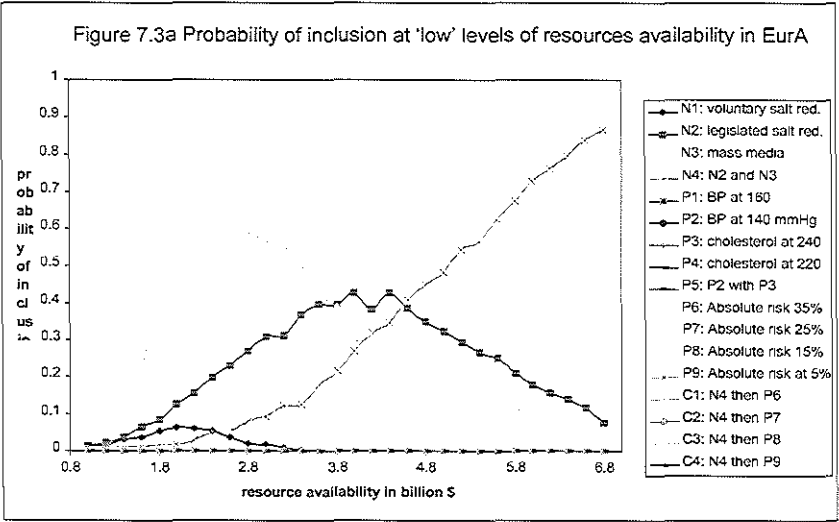
- C1 – P6 & N4
- C2 – P7 & N4
- C3 – P8 & N4
- C4 – P9 & N4

Figure 7.2c. Annual Costs and Effectiveness of CVD risk factor interventions, SearD



<b>Personal Interventions (P)</b> P1 – treatment of hypertension at 160 mmHg P2 – treatment at 140 mmHg P3 – treatment of cholesterol at 6.2 mmol/L P4 – treatment of cholesterol at 5.7 mmol/L P5 – combination of I1 and I3 P6 – absolute risk approach, 35% threshold P7 – absolute risk approach, 25% threshold P8 – absolute risk approach, 15% threshold P9 – absolute risk approach, 5% threshold	<b>Non-personal Interventions (N)</b> N1 – voluntary salt reduction N2 – legislated salt reduction N3 – mass media targeting cholesterol N4 – combination of P2 and P3  <b>Combined Personal and Non-Personal Interventions (C)</b> C1 – P6 & N4      C3 – P8 & N4 C2 – P7 & N4      C4 – P9 & N4
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Figure 7.3 shows the stochastic league diagram for the cardiovascular cluster of interventions for the sub-region EurA only as an example when low (figure 3a) and high (figure 3b) levels of resources are available. The vertical axis shows the probability that an intervention will be included in the optimal package for the level of the resource constraint on the horizontal axis. This takes into account uncertainty around the input parameters. The Figure shows that the optimal mix will differ depending on the resources available. At relative low resource levels, population wide interventions are likely the most efficient choice; at higher resource levels, the most efficient choice are combined population wide interventions with the absolute risk interventions. It remains, of course, to be seen if these preventive CVD interventions of any form is cost-effective compared to other ways of using scarce health resources.



## Discussion

In all regions, these selected non-personal and personal health interventions to reduce blood pressure and cholesterol are very cost-effective. This results is at odds with the perception that CVD prevention strategies should strictly be the concern of the very wealthy. Implied in these results is a further frameshift in thinking about priorities and public health strategies for developing regions. Even though the benefits documented here are already large, the potential of the non-personal interventions may be even larger. The effect size of these interventions observed in North Karelia, Finland was substantially larger than in the North American demonstration/cluster trials like the Stanford 5-city study [272-274] and the assumptions used here reflect both experiences. With greater understanding of the factors that influence the effectiveness of these non-personal interventions, it could well be possible to develop strategies that increase the population health benefits even further.

The beneficial effects of salt reduction have been subject to debate in the recent literature with one review suggesting that the impact of salt reduction on blood pressure was minimal [275]. That review focused on interventions involving individual dietary advice to reduce salt intake rather than the option to reduce the salt content of processed food as assessed here. Indeed, it concluded that reduction in salt intake population-wide through cutting salt concentrations in processed foods might achieve small reductions in blood pressure across the whole population for sustained periods of time, which would then have substantial health effects at the population level. This was the motivation for the intervention analysed here. In addition, there is evidence that small and repeated reductions in salt intake are not discernable on taste, (eg less salt does not necessarily mean less taste[276] ) so that people are not likely to resist the new foods for that reason.

The absolute risk approach to managing blood pressure and cholesterol is very cost-effective in all regions, and has the potential to lead to dramatic reductions in ischaemic heart disease and stroke. Many other combinations of medicines are likely to be as cost-effective as those evaluated here. A meta-analysis of 354 trials, involving 56,000 participants, showed the blood pressure reductions produced by the major classes of drug at standard dose are similar, independent and additive, and that using half standard dose reduces efficacy only by 20% while more than halving effects [269,277,278]. There are also probable or proven benefits of these interventions on other important outcomes not measured here, such as dementia, renal failure, peripheral vascular disease, congestive heart failure and the need for coronary artery bypass grafting [279-283]. Additionally, while the effects of blood pressure and cholesterol lowering drugs appear to be due largely to the amount of risk factor reduction achieved [266,267], there may be some additional benefits due to specific agents, such as coronary disease risk reduction with ACE inhibitors [283]. Implementation of risk screening can and should be tailored to the resource levels of national health systems. In high-income countries, risk assessment on the basis of age, sex, measured blood pressure, cholesterol, body mass index, diabetes, tobacco use and clinical history of previous CVD events is practical. In low-resource settings, however, adequate risk screening could be based solely on age, sex, measured blood pressure, body mass index, tobacco use and past CVD events. This would require no sophisticated technology or blood sampling. A 'risk pill' of anti-hypertensives, statin and aspirin could also be packaged as a single compound facilitating compliance.

As the absolute risk threshold used to trigger treatment is lowered, larger and larger fractions of the adult population would be on long-term drug treatment and the number of adverse events would increase. The consequences of this medicalization of potentially the majority of the adult population should be carefully considered. Issues of long-term compliance may also limit the applicability of the approach in certain populations, including younger people. The potential huge benefits and the apparent cost-effectiveness of the absolute risk approach do seem to justify some large-scale population effectiveness studies. States or provinces in countries facing major CVD challenges could be enrolled to see if the expected population benefits can be achieved in the short-time frame implied by the analysis.

It is well established that in developed countries, levels of blood pressure and cholesterol tend to be worse in the poor than in the rich [284]. Unfortunately, knowledge on how to manage these risks is used more effectively by the higher income, more educated population groups. Consequently, the coverage of interventions to reduce blood pressure and cholesterol is probably lower in the poor. Because of the distribution of these risks, there is a potential for both non-personal and the absolute risk approaches to substantially contribute to the reduction in adult health inequalities. It is a challenge for public health to develop innovative strategies to encourage the uptake of the latter in the poor and disadvantaged [285]. 'Out of the box' thinking may be needed. Studies show that intervention uptake can be affected by financial incentives. Perhaps, lottery tickets should be given to those that reduce their absolute risk by a certain amount in a year.

Why is this analysis apparently suggesting a much bigger impact at lower cost for personal health service interventions to manage blood pressure and cholesterol than many have been expected? First, as part of the Comparative Risk Analysis module of the Global Burden of Disease 2000 project, a clearer picture of the burden of these risk factors worldwide has emerged [248]. Second, new ways of using existing drugs such as the absolute risk method have been developed. Third, lovastatin is now off-patent and other statins will follow soon, substantially reducing the cost of these regimens. Fourth, developments in the analysis of hazard data to deal with the effect of measurement error and regression dilution bias [263,286-288] have led to a nearly doubling of the estimated impact of reductions in blood pressure and cholesterol on outcomes. These changes remind us why it will always be important to update and reevaluate strategies that address major public health problems.

The non-personal interventions considered here were even more cost-effective than the personal interventions in the three regions despite having a lower overall impact on population health. Care should be taken in interpreting these results because the estimates of changes resulting from the mass media intervention were based on changes in behaviour observed in a developed country setting, but even with a halving of the assumed effectiveness, this conclusion is not altered. Based on this assumption, non-personal interventions would be the first to be introduced. Moreover, the non-personal interventions assessed here are only a selection of those that are possible, and their very nature makes reliable assessment of effects challenging. But this challenge must be accepted. For example, assessing strategies to achieve moderate but widespread changes in manufactured food (e.g. in overall fat content) would be very worthwhile, since sub-optimal cholesterol and blood pressure levels have major dietary components to their aetiology.

Three final considerations are pertinent to the policy debate to which this paper contributes. First, the combination of medicines that prevent people at high risk of cardiovascular disease from having an event would cost just less than \$14 per person per year if the lowest cost medicines were purchased internationally. This is simply the costs of the medicines and does not include distribution mark-ups. The ability of poor countries to finance this, and all the other possible cost-effective interventions, from their own resources is limited – some countries spend less than \$10 per capita on health each year. The availability of low cost, effective ways to improve health in all settings, many of which are not affordable at current levels of health expenditure, is why WHO has argued strongly for massive injections of resources for health from richer countries that could be used to reduce the burden of disease among the poor.

Second, this paper has focused on reducing the health consequences associated with cholesterol and blood pressure. It shows which interventions should be given priority when developing a strategy for the control of cardiovascular disease. This is important information for policy-makers responsible for cardiovascular disease control or health promotion. It does not, however, indicate whether controlling cardiovascular disease should receive priority over reducing the risks associated with unsafe sex, for example. This requires consideration of the costs and effects of all possible alternatives. WHO seeks to provide this information through its CHOICE project, and initial results covering several major risks to health can be found in the World Health Report 2002 [249].

Third, cost-effectiveness is only one of the key inputs to final decision about how to allocate scarce resources. Policy-makers have other concerns as well, such as reducing poverty and inequalities, and questions of human rights and community acceptance also influence policy. Another key concern is how different types of interventions can be incorporated into the health infrastructure of the country, or how the infrastructure could be adapted to accommodate the desired strategies. The information presented here is one, but only one, of the critical inputs required to inform the decision making process about efficient ways to reduce risks to health.

# Annex 7.1. Epidemiologic sub-regions

Region*	Mortality stratum**	Countries
AFR	D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome And Principe, Senegal, Seychelles, Sierra Leone, Togo
AFR	E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic Of The Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
AMR	A	Canada, United States Of America, Cuba
AMR	B	Antigua And Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts And Nevis, Saint Lucia, Saint Vincent And The Grenadines, Suriname, Trinidad And Tobago, Uruguay, Venezuela
AMR	D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
EMR	B	Bahrain, Cyprus, Iran (Islamic Republic Of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
EMR	D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
EUR	A	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
EUR	B	Albania, Armenia, Azerbaijan, Bosnia And Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, The Former Yugoslav Republic Of Macedonia, Turkey, Turkmenistan, Uzbekistan, Yugoslavia
EUR	C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
SEAR	B	Indonesia, Sri Lanka, Thailand
SEAR	D	Bangladesh, Bhutan, Democratic People's Republic Of Korea, India, Maldives, Myanmar, Nepal
WPR	A	Australia, Japan, Brunei Darussalam, New Zealand, Singapore
WPR	B	Cambodia, China, Lao People's Democratic Republic, Malaysia, Mongolia, Philippines, Republic Of Korea, Viet Nam, Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States Of), Nauru, Niue, Palau, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu

\* AFR = Africa Region; AMR = Region of the Americas; EMR = Eastern Mediterranean Region; EUR = European Region; SEAR = South East Asian Region; WPR = Western Pacific Region

\*\* A sub regions have very low rates of adult and child mortality: B = low adult, low child; C = high adult, low child; D = high adult, high child; E = very high adult, high child mortality



## Annex 7.2. Assumptions on effectiveness and costs for non-personal interventions

Model variables		Assumptions	Sources
Basic epidemiology	Ischaemic heart disease	Acute myocardial infarction; angina pectoris; congestive heart failure.	Murray and Lopez, 1996[52]
	Cerebrovascular disease	First-ever fatal stroke cases; long-term stroke survivors.	Murray and Lopez, 1996[52]
Risk factor and epidemiology	Blood pressure	Region-, age-, and sex-specific systolic blood pressure levels; age-specific relative risks of CVD event for 1mmHG change in systolic blood pressure (see Annex 4).	World Health Organization, 2002 [249]
	Cholesterol	Region-, age-, and sex-specific cholesterol levels; age-specific relative risks of CVD event for 1mmol/l change in total blood cholesterol (see Annex 4).	
	Body mass index	Region-, age-, and sex-specific body mass index levels age-specific relative risks of CVD event for 1 unit change in body mass index (see Annex 4).	
	Smoking	Region-, age-, and sex-specific prevalence of long-term smokers; age-specific relative risks of CVD event for unit change in prevalence of long-term smokers (see Annex 4).	
Programme level costs	Intervention N1	Central administration and planning costs at 95% coverage.	Johns,2002; Adam, Evans et al, 2002[252,254]
	Intervention N2	Central administration, planning and enforcement costs at 95% coverage.	
	Intervention N3	Central administration costs, planning, media costs and printed materials at 80% coverage.	
Effectiveness	Intervention N1	Region- age- and sex-specific blood pressure changes associated with a 15% reduction in total dietary salt intake (see Annex 5).	Law, Frost et al, 1991 Frost, Law et al,1991[289] Law, Frost et al 1991[290]
	Intervention N2	Region- age- and sex-specific blood pressure changes associated with a 30% reduction in total dietary salt intake (see Annex 5).	
	Intervention N3	2% reduction in total blood cholesterol levels.	Lawes, Feigin et al,2002[291] Tosteson, Weinstein et al,1997[292]
	Intervention N4	Combined effect of interventions N2 and N3.	

### Annex 7.3. Assumption for personal and combined interventions

Model variables		Assumption	Sources
Basic epidemiology	Ischaemic heart disease	Acute myocardial infarction; angina pectoris; congestive heart failure.	Murray, Lopez, 1996[52]
	Cerebrovascular disease	First-ever fatal stroke cases; long-term stroke survivors.	
Risk factor and epidemiology	Upper gastrointestinal bleeding	Adverse effect of anti-platelet therapy with low dose aspirin.	Hernandez-Diaz, Rodríguez, 2002[293]
	Blood pressure	Region-, age-, and sex-specific systolic blood pressure levels; global age-specific relative risks of CVD event for 1mmHg change in systolic blood pressure (Annex 7.3).	World Health Organization, 2002 [249]
	Cholesterol	Region-, age-, and sex-specific cholesterol levels; global age-specific relative risks of CVD event for 1mmol/l change in total blood cholesterol (Annex 4).	
	Body mass index	Region-, age-, and sex-specific body mass index levels; global age-specific relative risks of CVD event for 1 unit change in body mass index (Annex 4).	
	Smoking	Region-, age-, and sex-specific prevalence of long-term smokers; global age-specific relative risks of CVD event for unit change in prevalence of long-term smokers (Annex 4).	
Intervention coverage		Coverage of antihypertensive drug treatment among respondents aware of high blood pressure.  Coverage of cholesterol-lowering drug treatment among respondents aware of high cholesterol.	Molarius, Tuomilehto, et al, 1998; Tolonen, Kullasmaa et al, 1999; Tolonen, Ferrario et al, 1999[294-296]

Model variables	Assumption	Sources
Patient level costs	Intervention P1 & P2 <i>Drug treatment:</i> 50mg/day atenolol (beta-blocker) ; 25mg/day hydrochlorothiazide (diuretic).  <i>Provider visits:</i> 4 health-care provider visits/year; 1.5 outpatient visits/year for health education.  <i>Laboratory tests:</i> annual renal function, lipid profile and blood sugar tests.*	Unit prices of health facilities are based on Adam et al. [254]    Unit price drugs are based on the International Drug Price indicator by Management Science for Health ( <a href="http://www.erc.msh.org">www.erc.msh.org</a> )
	Intervention P3 & P4 <i>Drug treatment:</i> 30mg/day lovastatin.  <i>Provider visits:</i> 4 health-care provider visits/year; 1.5 outpatient visits/year for health education.  <i>Laboratory tests:</i> total cholesterol and hepatic function.*	Unit prices laboratory tests are based on Arizona Health Care Cost Containment System (AHCCCS) Fee Schedule
	Intervention P5 <i>Drug treatment:</i> 50mg/day atenolol (beta-blocker) ; 25mg/day hydrochlorothiazide (diuretic) and 30mg/day lovastatin.  <i>Provider visits:</i> 4 health-care provider visits/year; 1.5 outpatient visits/year for health education.  <i>Laboratory tests:</i> annual renal function, lipid profile and blood sugar tests; total cholesterol and hepatic function.*	( <a href="http://www.state.me.us/wcb/departments/omrs/1999%20MFS/radiology.htm">www.state.me.us/wcb/departments/omrs/1999%20MFS/radiology.htm</a> )
	Intervention P6-P9 <i>Drug treatment:</i> 50mg/day atenolol (beta-blocker) ; 25mg/day hydrochlorothiazide (diuretic), 30mg/day lovastatin and 100 mg/day acetylsalicylic acid (aspirin).  <i>Provider visits:</i> 4 health-care provider visits/year; 1.5 outpatient visits/year for health education.  <i>Laboratory tests:</i> annual renal function, lipid profile and blood sugar tests; total	Hay, Lyubashevsky, et al, 1996[297]

Model variables	Assumption	Sources
	cholesterol and hepatic function.*	
	Upper gastrointestinal bleeding	Secondary level hospital stay of 2.7 days for GBD non-A sub regions and tertiary level hospital stay of 4.8 days for GBD A sub regions.
Effectiveness	Intervention P1 & P2	33% reduction of the difference between actual systolic blood pressure and 115 mmHg.
	Intervention P3 & P4	20% reduction in total blood cholesterol.
	Intervention P5	Combined effect of P2 and P3.
	Intervention P6-P9	Combined effect of P2 and P3 with additional 20% reduction of absolute risk for antiplatelet therapy.
	Intervention C1-C4	Effects of N4 evaluated first. Then the reduced number of people at risk of a Cardiovascular event are subject to the same costs and effects as with P6-9

\* Only for GBD A sub regions

**Annex 7.4. Relative risks of CVD events for unit changes in systolic blood pressure, total blood cholesterol, body mass index levels and prevalence of long-term smokers.**

Relative risks for ischaemic heart disease					
	Age groups				
	30-44	45-59	60-69	70-79	80+
Systolic blood pressure (mmHg)	1.07	1.05	1.03	1.02	1.01
Total blood cholesterol (mmol/l)	3.65	2.08	1.55	1.42	1.42
Body mass index (kg/m <sup>2</sup> )	1.11	1.09	1.05	1.04	1.03
Relative risks for stroke					
	Age groups				
	30-44	45-59	60-69	70-79	80+
Systolic blood pressure (mmHg)	1.09	1.07	1.05	1.03	1.02
Total blood cholesterol (mmol/l)	1.48	1.35	1.25	1.17	1.09
Body mass index (kg/m <sup>2</sup> )	1.19	1.09	1.06	1.06	1.02
Relative risks for smoking and cardiovascular death					
	Age groups				
	30-44	45-59	60-69	70-79	80+
Male	2.43	2.43	1.84	1.70	1.38
Female	2.18	2.18	2.12	1.70	1.31

**Annex 7.5.** Percentage reduction in systolic blood pressure for 15% and 30% salt reduction intake in three regions.

	AmrB				EurA				SearD			
	15% reduction		30% reduction		15% reduction		30% reduction		15% reduction		30% reduction	
	Male	female	male	Female	male	Female	Male	female	male	female	male	female
30-44	-1.1%	-0.8%	-2.2%	-1.6%	-1.3%	-0.9%	-2.6%	-1.9%	-1.1%	-1.0%	-2.1%	-1.9%
45-59	-1.3%	-1.1%	-2.7%	-2.2%	-1.6%	-1.3%	-3.1%	-2.6%	-1.4%	-1.2%	-2.8%	-2.5%
60-69	-1.7%	-1.5%	-3.4%	-2.9%	-1.9%	-1.6%	-3.8%	-3.3%	-1.9%	-1.6%	-3.7%	-3.3%
70-79	-2.0%	-1.7%	-4.0%	-3.4%	-2.2%	-1.9%	-4.4%	-3.7%	-2.2%	-2.0%	-4.5%	-3.9%
80+	-2.4%	-2.0%	-4.8%	-3.9%	-2.6%	-2.1%	-5.2%	-4.3%	-2.7%	-2.4%	-5.4%	-4.8%

Footnote - These estimates were made by applying the relationship between sodium intake and blood pressure as estimated by Law et al [289,290,303] to the WHO age, sex and region subgroups,[291] there have been no re-analyses of the strength of this association in this paper.

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## **Chapter 8**

### **Multiple criteria in sector-wide priority setting**

Based on:  
Diffusion and utilization of magnetic resonance imaging in Asia.  
Hutubessy RC, Hanvoravongchai P, Edejer TT.  
Int J Technol Assess. Health Care (2002) 18(3):690-704.





## Introduction

So far throughout this book cost-effectiveness analysis (CEA) has been presented as a tool primarily concerned with efficiency. This implies that it is not able to explicitly consider equity issues or focus on interventions that give priority to vulnerable groups or the poor. The health system is concerned not just with the generation of health itself, but also with achieving other key social goals including being responsive to consumers and ensuring that the financial burden of paying for the health system is distributed fairly across households [42]. The ideal health system seeks to reduce inequalities in health and responsiveness as well as increasing aggregate levels. The information economic evaluations provide would need to be evaluated against the impact of different mixes of interventions on other social goals. Factors such as the quality of life in a community, improving equity and reducing poverty can lead to very different choices, relative to interventions chosen solely on the basis of efficiency. To achieve these health systems objectives it is important to know what a health system does i.e. how they carry out certain functions. According to the World Health Report 2000 [5] four essential functions can be distinguished: delivering personal and non-personal health services; raising, pooling and allocating the revenues to purchase those services; investing in people, buildings and equipment; and acting as the overall stewards of the resources, powers and expectations entrusted to them. Stewardship occupies a special place because it involves oversight of all the other functions, and it has direct or indirect effects on all health systems outcomes. This chapter will focus on the fourth function called stewardship. The role of the government as a important player in the role of steward will be examined. Particularly the state's task as the overall steward or trustee of the health system will be discussed i.e. to see to it that private organizations and actors act carefully and responsible. A large part of stewardship consists of regulation, whether undertaken by the government or private bodies which regulate their members, often under general rules determined by governments.

The stewardship function will be illustrated with the experience of the introduction of big ticket technologies in a number of developing country settings in Asia [304]. It will be shown that a successful implementation of economically viable interventions is dependent on a set of other highly context specific factors such as economic environment, the legal and regulatory framework and health care financing system. The study describes and explains the diffusion and utilization pattern of a costly technology like magnetic resonance imaging (MRI) in several Asian settings. A number of recommendations are formulated that may guide decision makers to a successful implementation of interventions, in addition to issues of technical and allocative efficiency.

## The case of magnetic resonance imaging in the Asian Region

Since its introduction in the early 1980s, magnetic resonance imaging (MRI) has become a familiar part of medical apparatus available for the diagnosis of different conditions. Its rapid diffusion has been documented in several countries, mostly developed. By

1993, there were more than 4,000 units worldwide [305]. In the US alone, over 2,700 were in use by 1997 [306]. Similar information is less available for developing countries.

There are several routes for the diffusion of technology in developing countries [307]. In the public sector, a common route is through "tied aid" where purchase of equipment is conditional on sourcing from the donor country. In the private sector, one major route is through investments by individuals or groups of individuals who believe there is a market for such equipment, and have the capital to invest. In many cases, these individuals are wealthy doctors who bring in equipment, which they themselves use. In both public and private sectors, a marketing strategy commonly employed is rent-free "loan" of new equipment. The cost of the equipment is bundled into prices of reagents set in an "exclusivity contract" between the health facility and the supplier. If the full cost of the equipment cannot be bundled into the cost of supplies and consumables, an option-to-buy clause after a pre-specified rent-free loan period is specified in the contract. This loan period is usually long enough to create dependence of the health facility on the loaned equipment. Thus, an optional action becomes, more often than not, mandatory to avoid disruption of set routines. A final route of technology acquisition in developing countries is through universities and research institutes who collaborate with their counterparts in the developed world and who get equipment as part of their share in the research grants.

In many of the developing countries, technology can enter "generally without control or supervision by any agency of the receiving government [307]." Lack of regulation gives rise to several areas of concern on the quality of care provided, for example:

*"Me too" phenomenon.* Once the market for equipment has been established a stream of "upgrades" can follow. Hospitals are judged on their technological superiority by clients who believe that the more sophisticated the equipment, the better the care [308].

A "me too" phenomenon is spawned. Hospitals, despite their close proximity with each other and potential ease of referral, will insist on "in-house" availability of equipment. Smaller or lower capitalized hospitals will attempt to purchase equipment, albeit of a lower model and cost. Discards from hospitals in developed countries that have upgraded are purchased by hospitals in developing countries on a "second hand" basis. Depending on how old these models are, some models may run into maintenance problems because the manufacturer may have discontinued production of spare parts.

*Maintenance and operation of equipment.* When imported technology is tied to sourcing from the donor country, problems may arise with maintenance and availability of spare parts [309], especially if there is no local distributor. Once funding assistance has been accepted, "white elephants" loom on the horizon. Another area of concern is the scarcity of qualified individuals to maintain the machine in good working condition, to operate the machine and to interpret the results. The few qualified individuals present in health facilities are constantly being "pirated" by rival hospitals within or even outside the country.

*Physician-entrepreneur.* The phenomenon of the "physician-entrepreneur" has been described elsewhere [308]. Physicians become entrepreneurs when they purchase expensive equipment from which they expect a profitable return on investment. This places the physician in a potential "conflict-of-interest" position [310]. On the one hand, he/she is expected to act on behalf of his patients and undertake diagnostic and treatment interventions based on medical indications. On the other hand, he is an

entrepreneur who wishes to recoup his investment in a reasonably short period of time and he may be tempted to take advantage of situations where indications are not explicitly stated, or are vague with considerable leeway.

Such concerns make it imperative to understand the extent and determinants of the system wide diffusion and utilization of new medical technologies, which are believed to drive health care costs upward [311].

## **The Asian MRI study group and objectives**

In 1997 and 1998 some Asian countries witnessed a dramatic recession of their economies and the viability of some of their expensive investments in health were threatened. The onset of the economic crisis in Thailand was in July 1997, immediately followed by Indonesia and some months later by the Philippines. In the same period members of the Asian Health Technology Assessment Network met twice in Bangkok, Thailand (December 1997 and March 1998) to discuss the details of their first collaborative project on the diffusion and utilization of health care technology and its impact on quality of care. The following countries were represented in this collaborative study: China (represented by Shanghai and Hong Kong), India (represented by the State of Tamil Nadu), Indonesia, Republic of Korea, Malaysia, Philippines and Thailand (see appendix 1).

Magnetic resonance imaging (MRI) was selected as the technology to be evaluated because of its potential to illustrate some of the concerns previously mentioned. MRI is an important imaging modality for examinations of the brain, spine, head and neck. It is a relative new imaging method that uses a combination of magnetic fields and radio waves. Being a piece of imaging equipment, it was felt that there would most likely be central sources of data about the presence of MRIs in different hospitals because of licensing requirements and safety concerns.

Costs and technical performance of MRIs are likely to vary depending on the type and strength of their magnets. Hence, it was thought that the presence of different technical specifications of magnets of MRIs might lead to different patterns of diffusion (i.e. because of lower costs of purchase and maintenance for type of magnet) and utilization (i.e. expectation of higher resolution and better images with magnets of higher strengths) that could be analyzed in the study.

The following objectives of the Asian MRI study group were agreed upon:

1. To compare the diffusion of MRI in each country according to
  - a. type of technology acquired
  - b. mode and time of acquisition
  - c. host institution by location, ownership, type and size of institution, teaching status;
2. To determine variables in the economic, legal/regulatory, health care sector environment which can potentially explain differences in the diffusion of MRI in each country;
3. To describe utilization patterns of MRI in selected hospitals in each country;
4. From the different country experiences, to provide general recommendations to facilitate rational diffusion and utilization of MRI.

## Materials and Methods

### ***Data Collection***

All countries participated in the diffusion phase of the study, and depending on the availability of institutional resources, also in the utilization phase of the study. Most recent data, preferably 1997/98 were collected at national level for the diffusion study and at hospital level for the utilization study. For pragmatic reasons, in the two largest study countries, India and China, data collection was limited to the regional level: for India data came from State of Tamil Nadu while China limited their data collection to Shanghai and Hong Kong. A standardized questionnaire was developed for the survey and distributed among the participating members of the project. Data was entered centrally using MS Excel™ and descriptive statistics were generated.

### ***Data Sources***

#### ***National level data including MRI diffusion data***

To give a general picture of the member countries in the study, main demographic, epidemiological, socio-economic and financial features at country level were collected from the different sites e.g. total population, life expectancy at birth, proportion urban versus rural population, literacy rate, poverty threshold etc. Most of the data from the national level came from existing documents from different national ministries and regulatory bodies, supplemented with key informant interviews and small, purposeful surveys. Missing country or province data was completed using the World Development Indicator/World Bank database [312].

Key variables collected on the adoption and diffusion of MRI in the different study sites were the total number of MRI installed, year of first MRI installed, brand names, MRI strength, type of MRI, location, and ownership. Key informant interviews were carried out to determine the influence of regulatory and non-regulatory factors on the decision of a health facility to acquire an MRI.

#### ***Hospital utilisation level data***

For the hospital level data collection, convenience sampling was based on access to patient records in a hospital (preferably public and MOH). A hundred consecutive patient charts were sampled in two time periods: approximately 3 months before and 3 months after the onset of economic recession. The remaining data were gathered by key informant interviews of the administrators of the hospital and by focus group discussion with physicians using MRI facilities. Key variables collected were number of patients, including background information of the patients who underwent MRI scan, sites of organ scan, specialty of prescriber of MRI, and mode of payment of patient receiving MRI.

## Results

### *General description of the study countries*

General country information can be found in *Table 8.1*. Except for Hong Kong, we report the national numbers and features of all the member countries in the project. The study countries represent almost 44% of the global population in 1998 [312]. Most of the study countries have a predominantly rural population. The top 3 study sites with the highest ratio of health spending to GDP are Hong Kong, Republic Korea and Thailand (more than 5%).

Furthermore the public health component of total health expenditure varies from around 22% in India to 56% in Malaysia [312].

### *Diffusion pattern*

As an indicator of medical technology in the region the number of CT per million population shows wide variation e.g. 179 CT scans per million population for the Republic of Korea compared to 0.3 CT scan per million population in Indonesia (*Table 8.2*).

*MRI availability:* The number of MRI per million population shows quite similar patterns to those of the number of CT scans in the study countries (*Table 8.2*). The same countries anchor the high (Korea) and low (Indonesia) ends of distribution for both MRIs and CT scans. Roughly the region can be categorized into three groups according to MRI availability: first, the Republic of Korea with more than 5 machines per million population; second, Hong Kong, Shanghai, Malaysia with approximately 1-2 machines per million population; and, finally Thailand, Tamil Nadu, Indonesia and the Philippines with less than 0.5 machine per million population.

*Adoption rate:* In general the study sites adopted their first MRI over the period 1987–1990. In terms of average adoption rate the Republic of Korea has the highest rate of 24.5 MRIs per year followed by Malaysia (3.2 MRIs per year), Thailand (2.8 MRIs per year) and Hong Kong (2.0 MRIs per year). The remaining study countries introduced less than 2 MRI on average per year.

*Figure 8.1* gives a more detailed pattern of the adoption of MRI in the region. The horizontal axis plots the year of adoption – starting from 1987 when the first MRI was installed in the region – while the vertical axis denotes the total MRI installed per million population at the different study sites. The steeper curve for the Republic of Korea starting in 1988 characterises it as an early adopter with the persistent increase until 1998. The remaining study sites which have an almost straight or concave curve characterized as predominantly consisting of early adopters of the MRI but resulting only in a small increase of MRIs per million population.

*Ownership and location:* All Shanghai's MRIs are owned by the government, whereas Thailand has 68% and Hongkong 50% in the public sector. In the remaining countries, all (Philippines and Korea) or a majority (Indonesia and Malaysia) of MRIs are owned privately. Many of them are located in non-university affiliated tertiary care hospitals.

Thailand has a unique phenomenon of hosting a third of their MRIs in free-standing locations (*Table 8.3*).

**Table 8.1.** General country information, year 1998

	China	India	Indonesia	Korea	Malaysia	Philippines	Thailand	Hong Kong
Population, total (million)	1,238.6	979.7	203.7	46.4	22.2	75.2	61.2	6.7
Urban population (% of total)	31.1	27.8	38.8	80.4	55.9	56.8	21.0	100.0
GDP per capita (current US\$)	774	439	462	6,908	3,268	866	1,819	24,889
GDP per capita, PPP (current international \$)	3,105	2,077	2,651	13,478	8,137	3,555	5,456	20,763
Official exchange rate (LCU per US\$)	8.3	41.3	10013.6	1401.4	3.9	40.9	41.4	7.7
Health expenditure, total (% of GDP)	4.55*	NA	1.33	5.58*	2.37	3.70	6.18	5.02**
Health expenditure, public (% of GDP)	1.97*	NA	0.63	2.54*	1.33	1.67	1.65	2.25**
Health expenditure per capita (current US\$)	33.27*	NA	6.14	578.28*	77.51	32.01	112.47	1,134.40**

Source: [312] Note: \*1997 \*\*1995



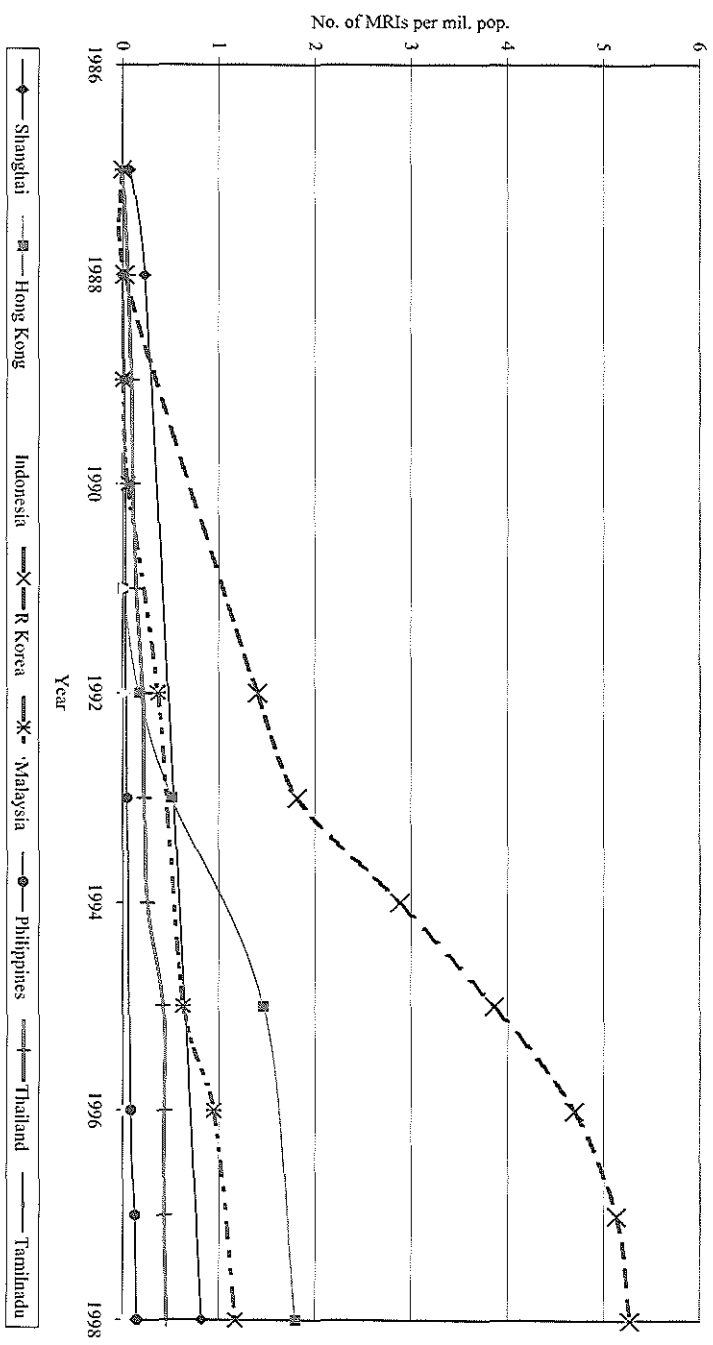


Figure 8.1. MRI diffusion pattern for study countries from 1986 until 1998 (per million population)

**Table 8.2.** Number, number per million and year of first installed MRI in the Asian region

Country	Number of CT scans per million	Total number of MRI by 1998	Number of MRIs per million	Year of first MRI installment	Average number of MRI adopted per year
Shanghai (China)	67	12	0.92	1987	1.0
Tamil Nadu (India)	NA	10	0.18	N.A.	N.A.
Indonesia	0.3	9	0.13	1990	1.1
Republic of Korea	179	245	5.4	1988	24.5
Malaysia	3.3	26	0.8	1990	3.3
Philippines	1.1	11	0.16	1989	1.2
Thailand	3.8	28	0.47	1988	2.8
Hong Kong (China)	2.1	12	1.81	1992	2.0

**Table 8.3.** MRI ownership characteristics in the Asian region

Country (number of MRI in 1998)	Public/private ownership ratio	Hospital/Free standing ratio	Capital/ Rural ratio	University/ Others	Tertiary Care/ Others
Shanghai ,China (12)	100/0	100	NA	13/67	83/17
Tamil Nadu, India (10)	0/100	90	40/60	20/80	100/0
Indonesia (9)	33/67	89	66/33	22/78	NA
Republic of Korea (245)	0/100	95	40/60	30/70	29/71
Malaysia (26)	31/69	100	100/0	8/92	100/0
Philippines (11)	0/100	91	60/40	27/73	100/0
Thailand (28)	68/32	68	68/32	29/71	NA
Hong Kong, China (12)	50/50	100	NA	17/83	NA

**Table 8.4.** MRI characteristics in the Asian region

Country (number of MRI in 1998)	Magnetic Strength	Magnetic Type	Brand								
	Low/mid/high	Sup/Res/Per*	Siemens	GE	Elscint	Hitachi	Philips	Toshiba	Shimadzu	Picker	Others
Shanghai ,China (12)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tamil Nadu, India (10)	90/0/10	NA	20	30	0	10	30	10	0	0	0
Indonesia (9)	87.5/12.5/0	38/13/49	0	14	0	29	0	29	14	0	14
Republic of Korea (245)	13/54/33	87/3/10	28	24	1	10	9	8	10	5	5
Malaysia (26)	27/61/12	27/0/73	9	2	0	8	3	4	0	0	0
Philippines (11)	54/36/10	NA	27	46	27	0	0	0	0	0	0
Thailand (28)	57/0/43	88/0/12	3	33	6	16	3	10	26	3	0
Hong Kong, China (12)	0/25/75	100/0/0	42	33	0	0	25	0	0	0	0

\* Sup = Superconductive; Res = Resistive; Per = Permanent

**Table 8.5.** Overview of regulatory framework in Republic of Korea, Malaysia, Philippines, Thailand and Hong Kong.

Description of Legal/ Regulatory Mechanisms	Republic of Korea	Malaysia	Philippines	Thailand	Hong Kong (China)
Big ticket acquisition propose	No	User & Planning division, Ministry of Health (MOH)	Head radiology department.	Hospital/University/Ministry of Public Health (MoPH) /Private	Hospital authority (HA)
Certificate of Need	No	Justification Required	Justification of need	No	Justification of need
"Need" decided by	Each hospital	MOH	Hospital chief	NA	HA
Evidence of effectiveness before purchase	No	Health Technology Assessment (HTA)	No	Yes	Yes
Body to decide tech is effective	No	HTA	Radiologists and clinicians	MOPH	HA
Evidence of safety before purchase	Yes	HTA	No	Yes	Yes
Body to decide tech is safe	Korean Food and Drug Administration (FDA)	HTA	None	MOPH	Expert committee
Evidence of CE before purchase	No	Yes	No	No	Yes
Body to decide technology is cost-effective	No	HTA	None	None	HA
Financial incentives to purchase	No	No	No	No	No
Financial disincentives to purchase	No	No	Maintenance and operating costs	Capital and maintenance cost	No

Body to approve purchase	No	MOH	Hospital chief	NA	HA Board
Criteria for brand chosen	No	Open tender	Public bidding	Open tender	Open tender
Body to decide which brand	No	Tender board, MOH	Bidding committee	Tender board	Central tender board
Body to decide on location	No	MOH	Hospital Chief	MOPH	HA
Registration agency	No	Atomic Energy Licensing Board	Radiation Health Service, Department of Health.	MOPH	No
Registration requirement	No – radiologists	All above	NA	Voluntarily	NA
On site inspection	No	Yes	NA	Randomly	No

NA = not applicable

*Technical characteristics:* On average, about half the MRI units installed (approximately 50%) in the selected countries have a low magnetic field strength (MFS). On both extremes are Tamil Nadu and Hong Kong: 90% of the MRI installed in Tamil Nadu have a low MFS while Hong Kong has either mid or high MFS MRIs. The majority of the MRIs in Indonesia, Malaysia, Thailand, Republic of Korea and Philippines are superconducting electromagnet MRIs (*Table 8.4*).

*Brand:* No single brand is dominating the market or has a monopoly in the region. On average almost 50% of the market share is possessed by Siemens and General Electric Co (*Table 8.4*).

*Purchase costs:* For Thailand acquisition costs range from 1 million US\$ to 2.1 million US\$ with poor to good perceived viability. For the Republic of Korea purchasing costs by lease vary from 200,000 US\$ to 270,000 US\$. Purchase cost in the Philippines is 1 to 2 million US\$ of which maintenance costs are approximately 25,000 US\$.

### ***Regulatory framework***

Description of the regulatory framework is based on the experience of Thailand, Malaysia, Republic of Korea, Hong Kong and the Philippines (see *Table 8.5*). Based on expert opinion, some form of legal framework for the acquisition of big-ticket technologies is absent or is only applicable to the public sector in these countries. For example, no formal procedure like a Certificate-of-Need (CON) mechanism is required by a governmental body. Instead, a 'Justification-of-Need' has to be delivered by the Ministry of Public Health in the case of Thailand or by the Hospital Authority (HA) Board in Hong Kong. For a country like the Philippines it is not even necessary to produce documentary evidence of the effectiveness and safety of the technology before purchasing. A description of the technical specifications suffice as a basis for making a purchase decision, particularly in hospitals in the private sector.

In all five study sites there is a regulatory body e.g. Ministry of Health, Hospital Chief or HA Board which approves the purchase of the technology. Brands are chosen through open or public bidding. In all the study sites decisions on which brand to buy are made by physicians (Republic of Korea) or tender or a bidding board (Malaysia, Philippines, Thailand and Hong Kong). According to experts in all the countries there is no financial incentive (e.g. tax-free importation) to purchase an MRI.

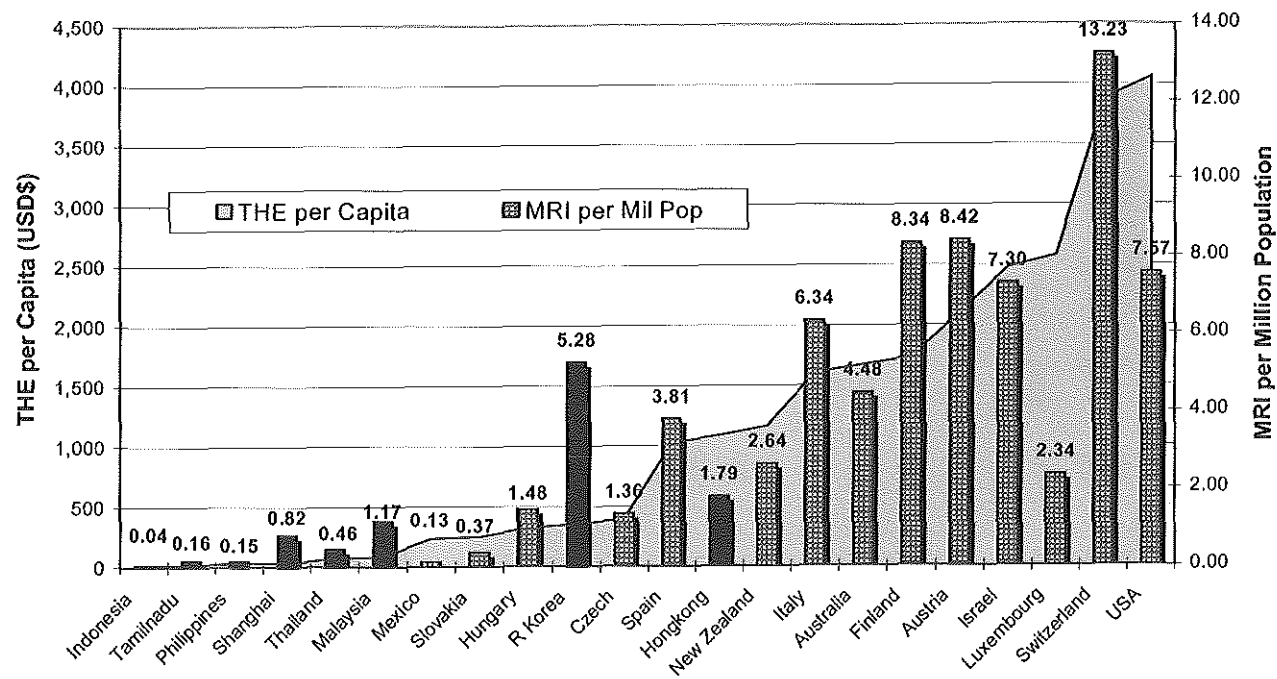
Based on the survey the considerable maintenance and operating costs tends to be a restraining factor for the adoption of MRI. In some of the countries specifications or upgradability, rather than price or length and type of service of the technology, is an important decision feature during the purchase process.

Finally, comparing the distribution of MRIs with regard to ownership (see *Table 8.3*), there is a tendency of countries with a rather weak regulatory framework to have predominantly private MRIs.

**Table 8.6.** Utilisation pattern of Republic of Korea, Philippines and Thailand

Utilisation Data	R Korea		Philippines		Thailand	
	Pre crisis	Post crisis	Pre crisis	Post crisis	Pre crisis	Post crisis
Number of Patients	96	94	100	100	100	100
Average waiting time(days)	3.5	3.5	NA	NA	0	0
Sex						
Female	45%	43%	45%	37%	52%	54.0%
Male	54%	56%	55%	63%	48%	46%
Mean Age	42	45	37.6	37.7	49	47
Proportion of Outpatient	29%	36%	100%	94%	61%	71%
Organ						
Brain	59%	48%	44%	38%	36%	34%
Head&neck	0	0	0%	0%	16%	10%
Spine	16%	19%	36%	39%	40%	45%
Muscular skeletal	8%	9%	7%	17%	1%	6%
Abdomen/ pelvis	5%	6%	8%	4%	1%	0%
Cardiovascular	0	0	0%	0%	0%	1%
Others	0	0	0%	0%	5%	4%
Specialty						
Neurologist	42%	44%	NA	NA	33%	20%
Ortho	13.5%	20%	NA	NA	38%	40%
GP	4.5%	1%	NA	NA	3%	1%
Others	40%	35%	NA	NA	26%	39%
Payment Method						
Out-of-pocket	100%	100%	NA	67%	71%	65%
Private insurance (in full)	0	0	NA	10%	0%	12%
Private insurance with copay	0	0	NA	1%	29%	13%
Public insurance (in full)	0	0	NA	0	0%	4%
Public insurance with copay	0	0	NA	0	0%	5%
Others	0	0	NA	0	0%	0%
Charity	0	0	NA	0	0%	0%





**Figure 8.2.** Number of MRI per population and total health expenditure (US\$) in study countries (black columns) and selected OECD countries (patterned column) in 1998.

## Utilisation pattern

Only three study countries succeeded in collecting pre- and post-crisis utilization data (Thailand, Korea and Philippines) for about 100 patients. Only data on MRI from private hospitals are included. An overview of the utilisation pattern is given in Table 8.6.

*Patient characteristics:* In the three study countries, there is almost the same proportion of male to female patients receiving MRI. The mean age of the patients range from late 30s to late 40s. Outpatients make up the majority of patients receiving MRI in Thailand and the Philippines but this is not true in Korea where two thirds of the patients who receive MRI are hospitalized.

*Area imaged/indication for imaging:* Utilisation data from the three study sites show that in general MRI is performed in accordance with proven clinical applications. Overall, brain and spine examinations account for approximately 70% of the workload in all study sites. For the Republic of Korea over half of MRI are for brain examination while in Thailand the majority of the MRI examinations were used for the spine (see Table 8.6).

*Specialty of referring physicians:* Only two countries had data on the referring physician. In Thailand most patients were referred by orthopaedists for musculoskeletal/orthopaedic diagnosis while in the Republic of Korea the predominant group utilizing MRI were mostly radiologists for neurological diagnosis.

*Fees and mode of payment by patients:* In the three countries, many patients pay out-of-pocket for MRI services. In Thailand and the Philippines there is a proportion of patients who get the services with some form of public or private insurance with full or partial coverage. The impact of the economic crisis can be seen in case of MRI services in Thailand. The proportion of patient paying out-of-pocket for MRI investigation decreased from 71% to 65%. The average charge of an MRI examination of the head in Thailand and Republic of Korea is approximately 191 US\$ and 357 US\$ respectively<sup>9</sup>. For comparison, the average charge for a CT-scan of the head in Thailand and Republic of Korea is only 122 US\$ and 120 US\$ respectively.

## Discussion

Based on the introduction of big ticket technologies in the Asian region this chapter has shown that in order to achieve successfully health system objectives (i.e. in particular health maximisation and reduction in equality in health) it is also crucial to examine what the system does in terms of its functions. In this chapter the link between the government in its role as steward, being service provider and financier of big ticket technologies has been examined. Even if there is proven evidence of cost-effectiveness of certain MRI applications health systems should ensure access to this proven diagnostic therapy to different parts of the population. A parallel can be made with the desire to promote direct observed therapy, short course (DOTS) as a golden standard

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<sup>9</sup> The costs associated with receiving an MRI examination vary widely depending on the complexity of the images required, physicians' charges for interpretation and other variables.

at a global level for TB control. These gold standards focus on biological and technical solutions, but, when applied in varied national and community level context, it takes inadequate account of the wide range of influences that affect policy implementation, such as cultural acceptability, medical pluralism, the impact of health reforms on resources, and health systems management.

The results of the Asian MRI study as presented will be discussed in terms of both health systems policy and public financing/provision perspective. For example technical efficiency issues are concerned with the 'ideal' number of MRI installed per capita in the Asian region while the allocation of MRIs across different socio-economic groups will be described in detail as an example of allocative efficiency. It remains however speculative what the alternative resource allocation purposes would be given the limited perspective assessment of the study. The application of sectoral CEA proposed in this book which addresses both technical and allocative efficiency issues would likely have resulted in a both efficient and equitable outcomes

### ***The adoption and diffusion of MRIs in Asia***

The Asian countries involved in the study display a wide spectrum of economic productivity as measured in terms of GDP per capita. This spectrum of GDP per capita is also reflected in the spectrum of the number of MRIs per million population which varies tenfold from a high of 5 per million population in Korea to a low of less than 0.5 MRIs in Indonesia and the Philippines. Not surprisingly, there is some concordance between GDP per capita and MRI per million population.

If we compare the current average number of MRI per million population in Asia with other regions of the world, it can be concluded that it is quite modest. Using the average of 1.3 MRI per million population in the countries involved in this study, the region as a whole would be ranked at the bottom of the OECD list of MRIs (see Figure 8.2). However, as previously stated, the average hides a considerable spread, and some Asian countries like Korea, an OECD member, can compare favourably with other OECD countries. Furthermore, taking into consideration the total health expenditure (THE) per capita Figure 2 supports the findings by Lázaro and colleagues [313] that lower-income economies devote a larger fraction of their health expenditure to expensive 'big ticket' medical technologies compared with the same fraction in high-income countries. Because there is no 'golden standard' for the appropriate number MRI per inhabitants it is difficult to claim whether this number is too low or what the "ideal" number of MRIs in the region should be.

From the results, there appears to be 2 patterns of diffusion of big-ticket items like MRIs.

One set of countries seems to be composed of mostly early adopters and another set of countries appears to be composed mostly of late adopters. There appears to be no concordance of the pattern of diffusion with either the presence of a regulatory framework or the absolute numbers of MRIs. It was initially hypothesized that a pattern of late adoption would be seen if there was a regulatory framework which required evidence of effectiveness before an MRI can be approved for purchase. For example, in Canada, the MRI was first introduced as a research tool in 1982 and the first clinical use was in 1985. There was slow diffusion of MRI because of Canada's global budgeting system of the Canadian hospitals. There were little funds to buy new,

expensive technology like the MRI and a technology assessment report emphasized the lack of evidence of the diagnostic superiority of MRI (5).

On the other hand, in Japan, which most recently became first in rank in terms of MRIs installed per million population, the main determinants of diffusion include the technical attributes, the market situation of the medical engineering industry, the reimbursement system and Japan's socio-cultural background. It was specifically mentioned that the introduction of MRI in Japan was not linked to formal assessments of effectiveness [314]. Perhaps the Asian experience of rapid adoption and diffusion of MRI in primarily private and urban areas is facilitated not only by the lack of a regulatory framework which is implemented in the public as well as the private sector, but also by the socio-cultural context. In particular, the so-called "Me Too" phenomenon coupled with the economic surplus in those early years could lay the rapid and widespread use of this technology. As mentioned earlier, competitiveness of hospitals is judged by their technological superiority by clients who believe that the more sophisticated the equipment, the better the care.

The relative low number of MRIs per million population that have been installed in the Asian region – in comparison with the OECD numbers – is a quite remarkable finding of this study (except in the case of Korea). At least before the onset of the financial crisis in 1997 when the Asian economies were booming, one would expect more MRIs to have been installed. Also because of the absence of a regulatory framework in this region for big-ticket technologies like MRIs, there would be no barriers, other than economic, to investing in such technologies. Evidence from the early 80s in the United States showed that CON stringency had a strong negative impact on the adoption of the first MRIs in that country [315]. Thus, it appears that the limited numbers of MRIs in the region is probably due to its high acquisition cost, and perhaps also lack of technical know-how on the part of the investors, and the availability of better investment potentials other than high-tech technologies.

Probably because of lower or even no acquisition costs either through second-hand purchases or through donations respectively, many MRIs with low MFS are present in the region. However, this does not necessarily imply low quality imaging. Literature shows that the relationship among the variables contributing to image quality is complex and extends far beyond MFS [316-319]. In addition, there are no completed studies which can directly demonstrate the superiority of higher MFS over low MFS. Preliminary results from two studies show no significant diagnostic difference between low (0.5 or 0.64T) and high (1.5 T) MFS [307,316].

### ***Utilization pattern of MRIs in the Asian region***

The utilization pattern of the study findings are in accordance with the existing evidence where diagnostic improvements resulting from MRI mainly involve the central nervous system, the spinal cord and the neuromuscular system [305]. However, because of the continuing heavy financial burden of maintenance and operation of an MRI, there is danger of shifting to examinations of organs where MRI still has some limited application. It was hypothesized that a change in utilization patterns might be demonstrated before and after the crisis but this was not shown in the limited data available.

Looking at international experience on appropriate use of MRIs there are similarities with the Asian experience. For example in British Columbia, 69.4% of MRI services were for patients referred by neurologists. Only 4.5% were referred by general practitioners[306]. Among in-patients in France, neurologic and neurosurgical indications accounted for two thirds of MRI examinations [320]. During the first years of its introduction in the US, procedures involving the head and spine accounted for 77% [321].

The countries in this collaborative initiative were part of the surging world economy in the early 1990s and due to the increased wealth in the region and increased education of its populace, demand for health care grew and the private sector expanded to account for 40%-81% of health care expenditures. Most of the expensive technology, like the MRI, now belongs to the urban and private sector [309]. Access has been limited by geography and ability to pay, bringing issues of equity into focus. A detailed study in 8 hospitals in Thailand shows that there is inequity in terms of MRI access amongst different payment group. The rate of MRI utilization is very much lower for those under public assistance scheme comparing to those paying out-of-pocket or those covered by Civil Servant Medical Benefit Scheme [322].

In order to avoid costs escalations and inefficiencies in national health systems it is recommended to strengthen legal frameworks and regulatory bodies for the introduction of big-ticket technologies in both public and private sector. In particular, implementation of regulations in the private sector should be taken as a policy opportunity to improve the delivery of health care. For example, a Certificate-of-Need plus a technology assessment report could be required from those who plan to acquire such machines.

For several of the countries in the study, there is no agency formally tasked to undertake health technology assessment. Expertise in this area needs to be built up because some technology assessment reports from the developed countries cannot be imported in total for direct application to developing countries. Authorities need to be able to decide which parts of the technology assessment report can be generalized to their own setting and which ones will need adjustment or tailoring.

In addition, unequal access to such services e.g. for rural populations and disadvantaged groups could be improved through more equitable financing. The wide spectrum in the number of MRI per million population only demonstrates variations among countries and at the most can be interpreted as a signal that there may be evidence of under-availability in some countries and even excess availability in others.

The conclusions of this collaborative study need to be interpreted with caution. First, due to the pragmatic approach of the collaborative initiative, it has to be emphasized that the study has a descriptive retrospective design which limited the ability to analyse the data in an ideal way. Secondly, some data in particular on utilization are incomplete and outdated by the time this study is published. Thirdly, for pragmatic reasons we had to limit country experiences of India and China to regional data. Fourthly, the study sites have different health systems and epidemiological profiles which make the direct comparison of MRI diffusion and utilization problematic. This limits our ability to completely understand and analyse the diffusion of MRIs in the region. We are well aware of the complex combination of economic, organisational, political, institutional, medical, social-demographic and cognitive factors, and this varies in time. We believe however, that the patterns showed in this study highlights common areas of concerns: the need of incorporating health technology assessment tools in policy making in Asia.

Despite the limitations of the study, one can clearly say that the present health care systems in the countries studied, as exemplified in this one-time, limited case study on MRI diffusion and utilization, still deviate from the ideal as described by Hillman et al. as early as 1985 [323]:

“In an optimal medical care system, new technologies and innovations would be adopted rapidly once their safety and efficacy are established and once favourable cost-effectiveness ratios are anticipated. The technologies would be purchased and sited in the most efficient and appropriate settings and would be available equally to everyone in need. Payment would reflect the actual costs of appropriate and efficient medical care at all time, regardless of which technologies are used and whether they are cost-saving or cost-increasing”.



## Chapter 9

# Discussion

*Based on:*

Generalized cost-effectiveness analysis for national-level priority-setting in the health sector  
Hutubessy RCW , Chisholm D, Tan Torres – Edejer T.  
Submitted for publication





## Introduction

This thesis has set out to address conceptual and implementation issues of sectoral cost-effectiveness analysis (CEA) for priority setting in health. By sectoral CEA we mean that all alternative uses of resources are evaluated in a single exercise, with an explicit budget constraint [3,13,183,324]. The main conclusion of this thesis is that for sector wide priority setting, a broader type of economic evaluation, that of generalized CEA, is required, complemented with the traditional context-specific incremental approach. It can be useful as a long-term planning tool for policy-makers to determine which interventions should be included in the optimal mix if more resources become available in the future. The way uncertainty in CE information is presented in this thesis, by means of stochastic league tables, will guide decision-makers on how to allocate future resources. In particular the proposed method is suitable for sectoral analysis since it takes into account the affordability of the selected interventions and the assessment of multiple interventions simultaneously. Given the uncertainty around CE results as shown in chapters 5, 6 and 7, CEA can no longer be used mechanistically to produce results of rankings of interventions, but rather must take into account the wider political processes that are part of the process of priority-setting.

The cost-effectiveness information currently available in the literature is almost entirely derived from the high income countries of North America, Western Europe and Australasia [47,61]. For some disease areas (e.g. mostly non-communicable diseases) information is lacking from Latin America, Africa and Asia, where the majority of the world's poor live (see chapter 2). There are a number of ways in which this deficiency could be addressed. First, the results of cost-effectiveness studies in developed countries could simply be extrapolated to developing countries. This would be easy and quick but would run the risk of giving misleading answers and potentially could encourage wrong decisions to be made. Secondly, cost-effectiveness studies could be replicated in every country in which decisions need to be made for a certain disease area. This would be the safest way to proceed. However, it would be slow and costly. It would also divert limited research resources away from answering more pressing questions. The third option is to modify and use computer simulation models, which in most cases have been developed for use in European and North American settings. These models could be adapted in order to make them relevant to developing countries to address region-specific issues and by using regional or country specific data. The application of the broader type of sectoral CEA that has been proposed in this thesis could be viewed as an example of the latter category of applications of economic appraisals which provides policy makers with guidance for sector wide priority setting. As discussed in chapters one and two, this type of CEA addresses most of the common problems (methodological inconsistency; data unavailability and lack of generalisability of cost-effectiveness information) that have been experienced by decision-makers interested in using the results of CEA for allocative efficiency problems in health policy. Having gone through the first four theoretical chapters and the practical examples in chapters five, six and seven, this chapter draws some conclusions on the opportunities and limitations of putting the concept of sectoral CEA into practice. Finally, implications for health policy will be presented.

## Conceptual and practical issues in sectoral cost-effectiveness analysis

Reflecting in part the preceding chapters of this thesis, some critical conceptual and implementation issues of sectoral cost-effectiveness analysis will be discussed.

### *Conceptual issues*

**Counterfactual** As has been emphasised throughout this thesis, the comparator situation of the counterfactual is crucial for the generalised CEA framework since it meets an important condition for sectoral analysis. By choosing one common comparator in sectoral analysis, the analyst can provide policy makers with comparable CE information for different disease programs, including existing ones. The broader use of CEA gives policymakers a wider and longer term perspective on the possible outcomes and use of CEA information, e.g. setting priorities considering intervention mixes within broad programmes and as a result, identifying existing inefficiencies. In this thesis, parameters reflecting the history of disease have been estimated based on different methods and assumptions. In chapter five the natural (or counterfactual) incidence rate of diabetes mellitus was assumed to be similar to that of badly regulated diabetes patients (a minimum glycosylated haemoglobin (HbA1c) level of 10%). This level of control compares to the Dutch level of control observed about 15 years ago. In chapter six the situation in the absence of stroke care in the Netherlands was estimated by using stroke epidemiology and transition rates from 1985 assuming that after 1985 the interventions considered became effective in the Netherlands. Finally the counterfactual for cardiovascular risk factors in different sub-regions of the world was estimated by 'back-adjusting' using coverage and known effectiveness data of cardiovascular disease interventions. In order to arrive at a valid or plausible 'counterfactual' set, there are a number of key requirements and challenges that the analyst needs to satisfactorily address: Firstly, in most settings interventions do exist and effectiveness estimates from trials are conducted with other existing interventions in place that may influence outcome. In addition, evidence on intervention efficacy or effectiveness is not always generalizable across different settings due to differences in infrastructure (see also section below under '*From modelling results to practice*'). For instance the impact of salt reduction on blood pressure levels as presented in chapter 7 will depend on the existing legal infrastructure in a particular setting. Therefore the suggested solutions as proposed in chapters five to seven (using trial data and 'back adjusting' current rates) should be considered as a second best solution. If natural history data exists this would be the preferable method for constructing the counterfactual. A second problem relates to the validation of this hypothetical counterfactual, since this fictitious situation of non-intervention is not in fact observable. How, then, to validate the counterfactual of stroke in chapter six and diabetes in chapter five? Thirdly, conceptually, the CE outcomes across different disease clusters are comparable and could be ranked in the same league table. However, in reality interventions may interact on either costs or effects or both, which will make it

problematic to put the different disease-specific counterfactuals together in one ‘mega’ league table of interventions.

**Definition of interventions** Another key issue in generalised CEA concerns the definition of interventions. In order to assess their full effectiveness, health interventions should be evaluated at different coverage levels and/or in combinations. This allows also for non-linearities in the cost-functions of a broad range of interventions [3]. In chapter two it was discussed that groups of interventions that are interrelated should be evaluated together in a cluster. There are two situations when this is the case. Firstly, many interventions interact in terms of either costs or effects at the population level, and interacting interventions are done in different combinations in different settings. Secondly, because of the nature of the analysis, by comparing mutually exclusive and independent sets of interventions, the problem of increasing coverage or improved treatment adherence by the patient (with additional costs and/or benefits) is reduced to the clustering of interventions. The usefulness of this method is best illustrated in chapter seven where both non-personal and personal interventions against CV risk factors are combined using different absolute and relative threshold levels of blood pressure and cholesterol. Non-personal interventions, e.g. combined population wide salt reduction and mass media campaigns to reduce the cholesterol level appear to be a cost-effective option in resource poor settings. If more resources become available personal interventions, e.g. the absolute risk approach of a mix of medicines, will appear in the optimal mix. As has been illustrated in chapter 7, combining these interventions into one mutually exclusive set makes the analysis comprehensive and allows the analyst to plot the cost-effectiveness expansion path joining the interventions that would be selected at increasing levels of resource availability.

**Stochastic league tables** Chapter four discusses how decision-makers should interpret the CER of interventions when uncertainty intervals overlap. It is shown how the incorporation of uncertainty around costs and effect of interventions into a stochastic league table provides additional information to decision makers for priority setting. Stochastic league tables inform decision-makers about the probability that a specific intervention would be included in the optimal mix of interventions for various budget levels, given the inherent uncertainty surrounding costs and effects of the intervention. This way of presenting uncertainty in CE information, taking into account the affordability of selected interventions and assessing multiple interventions simultaneously, will better guide policy makers on how to allocate resources. In addition, it allows decision-makers to trade off efficiency against other health systems goals.

The benefit of using stochastic league tables is well-illustrated in chapter five, where two sets of interventions for primary and secondary diabetes care were evaluated together, but in independent sets. The probability of inclusion in the optimum set for each intervention mix by budget level for both patient groups were presented. Depending on the resource availability, the optimal mix is different; in affluent countries, priority should be given to the guideline treatment of complications, as current diabetes care shows inefficiencies. However, the most likely optimal strategies in resource-poor countries are the implementation of guideline treatment of complications and primary diabetes control. The uncertainty analysis proposed in this thesis is a relatively new approach yet is comparable to (and consistent with) traditional uncertainty analyses (see chapter 5)

[168,325]. It meets the specific requirements of sectoral CEA by assessing the uncertainty of the costs and effects of multiple interventions at different levels of available resources. However, more research is needed on how to visualize and interpret the probabilities of inclusions of multiple interventions across different sets of diseases, since they are not directly comparable. In addition, little is known regarding how decision-makers with different attitudes toward risk behaviour should interpret and use stochastic league tables in practice. Finally, given the data requirements of the stochastic league table approach (e.g. the subjective distributional information needed prior to data collection) there might be useful opportunities to see how this method could be combined with the current developments in Bayesian techniques [326,327].

**Standard methodology** Ideally, generalised CEA should provide consistent results, in terms of the use of standard methodologies and use a similar reference point or counterfactual against which to compare interventions. If there were agreement on a single international consensus guideline on sectoral CEA (e.g. the set of guidelines proposed by WHO-CHOICE [145]), two major sources of variability would be removed. Firstly, applying the same reference point or counterfactual for estimation of effectiveness would make studies more comparable and transferable [328]. Secondly, accepting a single international agreed CEA guideline would reduce variability in cost estimates [329].

Chapter seven has shown that using a standardized methodology to estimate regional cost-effectiveness numbers for CV disease risk factors resulted in a unique statistical database allowing analysts to assess personal and non-personal interventions across both industrialized and poor regions. One of the major findings is that the 'absolute risk approach' to manage blood pressure and cholesterol is very cost-effective in all regions and has the potential to lead to dramatic reductions in ischaemic heart diseases and stroke. Furthermore, the use of a standard methodology allows comparing CE results for CV disease clusters with those for the diabetes cluster in a single league table.

## **Implementation issues**

**Transaction costs** Generalised CEA gives policy-makers a wider and longer term perspective on the possible outcomes and use of CE information, e.g. identifying existing inefficiencies. However, the ability to shift resources from an existing package to the next best alternative is not cost-less [153] and will incur costs which differ from the costs required to deliver the interventions, i.e. transaction costs<sup>10</sup>. Ignoring possible deviations in existing capacity and infrastructure to absorb such changes may mean that there is a significant difference between the 'theoretical' CE ratio based on generalised CEA and one achievable in any particular setting [153]. However, the budget implications of a portfolio shift will depend on how dramatic the change will be when moving from the current mix of interventions to the optimal mix indicated by generalised CEA. If several incremental steps are required to reach the generalised solution, transaction costs will

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<sup>10</sup> According to Mishan [362] these costs can be broken down into sub-categories. Firstly, the costs of negotiating agreement between parties having conflicting interest over spill over effects. Secondly, costs of administration and supervision that are necessary to maintain the mutually agreed solution. Thirdly, capital outlays, if any required to implement the agreement in question.

certainly matter and may in fact jeopardise any successful change in portfolio mix of interventions. For instance, the incremental change of moving from the current situation where an existing vaccination program is in place and adding a new vaccine to the target population might have dramatic budgetary implications. The vaccination program might require major infrastructural revisions e.g. adapting the cold chain, starting a media campaign and extending an outreach program. In contrast to this, a procedural change in a surgical therapy may have less dramatic budgetary consequences. In summary, depending upon where the current mix of interventions is located on the expansion path, transaction costs may or may not be relevant to decision-maker's choices.

***From modelling results to practice*** Many factors may alter the actual cost-effectiveness of a given intervention programme during implementation. These include: the availability, mix and quality of inputs, especially trained personnel, drugs, equipment and consumables; local prices, especially labour costs; implementation capacity; underlying organization structures and incentives; and the supporting institutional framework [103,330-333]).

From a health systems perspective Lee, (1999) [334] raises the issue that cost estimates rarely provide an accurate reflection of the true costs of implementing a medical intervention. The reasons that such analyses may be misleading in this regard include the following: (1) The costs of pharmaceutical interventions vary substantially depending on the type of contracts between payers, pharmacy benefits management companies, and manufacturers. (2) Economic analysis are almost always out of date by the time they are published [335]: The costs of the intervention may have declined, and competing intervention may have been developed (e.g. lovastatin recently went off patent making CE ratios of statins more favourable). (3) Costs of care may be lowered by effective management (e.g. through negotiation, insurance companies may reduce prices).

Regarding effectiveness, as mentioned in chapter two, most model experiments are often based on proven efficacy data from experimental and context-specific trials. When interventions are implemented the CE ratios may be altered because of problems or differences in the health care process. According to Ruwaard and Kramers (1998) [336], who modified the original iterative loop model of Tugwell et al (1985) [337], the health care process is divided into five phases that are decisive in determining how effective health interventions are in practice.

First, contact with the health care system is uncertain. An efficacious intervention will have no effect if the patients never contact the health care system or the contact is too late. For example the CE estimates in these thesis for diabetes mellitus *might* be underestimated, since about 50% diabetes sufferers are undetected.

Second, the diagnostic phase is problematic for a number of diseases. For example, part of the ineffectiveness of the medication prescribed for chronic obstructive pulmonary disease (COPD) can be attributed to the fact that it is not adequately distinguished from asthma in the absence of lung function tests.

Third, ascertaining whether the intervention is indicated can be difficult. Criteria can often not be expressed in exact terms, there is little information on differences in efficacy groups of patients, and it is not always easy to determine prognosis. For example, the

reason why, in chapter seven, different risk factor thresholds were evaluated is that it is not possible to speak in simple terms of a 'normal' or an 'elevated' level of either cholesterol or blood pressure. The crucial factor is the degree to which the level is elevated, and this is an important guide in deciding whether or not to administer medication.

Fourth, the quality of executing the intervention matters. For instance, for drug therapy, the correct dosage will be an issue, while for surgical therapy it will be technical skills that determine the effectiveness.

The fifth and last phase involves patient compliance, which can reduce efficacy of an intervention. If patients do not follow advice and do not continue with treatments effectiveness can be greatly reduced. Again referring to chapter seven, the effectiveness of the pharmaceutical prophylactics to reduce elevated cholesterol and blood pressure levels could be overestimated, as it is not easy or possible for all patients to follow the recommended diet and to regularly take these medicines. The medicalization of potentially the majority of the adult population is one of the problems inherent in the gap between evidence about efficacy and effectiveness of the drug in practice.

**Contextualization** Even if the range of technical issues discussed above is addressed, there remains a legitimate concern that global or regional CE results may have limited relevance for local settings and policy processes. According to Kunmaranayake and Walker 2002 [153] there is a tension between generalised CEA that is general enough to be interpretable across settings, and CEA that takes into account local context. Local decision-makers need to contextualize generalised CEA results to their own cultural, economic, political, environmental, behavioural, and infrastructural context [338]. Some decision-makers, such as national and local public health officials, may need to assign priority to high-risk groups. Some recommended preventive services are provided at lower rates to people who are of low-income status, less educated or members of racial and ethnic minority [339]. Limitation in the results of generalised CEA and global/regional CEA should be taken as such, but these results are valuable in thinking about relative resource allocation from an international perspective. However, the implementation of these findings into national policy-making processes requires careful consideration of just how transferable the information is likely to be in each setting [153].

## Sectoral cost-effectiveness analysis and health policy

If both technical and pragmatic barriers for sectoral use of CEA can be addressed, the question remains how to make this information useful for policy makers. Two possible ways of using CEA in decision making will be discussed in this section: First, the use of sectoral CE information for health systems performance assessment and, second, how to use this information for public policy and priority setting.

**Health maximisation** In the introduction of this thesis it was mentioned that eventually sectoral CEA information could be used as an alternative to the top-down method of health systems performance assessment. The latter is based on econometric analysis of whether health systems resources are achieving the maximum possible benefit in terms of outcomes that people value e.g. level of health [340]. In *Figure 9.1*, goal attainment is measured on the vertical axis and input use on the horizontal. M shows the maximum possible level of goal attainment for the available resources, and L the minimum. L is not zero in health because health outcomes would not be zero in the absence of health system inputs.

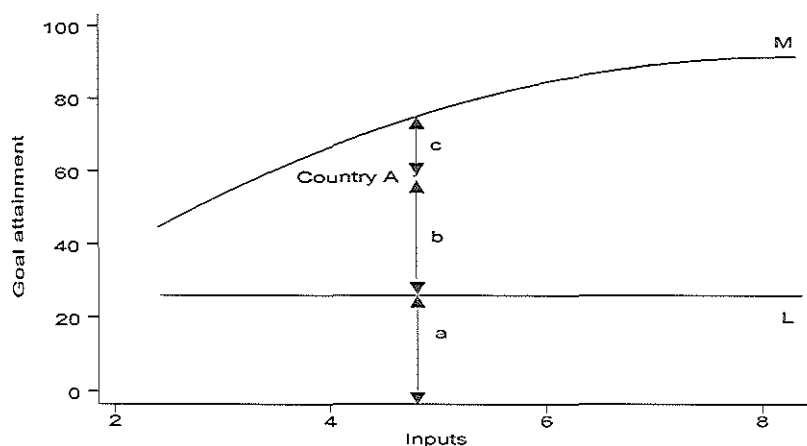


Figure 9.1. Health system efficiency

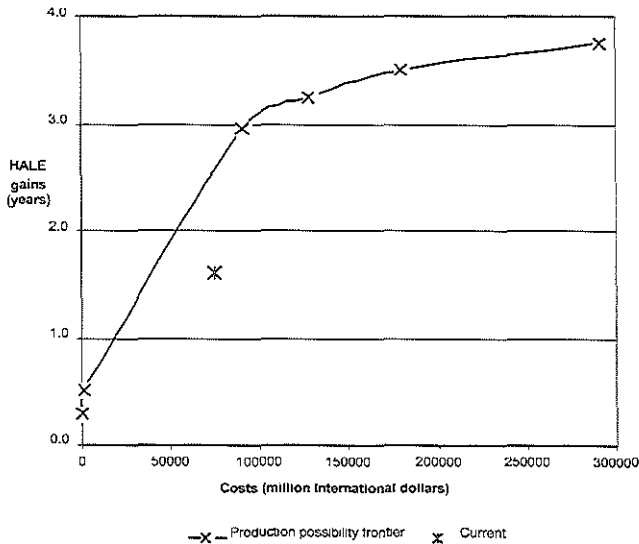
Efficiency can be defined as the ratio of attainment (above the minimum) to the maximum possible attainment (also above the minimum) – i.e. what proportion of the potential health system contribution to goal attainment is actually achieved for the observed level of resources. For a country at A it is  $b/(b+c)$ .

Inefficiency could be due to two causes. The first is waste – e.g. over-staffing of hospitals – or technical inefficiency. The second is the wrong mix of interventions for the health problems of the country and the available resources which can be referred to as allocative inefficiency.



The frontier M is the potential attainment when the most cost-effective mix of interventions is used for the available resources, or for country A ( $a+b+c$ ). The maximum possible contribution of the system is  $(b+c)$ , the contribution above the minimum. Current outcome A is determined by the mix of interventions that is actually used, so observed health system efficiency is related to actual coverage of the optimal mix of interventions. Information on the costs and effectiveness of a range of interventions is, therefore, valuable to policy-makers seeking ways of improving attainment and efficiency. Obviously, for many conditions and treatments, the production possibility frontiers are not known and depend on individual treatment response. In some cases, such information may be known with relative certainty which may allow exclusion of particularly bad buys, or inclusion of good buys, or even the complete ranking of all possible interventions [341]. The WHO-CHOICE project might be a first step in this direction [249].

To illustrate this with an example, *Figure 9.2* depicts the production frontier for the CVD risk factor interventions evaluated as presented in chapter 7 for AmrA. The vertical axis depicts health adjusted life expectancy (HALE) gained (obtained by transforming DALYs averted for each intervention to HALEs gained) and resource use or costs are shown on the horizontal axis. Available data on current coverage of the interventions in AmrA and their costs and effectiveness allow current attainment and costs to be estimated, represented as point \*. The higher line shows the frontier estimated from information about the costs and effects of the most efficient mix of interventions at any given level or resource availability. The point \* is below the frontier, suggesting that the health system in AmrA is not achieving its full potential in terms of reducing the risks associated with high blood pressure and cholesterol [342].



**Figure 9.2.** Maximum possible health gains from selected CVD risk factor interventions, sub-region AmrA

**Other health systems goals** Generalised CEA is not a prescriptive tool, but provides information on the relative cost-effectiveness of a broad range of interventions. As has been repeatedly stated throughout this thesis, CE information is one input to the decision making process – in which only the goal of maximizing population health status given the resources available is addressed. In the CE literature, the most discussed objectives have been health level and health equality [343]. According to Murray et al (2000) [42], other intrinsic goals can be identified for measuring the overall performance of the health system; first, not only increasing the average health status and but also reducing health inequalities should be an objective of the health system. Second, a health system should embody respect for persons in terms of dignity, confidentiality and the autonomy of individuals and families to decide about their own health. Third, a health system should be client oriented providing prompt attention, access to social support networks during care, good quality of basic amenities and choice of provider. Finally the financing of the health system should be organized in such a way that every household pays a fair share of the total health bill for a country. This implies that everyone is protected from financial risk due to health care. Taking into account these other health systems goals, the vertical axis in Figure 8.1 could then be expressed as overall goal attainment. As will be discussed below, some of these health systems goals might be in conflict with each other within the priority setting process.

**Priority setting** According to Kunmaranayake and Walker (2002) [153] in addition to the focus on national priority setting, there are now greater efforts to prioritise international public health resources as well as to raise additional funds for defined priority areas. Interesting to note in this respect are the recent developments on both national (i.e. in the UK, the National Institute for Clinical Evaluation [344]) and international (i.e. the Global Forum on Health Research [345]) health research priority setting in which cost-effectiveness is one of the key factors. The need for comparative data and hence standardized CE methodology to assess whether or not to pursue particular research and development possibilities is apparent. Economic evaluation makes comparisons between alternatives explicit and transparent, and as such facilitates priority setting, and hence, resource allocation. It should be emphasized that the CE tool cannot resolve the question whether society should pay for a new technology [346]. To determine whether technologies should be purchased, it is necessary to ascertain how much society is willing to pay for the health benefits of the technology; conducting CEA will not remove the need for difficult resource decisions. The answer to what should be provided involves a series of value judgements that can vary depending on the individuals and groups involved [347]. For example in Oregon in the US and in Sweden both the public and experts were involved in the priority setting process [348,349].

What makes it particularly difficult to set priorities is that the set of criteria, or health systems goals, are not always compatible. In particular efficiency and equity can easily be in conflict, because the costs of treating a given health problem differs between individuals, or because the severity of a disease bears little relation to the effectiveness of interventions against it or to costs. Gwatkin and Guillot contend that 'the fact that the most efficient interventions tend specifically benefit the poor is more a result of coincidence than of principle' [345]. In their benefit-incidence analysis of 44 countries across Africa, Asia and Latin America the authors showed, for example, that

interventions like oral rehydration and immunization – technologies developed with the needs of the poor particularly in mind – do not reach the target group. Only one-half of all cases of diarrhoea among children in the poorest 20% of families had been treated with some kind of oral liquid. Similarly, immunization programmes are not reaching the poor nearly so well as they are the better-off. On average immunization coverage in a developing country's poorest 20% is around 35%-40%, only a bit more than half of what it is among the average country's richest 20% regime [350,351]. In other words, cost-effectiveness show what combination of interventions would maximize the level of population health for available resources. It is, however, only one input- albeit an important one – to the decision-making process. The information it provides would need to be evaluated against the impact of different mixes of interventions on other social goals. Factors such as the quality of life in a community, improving equity and reducing poverty can lead to very different choices, relative to interventions chosen solely on the basis of efficiency.

Determining the priorities for a health system is an exercise that draws on a variety of technical, ethical and political criteria and is always subject to modification as a result of experience in implementation, the reaction of the public, and the inertia of financing and investment [151] (see also Chapter 8). In reality, social and political factors will often be taken into account by decision-makers, as has been clearly seen in the case of the Oregon experiment and also in the Netherlands. In the Netherlands, since 1990, priority setting has become one of the key issues used in making choices in health care. In 1991, the now famous Dunning Report was presented to the Dutch Cabinet. One of its main conclusions was that health services should satisfy four criteria: necessary care, effectiveness, efficiency, and individual responsibility. Because of the lack of CE data generally, and the application of inconsistent methodologies in available datasets, the efficiency criteria was not applied as the Commission would have intended [352]. For more or less similar reasons, the importance of efficiency criteria initially promoted in the state of Oregon was steadily diluted over time and efficiency was superseded by other mainly political considerations in the priority setting process [348,353-355].

If one believes that final priority setting decisions should not be left solely to the discretion of the decision-maker or to political considerations and that efficiency-equity trade-offs should explicitly be illuminated, adjustments to the existing tools are needed [356]. The use of a health-related social welfare function (HRSWF) to tackle the trade-off between health maximization and equality of health was first proposed by Wagstaff [324]. Since then several operationalisations of the efficiency-equity trade-off have been proposed [357,358]. A reason why in practice the priority setting process remains difficult concerns the lack of a model or, where it is available, the failure to implement it. An operationalisation of such a priority setting effort is a recent attempt by the US Preventive Services Task Forces. In order to quantify different criteria in the priority setting process, the Task Force performed a systematic assessment of the value of clinical preventive services recommend for average risk patients based on two dimensions; clinical preventive burden and cost-effectiveness [339,359]. However, some authors believe that the burden of disease criteria is only relevant for priority setting when economics of scale are associated with the intervention and significant positive externalities occur [341]. Other authors claim that the burden of disease criteria for priority setting is not at all necessary in particular when it is measured by DALYs [360].

According to these authors simple comparison of CE of interventions would appear to achieve the same end.

## **Conclusion and future research**

As demonstrated throughout this thesis, economic analysis can provide new insights and valuable contributions to pressing health policy concerns at national and international levels. At both levels of policy, there is a need to generate economic evidence that can both inform and support resource allocation decisions regarding new or existing initiatives and interventions. There are presently many gaps in this evidence base, so a primary objective for future research activities must be to begin the task of filling in existing gaps in knowledge. It is perhaps not surprising, but nevertheless paradoxical, that there is least evidence where arguably it is most needed, namely in assessing the impact of low-cost interventions to currently underserved populations of low-income countries.

Future research and conceptual thinking is required to use and apply the broader type of CEA information for health systems performance assessment as discussed in this chapter. In particular, the construction of the counterfactual requires more thought given data limitations and the need to contextualize CE data to make it more relevant for policy-makers. Such research may enhance the impact of economic evaluations so that they can directly influence health care decision-makers. However its impact on health policy will remain difficult to detect. More recently, a retrospective assessment of the Health of the Nation policy (Department of Health UK, 1998) concluded that 'there was little evidence that health economics had made any significant contribution to the way that the policy was pursued'. Sector-wide CEA as proposed in this thesis might be a useful and interpretable presentation of CE information to policy-makers. Clearly, the use of CEA in policy-making is not straightforward. The choice of alternatives is a political process and naturally involves a range of stakeholders; technocratic approaches are not value-free. Obviously, cost-effectiveness is only one source of information need for decision-making – factors such as improving equity and reducing poverty can lead to very different choices, relative to interventions chosen solely on the basis of efficiency.



## Summary



## Introduction

This thesis proposes the application of a type of cost-effectiveness analysis that can provide policy-makers with guidance for sector wide priority setting. This analysis, i.e. generalised CEA, explicitly takes 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. Generalised CEA should be considered as complementary to traditional incremental cost-effectiveness analysis: the possibility to analyse individual disease and to perform incremental analysis – one intervention (e.g. current) compared with another (e.g. new) – will remain. Furthermore, sectoral CEA allows decision makers to transfer CEA results more easily from one setting to another because interventions in different settings are compared to a common reference.

## The need for sectoral cost-effectiveness analysis

In the first two chapters the need and rationale for the sectoral cost-effectiveness analysis (CEA) approach were discussed. By sectoral analysis, we mean that all alternative health system uses of resources are evaluated in a single exercise with an explicit budget constraint.

**Chapter 1** of this thesis showed why there is a need for cost-effectiveness information for sector wide priority setting. It has been shown in the health economics literature that there is ample evidence for inefficiencies in existing health care. Economic appraisal seeks to improve efficiency by providing policy-makers with guidance about how scarce resources can be used to derive the greatest possible benefit. It can, with sufficient evidence, be used to identify the maximum possible level of population health attainable for given resource availability, and the mix of interventions that would achieve the maximum. As described in chapter one, there have been several sector-wide CEA attempts in the past but all do not fully fulfil the set of requirements set out here, including inability to assess the current mix of interventions, low generalisability and inconsistent methodological approaches. Most importantly, it is argued that the traditional context specific or incremental approach to cost-effectiveness analysis does not provide decision-makers with sufficient guidance for sector-wide priority setting in health care. The application of the broader approach to sectoral CEA i.e. generalised CEA has been proposed in this thesis. It could be viewed as a complementary analysis to incremental CEA, and provides policy-makers with more guidance for sector wide priority setting.

**Chapter 2** showed that the use of economic appraisals has dramatically increased over the last decade although many have been focused on the problems of more developed countries. The relatively sparse literature on communicable diseases has been dominated by interventions related to HIV/AIDS, hepatitis, malaria and tropical diseases. In order to show how to make economic appraisals more useful to policy-makers, chapter two focused on several issues which should be considered. Firstly, incremental



analysis is appropriate to local decision making when policy-makers are constrained to keep the current interventions in place and can consider only marginal improvements. However, it does not allow for analysis of existing interventions and results are not transferable across settings. Secondly, data on costs and effectiveness are often not presented appropriately. The challenge for effectiveness is to adjust the evidence from efficacy studies to allow for different patient or population groups, and local variations in adherence, coverage, and infrastructure. For costs, it is important to report the physical resources used as well as prices. Thirdly, some long-term effects are still not well incorporated into CEA, especially those affecting child development and drug resistance. Finally, it is important for analysts to provide decision-makers with estimates of the resources that would be required to implement interventions claimed to be cost-effective.

## Generalized CEA in practice

Chapter 3 and 4 provide guidance on how to perform generalized CEA in practice and how to deal with uncertainty around cost-effectiveness ratios (CER) in sectoral cost-effectiveness analysis, particularly how to communicate uncertainty in results to decision-makers.

**Chapter 3** outlined the specific steps necessary to undertake the broader approach to sectoral analysis in practice. As shown in this chapter the counterfactual is a crucial factor. Several ways have been proposed to obtain counterfactual rates for the disease under consideration: using natural history models, using trial data or back adjusting. In combination with epidemiological data on prevalence rates, a population intervention model for effectiveness estimation could be used. Another key element for generalized CEA is how to define and cluster interventions under consideration, which will determine how one conceptualizes the full CEA model. For example, interactions on the cost side between preventive and curative interventions will automatically include cost offsets evaluated in combination against the counterfactual. For transferability of cost data across settings it is important to report costs following the ingredient approach. The sunk costs of interventions also need to be taken into account.

**Chapter 4** raises the issue on the presentation of the results of uncertainty analysis in cost-effectiveness. The literature on this topic has been relatively academic with little attention paid to the question of how decision makers should interpret the information particularly when confidence intervals overlap. This question is especially relevant to sectoral CEA which provides information on the costs and effects of a wide range of interventions. Stochastic league tables were introduced to inform decision-makers about the probability that a specific intervention would be included in the optimal mix of interventions for various threshold levels of resource availability, taking into account the uncertainty surrounding costs and effectiveness. This information helps decision makers decide on the relative attractiveness of different intervention mixes, and also on the implications for trading gains in efficiency for gains in other goals such as reducing health inequalities and increasing health system responsiveness.

## Applications of Generalized CEA at country and regional level

The last three chapters, 5, 6 and 7 are attempts to apply generalized CEA to chronic diseases at different levels i.e. in the Netherlands and at the regional level. In these examples, interventions against diabetes mellitus and cardiovascular diseases are compared to the disease-specific or condition specific counterfactual. Emphasis is given to the interpretation of the stochastic league tables for guidelines on stroke and diabetes compared to current care in the Netherlands.

**Chapter 5** discusses the use of Stochastic League Tables approach in cost-effectiveness analysis of diabetes interventions and the common grounds and differences with other methods of presenting uncertainty to decision-makers. The comparison in this chapter uses the sectoral cost-effectiveness results of medical guidelines for Dutch diabetes type 2 patients in primary and in secondary care.

Stochastic league table defines the optimum expansion pathway, starting with the least costly and most cost-effective intervention mix. In the comparison multi-intervention cost-effectiveness acceptability curves are used as a way to represent uncertainty information on diabetes treatments.

In case of low budgets, treatment of secondary care patients is the optimum choice. Current care of diabetes complications is shown to be inefficient. When more resources are available countries may implement all guidelines and improve efficiency. SLT-approach and multi-intervention cost-effectiveness acceptability curves for uncertainty lead to similar results. However, SLT approach provides policy makers with information on affordability features and meets better the requirements for sectoral analysis.

**Chapter 6** describes stroke occurrence in relation to its treatment. There is international consensus emerging on the conditions of thrombolytic therapy, stroke units, and secondary prevention in improving stroke survival. The chapter presents the lifetime effects and medical costs of these interventions for the average stroke patient and identifies the optimum mix of interventions. A multi-dimensional life table distinguishing two states – a minor and a major stroke - after a first transient ischemic attack was applied. The table includes empirical utility weights for stroke disabilities and 5-year follow-up data on health care utilization and costs. It computes lifetime costs and QALYs, by stroke state. Effectiveness and cost data for the three interventions was pooled. The table computes QALYs and cost under the seven possible intervention mixes, showing uncertainty distributions. A stochastic league table of the intervention mixes presents the generalized results in comparison to the non-intervention baseline, and showed that results vary by age and sex - up to 2,7-3,7 times for QALYs and up to 1,4-2,0 times for cost. Stroke patients may gain a maximum of 0,5 QALYs per lifetime in the three combined interventions. Cost per QALY gained is lowest at younger ages for the stroke units and secondary prevention combined: for men about €55.000 and for women €73.000. Changes in costs and effects are small in comparison to the uncertainty ranges. All intervention mixes that include stroke units are the most likely optimum choices. It can be concluded from this study that the development of acute stroke units deserves priority above individual medical therapies.

**Chapter 7** focuses on a regional implementation of generalised CEA. Here estimates of the effects and costs were reported for selected interventions to reduce the risks associated with elevated levels of cholesterol and blood pressure in areas of the world with different epidemiologic profiles. Effect sizes were derived from systematic reviews or meta-analyses, and the impact on health outcomes projected over time for populations with different age, sex and epidemiologic profiles. Costs were taken from the literature or estimated by experts in 14 sub-regions of the world.

This regional application of GCEA illustrates the full potentials of sectoral CEA, e.g. comparability of results across interventions and sub-regions. Depending on the underlying risk factor epidemiology, the analysis showed that non-personal health interventions, including government action to stimulate a reduction in the salt content of processed foods, are cost-effective ways to reduce the impact of cardiovascular disease and would avert over 21 million DALYs per year globally. Adding treatment of people whose risk of a cardiovascular event over the next 10 years is above 35% is also cost-effective and would gain substantial additional health benefits, averting an additional 63 million DALYs per year globally.

This combination of personal and non-personal health interventions could reduce the global incidence of cardiovascular events by as much as 50%. It could increase the healthy life expectancy of the population by up to three years in parts of the developing world and by over four years in the developed world.

## **Multiple criteria in sector-wide priority setting**

**Chapter 8** raises the issue that sector-wide priority setting is not only about the choice of the optimal mix of interventions in terms of efficiency. In order to optimize the welfare of society it is also important to consider equity considerations like poverty reduction, equal treatment for equal needs and collective versus individual responsibility. A successful implementation of economically viable interventions is also dependent on a set of other highly context specific factors such as economic environment, the legal and regulatory framework and health care financing system. This chapter gives an illustration of these issues important in the sector-wide priority setting process, based on the experience of the introduction of big ticket technologies in a number of developing country settings in Asia. The study describes and explains the diffusion and utilization pattern of costly technologies like magnetic resonance imaging (MRI) in several Asian settings. A number of recommendations are formulated that may guide decision makers to a successful implementation of interventions, in addition to issues of technical and allocative efficiency.

Context-specific variables in the economic, legal/regulatory, and health care sector environment that potentially can characterize the use of MRI for different Asian countries (the Republic of Korea, Malaysia, the Philippines and Thailand) and regions (the cities of Shanghai and Hong Kong in China and the state of Tamil Nadu in India) were obtained from national representatives of professional bodies by using standardized questionnaires for the year 1997/98. In order to determine and compare how equitable and efficient the use of MRI in these developing country settings was, technical MRI characteristics, both public and private health care providers information and utilization data were obtained. On the provider side information was acquired according to type of

technology, mode and time of acquisition, and host institution by location, ownership, type and size of institution and teaching status. On the patient side utilisation data were collected at hospital level in three countries before and after the economic crisis in the region. For four countries plus Hong Kong background information on the legal framework for “big ticket” technologies was collected.

The diffusion pattern of MRIs in countries of the Asian region appears to follow two types of patterns of diffusion: one set of countries seems to be composed of mostly early adopters and another set of countries appears to be composed mostly of late adopters.

Some form of legal framework for the acquisition of big-ticket technologies is absent or is only applicable to the public sector in these countries. The installed MRIs have low magnetic field strength, vary with respect to brand and type, and are mostly in the private sector and in urban areas of the region. The maintenance and operating costs account for the low number of MRIs in the Philippines and Malaysia.

The total number of MRIs per population in this region reflects a high share of country's health resources devoted to expensive high-technology devices. It is difficult to state the appropriate number of MRIs for each country; however, the study shows that there are observable problems in terms of efficiency, equity, and quality of MRI services. To avoid cost escalations and inefficiencies in national health systems, it is recommended that legal frameworks and regulatory bodies be strengthened for the introduction of big-ticket technologies in both the public and private sector. In particular, implementation of regulations in the private sector should be taken as a policy opportunity to improve the delivery of health care. Unequal access to MRI services, such as rural populations and disadvantaged groups, could be improved through more equitable financing. It is likely that application of sectoral CEA would have resulted in both efficient and equitable outcomes. Despite the limitations of the study, one can clearly say that the present health care system approaches to priority setting in the countries studied, as exemplified in this case study on MRI diffusion and utilization, still deviate from the ideal.

## Conclusions

**Chapter 9** gives an overview of the main conclusions of generalised CEA for sectoral priority setting, its practical and conceptual shortcomings and also highlights some of the policy implications of this type of sectoral CEA.

The main conclusion of this thesis is that for sector wide priority setting a broader type of economic evaluation, that of generalized CEA, is required, complemented with the traditional incremental approach. It can be useful as a long-term planning tool for policy-makers to determine which interventions should be included in the optimal mix if more resources become available. The way uncertainty in CE information is presented by means of stochastic league tables can guide decision-makers how to allocate future resources. In particular the proposed method is suitable for sectoral analysis, since it takes into account the affordability of the selected interventions and the assessment multiple interventions simultaneously.

As discussed in this chapter, for the optimal implementation of generalised CEA, some technical and conceptual problems need to be solved. Some examples are how to assess and validate the counterfactual, how to translate generalised CE results in to daily policy practice, and how to deal with transaction costs.

Finally, as cost-effectiveness is only one input to priority setting there should be some accounting for at least the distributional consequences of interventions. However, at the moment, practical priority setting models that explicitly quantify the trade-off between health gains and the proportions of people treated; health gains and the severity of illness; or, global population health and health distribution between groups in the population are lacking (and if they are available, are not implemented).

## **Samenvatting**



## Inleiding

Dit proefschrift belicht de noodzaak tot herziening van de meest gangbare methodologische toepassing voor kosten-effectiviteitsanalyses (KEAs) voor de gezondheidszorg (vanuit de incrementele benadering). De auteur bepleit een alternatieve, aanvullende methode: de niet-contextgebonden of de algemene kosten-effectiviteits analyse, die wordt toegelicht met illustraties uit de praktijk. Het gebruik en de toepassing van de twee bovengenoemde elkaar aanvullende methoden van kosten-effectiviteitsanalyses voor verdeling van middelen in de gezondheid vanuit een sectoraal perspectief, worden in dit proefschrift onder de loep genomen. Met sectoraal wordt hierbij bedoeld dat alle alternatief aan te wenden middelen voor het optimaliseren van gezondheid worden geëvalueerd in één exercitie, met een bepaald beschikbaar budget als gegeven.

De eerste, meest toegepaste methode is het zogenoemde contextgebonden gebruik, dat is gebaseerd op de incrementele kosten-effectiviteits analyse methodologie. Het aantal kosten-effectiviteitsanalyses ten behoeve van het evalueren van de doelmatigheid van specifieke interventies is de afgelopen twee decennia aanzienlijk toegenomen. In deze analyses domineert de vergelijking tussen bestaande en alternatieve interventies. Hierbij wordt de kosten-effectiviteit van een voorgestelde nieuwe interventie vergeleken met de kosten-effectiviteitsratio (KER) van een bestaand alternatief, of met een vast afkappunt ten aanzien van de veronderstelde bereidheid tot betalen voor een additionele gezondheidswinst. Dit type analyses wordt dikwijls uitgevoerd om kosten-effectiviteits informatie te genereren ter ondersteuning van beslissingen over nieuw te introduceren zorginterventies.

De tweede toepassing die centraal staat in dit proefschrift is de niet-contextgebonden of de algemene kosten-effectiviteits analyse ('generalised CEA'). Bij dit type van economische evaluaties worden de kosten en effecten van een breed pakket aan zorginterventies met elkaar vergeleken ten opzichte van de zogenoemde basisreferentie ('counterfactual'). De verkregen informatie stelt de beslisser in staat de meest gunstige mix van uiteenlopende zorginterventies samen te stellen die de meeste gezondheidswinst oplevert, gegeven de beschikbare financiële middelen. Hierbij wordt gebruik gemaakt van informatie over de kosten-effectiviteit van zowel bestaande als nieuwe interventies.

De kern van de methodologie voor het toepassen van algemene niet-contextgebonden KEAs is de keuze voor een referentie behandeling, de basisreferentie. Deze gestandaardiseerde hypothetische basis situatie van non-interveniëring van zorg (al dan niet ziektespecifieke zorg) levert de beleidsmaker een meer relevante kosten-effectiviteits analyse op dan de op incrementele benadering gebaseerde KEA informatie. Bij dit laatste type van economische evaluatie wordt meestal een vorm van reeds bestaande zorg als referentie behandeling genomen bij de introductie van een nieuwe technologie. Echter, deze methode stelt de beleidsmaker niet in staat een doelmatigheidsoordeel te geven over bestaande zorg of kosten effectieve zorg strategieën die in zijn land of regio nog niet worden toegepast. Een bijkomend effect is



dat de niet-contextgebonden kosten-effectiviteits analyse resultaten genereert die beter generaliseerbaar zijn van de ene context (bijvoorbeeld geografische- of onderzoekscontext) naar de andere. Benadrukt dient te worden dat beide methodes elkaar niet uitsluiten, maar naast elkaar gebruikt dienen te worden voor sectorale prioritering van zorgmiddelen.

## **De noodzaak voor de algemene vorm van sectorale kosten-effectiviteitsanalyses**

Hoofdstuk 1 en 2 van dit proefschrift behandelen de noodzaak van een sectorale kosten-effectiviteits analyse.

**Hoofdstuk 1** toont aan waarom er behoefte bestaat aan sectorale kosten-effectiviteitsanalyses. De doelstelling van deze kosten-effectiviteitsanalyses is beleidsmakers van informatie te voorzien die hen helpt bij het doen van doelmatigheidsuitspraken over een breed pakket van zowel nieuwe als bestaande zorginterventies. Hierbij dient een zo hoog mogelijke doelmatigheid nagestreefd te worden. De analist adviseert beleidsmakers over het zo gunstig mogelijk verdelen en besteden van schaars aanwendbare middelen. Het eerste hoofdstuk beschrijft enkele voorbeelden en toepassingen van sectorale kosten-effectiviteitsanalyses (bijvoorbeeld van de Wereldbank en de 'Harvard Risk' groep). De tekortkomingen van deze toepassingen komen aan de orde, alsmede de minimale vereisten waaraan economische evaluaties moeten voldoen. Zoals al eerder aangegeven kent de bestaande sectorale analyse het probleem dat alleen nieuw te introduceren zorginterventies in beschouwing worden genomen en niet de bestaande interventies worden geëvalueerd. Verder ontbreekt een standaard methodologie, hetgeen de vergelijkbaarheid van kosten-effectiviteit ratio's van verschillende interventies in de zogenoemde rang tabellen ('league tables') problematisch maakt. Bovendien is het moeilijk met deze methode interventies te generaliseren. Al met al bieden incrementele of context-specifieke kosten-effectiviteitsanalyses beleidsmakers te weinig houvast voor het nemen van sectorale prioriterings vraagstukken.

**Hoofdstuk 2** geeft een overzicht van economische evaluaties voor infectieziekten, voornamelijk uitgevoerd in ontwikkelingslanden. Het literatuuroverzicht toont aan dat het merendeel van de KEA literatuur in de afgelopen twee decennia zich heeft gericht op Noord-Amerika, West-Europa en Australasia. De spaarzame studies op het gebied van infectieziekten in ontwikkelingslanden richten zich voornamelijk op HIV/Aids, hepatitis en tropische aandoeningen zoals malaria. Twee tekortkomingen van het gebruik van KEA informatie voor sectoraal beleid, worden nader besproken.

Ten eerste wordt door middel van enkele voorbeelden aangetoond dat incrementele analyses met name zinvol zijn waar het gaat om context-gebonden verdelingsvraagstukken van middelen in de gezondheidszorg. Beleidsmakers zijn bij dit soort analyses gebonden aan de specifieke beleids- en onderzoekscontext. Bijvoorbeeld in het geval van beleid kan het gaan om een nationaal of regionaal perspectief met alle beperkingen van dien, terwijl de onderzoekscontext van ziekte specifieke aard kan zijn.

De incrementele benadering stelt de beleidsmaker echter niet in staat de huidige zorg cq. gebruikte technologieën te evalueren.

Een tweede tekortkoming betreft de transparantie van de gegevens. Ten behoeve van de generaliseerbaarheid, worden kosten en effectiviteits gegevens doorgaans niet op een consistente en zinvolle manier gepresenteerd. Problematisch aan de effectiviteit kant is dat doeltreffendheid ('effectiveness') van zorginterventies vaak gebaseerd is op werkzaamheid ('efficacy') gegevens van experimenteel onderzoek. Aan de kosten kant is het belangrijk de kosten gegevens zo transparant mogelijk te presenteren. Daarbij kan gedacht worden aan apart rapporteren van verbruiksgegevens en kostprijs informatie van interventies ('ingredient approach'). Verder worden lange termijn implicaties aan de effect kant niet altijd even zinvol opgenomen in kosten-effectiviteitsanalyses. Hierbij kan gedacht worden aan het effect van interventies op de cognitieve en fysieke ontwikkeling van jongeren en resistentie van medicijnen (bijvoorbeeld resistentie van malaria medicijnen). Tot slot is het belangrijk om beleidsmakers te informeren over de budget implicaties bij het implementeren van kosteneffectieve strategieën.

## **De theoretische beschouwingen van de algemene vorm van sectorale kosten-effectiviteitsanalyses**

De hoofdstukken 3 en 4 geven richtlijnen voor analisten en beleidsmakers voor het uitvoeren van algemene kosten-effectiviteitsanalyses en het interpreteren van de onzekerheid rondom de verkregen resultaten.

**Hoofdstuk 3** beschrijft de methodologische aanpassingen vanuit de incrementele benadering voor algemene KEAs. De gevolgen voor het bepalen van de kosten en effecten bij de toepassing van de basisreferentie staan in dit hoofdstuk centraal. Een hypothetische basisreferentie van algehele of gedeeltelijke non-interventiëring van zorg neemt een aantal belangrijke obstakels voor het gebruik van kosten-effectiviteit informatie voor sectorale allocatieve doelmatigheids vraagstukken weg. Zoals eerder aangegeven zijn KEA resultaten gemakkelijker te generaliseren van de ene context naar de andere dan context-specifieke kosten-effectiviteitsanalyses. Dit is een bijkomend voordeel, voor zowel derde wereld landen als de meer welvarende delen van de wereld. Het momenteel beschikbare aantal gezondheidstechnologieën overtreft vele malen de onderzoekscapaciteit om deze individueel te evalueren. Gerelateerd aan het concept van de basisreferentie en eveneens essentieel voor de sectorale kosten-effectiviteits analyse is de definitie van de te evalueren cluster van interventies. Groepen van interventies die aan elkaar gerelateerd zijn (zowel via kosten en/of effecten kant) dienen om twee redenen in dezelfde cluster van interventies geëvalueerd te worden. Ten eerste is het niet altijd noodzakelijk dat gezamenlijke gezondheidseffecten en -kosten van twee gerelateerde interventies additief zijn – synergie en schaafeffecten zijn mogelijk. Door in dezelfde ziekte cluster zowel interventies apart te evalueren als in combinatie met andere interventies kan de non-lineariteit van kosten en effecten vastgesteld worden. Ten tweede dienen elkaar uitsluitende interventies (bijvoorbeeld jaarlijks of 2-jaarlijks borstkanker screening binnen één en dezelfde populatie) in een ziekte cluster van interventies geëvalueerd te worden, zodat uitsluitend één van de behandelingen in de optimale mix van zorginterventies wordt opgenomen.

Voor het bepalen van de basisreferentie aan de effectiviteit kant worden drie stappen onderscheiden: 1) het definiëren van aan elkaar gerelateerde interventies; 2) de definiëring van het epidemiologisch profiel van de basisreferentie; 3) de constructie van een populatie model voor de schatting van gewonnen QALYs of vermeden DALYs bij de invoering van een zorginterventie. Met name de tweede stap, het bepalen van het epidemiologisch profiel van de basisreferentie is een uitdaging en behoeft extra aandacht in toekomstig onderzoek. De twee suggesties die in dit hoofdstuk geopperd worden hebben als nadeel dat er met name een gebrek aan data is. De gegevens voor de eerste suggestie, het gebruik van observationele patiënten gegevens onder de situatie van non-interveniëring van zorg, zijn dikwijls niet voor handen. Verder ontbreken vaak ook de gegevens voor de tweede suggestie – het ‘terug rekenen’ (back-adjusting) vanuit huidige zorg naar de situatie van non-interveniëring van zorg op basis van de effectiviteit van de interventie en de ‘coverage’ van de interventie. Tevens zijn vanwege het hypothetische karakter van de basisreferentie de verkregen epidemiologische waarden moeilijk te verifiëren. Aan de kosten kant heeft de vergelijking ten opzichte van de situatie van non-interveniëring van zorg gevolgen voor de bestaande infrastructuur en de gezamenlijke kosten. Omdat de sectorale kosten-effectiviteits analyse zich richt op het herverdelen van middelen hoeven deze kosten niet noodzakelijkerwijs nul te zijn – ze zijn immers noodzakelijk voor het leveren van zorg.

**Hoofdstuk 4** introduceert een nieuw ontwikkelde methode van presenteren van onzekerheid rondom de verkregen sectorale KEA resultaten voor beleidsmakers. De discussie in de literatuur is nogal academisch en er is weinig aandacht voor de vraag hoe deze informatie vertaald kan worden naar beleidsmakers, met name wanneer betrouwbaarheidsintervallen van kosteneffectiviteit ratio's overlappen. Het laatste is vooral relevant voor sectorale KEAs waarbij de kosten en effecten van een breed pakket van zorginterventies worden geëvalueerd bij verschillende budget niveau's. Dit hoofdstuk introduceert stochastische rangtabellen ('stochastic league tables') van zorginterventies die als doel hebben beleidsmakers te informeren over de waarschijnlijkheid dat een gezondheidsinterventie opgenomen wordt in de optimale mix van interventies, gegeven een bepaalde onzekerheid rondom kosten en effecten. Verder toont deze methode van onzekerheidsanalyse voor economische evaluaties aan wat de gevolgen zijn van de afruil tussen doelmatigheid en andere doelstellingen in de gezondheidszorg, zoals het reduceren van ongelijkheid in gezondheid.

## **Toepassingen van de algemene vorm van sectorale kosten-effectiviteitsanalyses in praktijk**

De hoofdstukken 5, 6 en 7 zijn een eerste poging tot het operationaliseren van algemene kosten-effectiviteitsanalyses in praktijk. In deze voorbeelden worden verschillende zorginterventies voor diabetes mellitus (DM) type 2, beroerte (oftewel Cerebro Vasculaire Accident (CVA)) en risicofactoren van coronaire hartziekten op nationaal niveau en regionaal niveau geëvalueerd. Hierbij worden zowel bestaande als nieuw te introduceren zorginterventies vergeleken met de ziektespecifieke basisreferentie. In de hoofdstukken 5 en 6 staat bovendien de interpretatie van

stochastische rangtabellen voor DM type 2 en CVA richtlijnen in Nederland centraal.

**Hoofdstuk 5** evalueert de overeenkomsten en verschillen van stochastische rangtabellen met traditionele methoden van presenteren van onzekerheid bij economische evaluaties aan beleidsmakers. Met name het gebruik van de zogenoemde 'cost-effectiveness acceptability curves' voor meerdere combinaties van zorginterventies staat bij deze vergelijking centraal. Ter illustratie is gebruik gemaakt van kosten-effectiviteits gegevens van de Nederlandse richtlijnen met betrekking tot intensieve controle en behandeling van diabetes type 2 patiënten en de daaraan gerelateerde complicaties. Vanuit sectoraal perspectief zijn zowel groepen patiënten in de eerste lijns als de tweede lijns zorg in de analyse meegenomen.

Uit de analyse blijkt dat bij lage budget niveaus primaire richtlijnen voor complicaties de optimale keuze is. De combinatie van primaire en richtlijnen interventies zijn kosten-effectief op basis van Nederlandse criteria. Echter, uit de analyse blijkt dat de huidige diabetes zorg in Nederland niet doelmatig georganiseerd is. In zijn algemeenheid kan gesteld worden dat indien het gezondheidszorg budget beperkt is, de behandeling van diabetes gerelateerde complicaties de meeste gezondheidswinst oplevert. Overheden met daarentegen een ruimer gezondheidszorg budget zouden zowel eerste- als tweedelijns richtlijnen voor de intensieve controle van DM type 2 en de behandeling van de daaraan gerelateerde complicaties moeten overwegen. In beide gevallen komt dit de efficiëntie van het gezondheidszorg systeem ten goede.

Op basis van het hierboven beschreven diabetes voorbeeld kan gesteld worden dat stochastische rangtabellen en 'multi-intervention cost-effectiveness acceptability curves' vergelijkbare resultaten opleveren. Echter, redenerend vanuit sectoraal perspectief is de toepassing van stochastische rangtabellen zinvoller wanneer het gaat om het presenteren van onzekerheid rondom kosten-effectiviteits resultaten van meerdere zorginterventies. Met name de onzekerheid rondom het al dan niet overschrijden van het te besteden budget is cruciale informatie voor beleidsmakers.

**Hoofdstuk 6** handelt over zorginterventies die als doel hebben de optimale mix te bepalen voor patiënten met een beroerte. Het beschouwt de levenslange gewonnen gezondheidseffecten en de medische kosten van dergelijke interventies. De aandacht in dit hoofdstuk is gericht op trombolysen, beroerte eenheden en secundaire preventie (o.a. aspirine gebruik) omdat over de effectiviteit hiervan relatief veel bekend is. Een multi-dimensionele levenstabel onderscheidt twee gezondheidstoestanden: enerzijds die van na een eerste beroerte een nieuwe mildeberoerte, en anderzijds die van een ernstige beroerte. Het model neemt zowel de op empirische gegevens gebaseerde gewichten voor beroerte utiliteiten mee als ook de vijf jaarlijkse follow-up gegevens van het gezondheidszorg verbruik cq de kosten. Op basis hiervan worden de geleefde QALYs en de patiëntgebonden medische kosten per gezondheidstoestand berekend. Vervolgens worden hieraan de gepoolde gezondheidseffecten en de daarmee gepaard gaande kosten van de drie zorginterventies toegevoegd. Het model berekent het aantal geleefde QALYs en de kosten voor zeven mogelijke combinaties van zorginterventies inclusief de daarmee gepaard gaande onzekerheid. Stochastische rangtabellen van deze laatstgenoemde zorg combinaties tonen de optimale combinatie aan van

zorginterventies volgens de beslisregels van algemene KEA ten opzichte van de situatie van non-interveniëring.

De analyse toont aan dat de resultaten in de basisreferentie variëren naar leeftijd en geslacht – 2,7 tot 3,7 keer meer geleefde QALYs en 1,4 tot 2,0 keer meer kosten. Beroerte patiënten winnen mogelijk een maximaal aantal van 0,5 QALYs per mensenleven bij de combinatie van de drie zorginterventies. De kosten per gewonnen QALY zijn het laagst bij patiënten uit jonge leeftijdsgroepen die gebruik maken van een combinatie van de beroerte eenheden en secundaire preventie: voor mannen is dit €55.000 and voor vrouwen is dit €73.000 per gewonnen QALY. De veranderingen in kosten en effecten onder onzekerheid zijn relatief gering. Gegeven deze mate van onzekerheid toont de analyse aan dat bij verschillende budget niveaus de kans groot is dat beroerte eenheden opgenomen worden in de optimale combinatie van zorginterventies. De conclusie van deze studie is dat voor de Nederlandse situatie beroerte eenheden de hoogste prioriteit behoeven boven andere medische therapieën bij CVA patiënten.

**Hoofdstuk 7** behandelt de eerste wereldwijde toepassing van algemene KEAs voor coronaire hartaandoeningen. Bij deze analyse zijn de gezondheidswinsten uitgedrukt in vermeden 'disability adjusted life years' (DALYs) voor 14 wereldregio's. De kosten van een 17 gezondheidsinterventies, op zowel bevolking- als individueel niveau, voor de risicoreductie van verhoogde cholesterol en verhoogde bloeddruk met verschillende epidemiologische profielen worden gerapporteerd. De doeltreffendheid van de interventies is gebaseerd op informatie die afkomstig is van meta-analyses en overzichtsartikelen. Het interventie effect op de uitkomstmaat is geprojecteerd over de tijd voor verschillende populatiegroepen naar leeftijd, geslacht en epidemiologische profielen. De kosten zijn gebaseerd op informatie van zowel overzichtsartikelen als schattingen van experts in 14 wereldregio's.

Deze regionale toepassing van algemene KEAs illustreert de mogelijkheden van sectoral KEAs, zoals de vergelijkbaarheid van KEA resultaten over ziektecategorieën en wereldregio's heen. De analyse toont aan dat afhankelijk van de onderliggende epidemiologie van gezondheidsrisico's in de verschillende wereldregio's interventies op volksgezondheidsniveau kosten-effectieve opties zijn. Een voorbeeld is de overheidsbemoeienis om de maximale hoeveelheid zout in geproduceerde voedselproducten wettelijk vast te leggen. Wereldwijd worden met dit soort interventies jaarlijks 21 miljoen DALYs vermeden. Wanneer tegelijkertijd patiënten met een absolute risico van meer dan 35% op een cardiovasculaire aandoening binnen 10 jaar zouden worden behandeld, dan zou dit eveneens substantiële gezondheidswinsten opleveren – op wereldbasis zouden jaarlijks 65 miljoen DALYs worden vermeden.

Geconcludeerd kan worden dat individuele zorginterventies gebaseerd op absolute risico's van cardiovasculaire aandoeningen en interventies op volksgezondheidsniveau de wereldwijde incidentie van coronaire hartaandoeningen met 50% kunnen verminderen. Deze combinatie van ingrepen heeft de mogelijkheid om de gezonde levensverwachting van de bevolking in ontwikkelingslanden met 3 jaar te verlengen en in geïndustrialiseerde landen met meer dan 4 jaar .

## Alternatieve criteria voor sectorwijde prioritering

**Hoofdstuk 8** behandelt alternatieve criteria bij het bepalen van de optimale mix van zorginterventies dan het doelmatigheids criterium. Bij welvaarts optimalisatie is het van belang om naast doelmatigheids overwegingen ook verdelingsaspecten mee te nemen in de analyse. Hierbij kan gedacht worden aan het bestrijden van armoede, het streven naar gelijke behandeling van individuen bij gelijke zorgbehoeften of collectieve versus individuele verantwoordelijkheid bij de financiering van zorg. Implementatie van duurzame strategieën voor optimale zorg zijn daarbij afhankelijk van context specifieke factoren zoals de economische situatie van een land, de wettelijke afspraken rondom het zorgsysteem en het financierings stelsel rondom de zorg. Dit hoofdstuk geeft een beschrijving van alternatieve criteria bij het prioriteren van zorginterventies waarbij ter illustratie gebruik wordt gemaakt van de introductie magnetische scan apparatuur (Magnetic Resonance Imaging, MRI) in enkele Aziatische landen (Thailand, Maleisië, Indonesië, de Filipijnen en Zuid-Korea) en regio's (de provincies Hong Kong en Shanghai in China en de provincie Tamil Nadu in India). De gebruikte studie tracht tevens een verklaring te geven van het diffusie en gebruikspatroon van MRI-scanapparatuur sinds de introductie van deze zogenoemde 'big ticket' technologie in Azië. Op basis van de bevindingen zijn een aantal aanbevelingen gedaan voor een succesvolle implementatie van dure interventies zoals MRI-scanapparatuur in deze landen en regio's.

Op basis van het aantal aanwezige MRI-scanapparatuur per inwoner in de studie populatie kan gesteld worden dat relatief veel financiële middelen zijn gemoeid bij de aanschaf en het gebruik deze 'big ticket' technologie. Toch is het niet eenvoudig aan te geven wat het optimale aantal aan MRI-scanapparatuur in deze aziatische landen zou moeten zijn. Echter, de studie resultaten tonen aan dat in het merendeel van de studie landen zich problemen voordoen wanneer het gaat om de doelmatigheid en verdelingsaspecten bij de introductie en het gebruik van MRI-scanapparatuur. Om kosten escalaties en ondoelmatigheid in zowel de private als publieke zorgsystemen van deze landen te voorkomen is het aanbevelingswaardig om de zorgregulering en wettelijke zorginstanties die gemoeid zijn met de introductie en gebruik van dure zorg technologieën te introduceren, al dan niet te verbeteren. Met name in de private zorgsector blijkt dat overheidsregulering met betrekking tot het gebruik van dure technologieën in de gezondheidszorg niet aanwezig is of te kortschiet hetgeen ongelijke toegang tot en financiering van zorg tot gevolg heeft.

## Tot slot

**Hoofdstuk 9** geeft een overzicht van de belangrijkste bevindingen van algemene KEAs voor sectorale prioriteiten stelling en schetst welke implicaties de resultaten hebben voor beleidsmakers.

De vorm van sectorale KEAs zoals die wordt geïntroduceerd in dit proefschrift heeft grote potenties voor de toekomst. De methode biedt bij uitstek oplossingen in een globaliserende wereld, waar ook nationale gezondheidssystemen niet langer

onafhankelijk van elkaar kunnen functioneren. Het biedt de mogelijkheid een optimale mix van interventies voor te stellen, in tijden waarin internationaal de middelen voor het voorkomen en behandelen van vele gezondheidsproblemen schaars zijn en waar het toepassen van de individuele KEA in alle mogelijke settings een te kostbare onderneming wordt.

Zoals in dit proefschrift wordt aangetoond is het echter noodzakelijk dat, voor een optimale toepassing in de toekomst, een aantal technische problemen wordt opgelost of verbeterd. Voorbeelden hiervan zijn a) de schatting en validatie van de basisreferentie, b) het vertalen van regionale schattingen naar het praktisch gebruik voor nationale overheden en c) de transactie kosten bij de implementatie van de optimale mix van zorginterventies. Bovendien is er dringend behoefte aan praktische modellen van prioriteiten stelling. Uiteindelijk geven economische evaluaties slechts één input in het hele prioriteringsproces. In veel landen wordt de prioriteitenstelling in praktijk niet effectief uitgevoerd. Een van de oorzaken daarvan is het feit dat er geen praktische modellen voor de prioriteitenstelling voor handen zijn, en indien aanwezig niet geïmplementeerd zijn.

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## **List of related publications and manuscripts**



## ***Publications and manuscripts reprinted in this thesis***

Chapter 1 Generalized cost-effectiveness analysis for priority setting in health.

Hutubessy RCW, Baltussen RMPM, Tan Torres-Edejer T, Evans DB.

*Applied health economics and health policy* (2002), 1 (2), 89-95

Chapter 2 Critical issues in the economic evaluation of interventions against communicable diseases.

Hutubessy RCW, Bendib LM, Evans DB.

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Chapter 4 Stochastic League Tables: communicating cost-effectiveness results to decision makers.

Hutubessy RCW, Baltussen RMPM, Evans DB, Barendregt JJ, Murray CJL.

*Health Economics* 2001;10: 473-477.

Chapter 5 Stochastic league tables to diabetes interventions

Hutubessy RCW, Niessen LW, Dijkstra LF, Casparie AF, Rutten FF.

*Submitted for publication*

Chapter 6 Generalised life time costs and effects of stroke interventions.

Niessen LW, Hutubessy RCW, Dippel DW, Kwakkel G, Limburg M.

*Submitted for publication*

Chapter 7 Effectiveness and costs of interventions to lower systolic bloodpressure and cholesterol: a global and regional analysis on reduction of cardiovascular disease risk

Murray CJL, Lauer JA, Hutubessy RCW, Niessen LW, Tomijima N, Rodgers A, Lawes CMM, Evans DB.

*The Lancet* (2003), 316:717-25.



Chapter 8 Diffusion and utilization of magnetic resonance imaging in Asia.

Hutubessy RC, Hanvoravongchai P, Edejer TT.

*Int J Technol Assess. Health Care* (2002), 18(3):690-704.

## ***Related publications and manuscripts***

Chapter 1 WHO-CHOICE: Choosing interventions that are cost-effective.

Hutubessy RCW, Baltussen RMPM, Tan Torres-Edejer T, Evans DB.

Chapter 60 in *Health System Performance Assessment: Debate, new methods, and new empiricism*, Murray CJL, Evans DB, eds. World Health Organization, (forthcoming): Geneva, 2003.

Chapter 3 Generalized Cost-effectiveness analysis: A guide.

Tan Torrest-Edejer T, Baltussen RPMP, Adam T, Hutubessy RCW, Acharya A, Evans DB, Murray CJL.

World Health Organization, Global Programme on Evidence for Health Policy: Geneva, 2003.

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*Cost-effectiveness and Resource Allocation* (2003) Vol 1, issue 1.

Chapter 4 Uncertainty in cost-effectiveness analysis: Probabilistic uncertainty analysis and stochastic league tables.

Baltussen RPMP, Hutubessy RCW, Evans DB, Murray CJL

*International Journal of Technology Assessment in Health Care* (2002) Vol. 18, 112-119.

Formal response to 'Determining the optimal combinations of mutually exclusive interventions: a response to Hutubessy and colleagues'

Baltussen RMPM, Hutubessy RCW, Evans DB, Barendregt JJ, Murray CJL

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Chapter 5 Insulin Therapy in Patients with Type 2 Diabetes Mellitus: The Netherlands.

Hutubessy RCW, H. Vondeling, JJJ. De Sonnaville, LP. Colly, JJJ. Smit, RJ. Heine

*Disease Management & Health Outcome (2001), Vol 9, NO.6, 337-344.*

Chapter 9 Generalized cost-effectiveness analysis for national-level priority-setting in the health sector

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## **Personal history**





Raymond Hutubessy studied Economics and Business Administration at the Maastricht University specialising in International Economics, and graduating in 1992. After being employed at the Faculty of Health Sciences at the Maastricht University as a research fellow, he moved in 1994 to the Faculty of Medicine at the Vrije Universiteit in Amsterdam where he worked as a health technology assessment researcher. There he was involved in various projects on economic evaluations within primary and secondary health care. In 1997 he joined the World Health Organization (WHO) at the WHO Representative's Office in Thailand as an Junior Professional Officer (JPO) seconded by the Ministry of Foreign Affairs of the Netherlands. During this period he was affiliated with the Centre for Health Economics at Chulalongkorn University where he held a position as a research-fellow and lecturer in the Master of Science Programme on Health Economics. He was involved in various health economic projects within the South-East Asian region. Concurrently he was involved in the Asian MRI study group through the Health Systems Research Institute (HSRI) at the Ministry of Public Health of Thailand. In 1999 he started as a health economist in the Global Programme on Evidence for Health Policy (GPE) at WHO headquarters in Geneva, Switzerland. He has been involved primarily in the methodological development and application of the work programme called Choosing Interventions that are Cost-Effective (CHOICE). Currently he is employed as a health economist at the HIV/AIDS, TB & Malaria (HTM) department of the WHO in Geneva.

Raymond Hutubessy is married to Mariou de Rouw and has three children.

