The Application of Cost-Effectiveness Analysis in Developing Countries

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

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ABSTRACT

Developing countries face imminent choices for introducing needed, effective but expensive new vaccines, given the substantial immunization resources now available from international donors. Cost-effectiveness analysis (CEA) is a tool that decision-makers can use for efficiently allocating expanding resources. However, although CEA has been increasingly applied in developing-country settings since the 1990’s, its use lags behind that in industrialized countries. This thesis explored how CEA could be made more relevant for decision-making in developing countries through 1) identifying the limitations for using CEA in developing countries 2) identifying guidelines for CEA specific to developing countries 3) identifying the impact of donor funding on CEA estimation 4) identifying areas for enhancement in the 1996 “Reference Case” (a standard set of methods) recommended by the US Panel on Cost-Effectiveness in Health and Medicine, and 5) better understanding the decision-making environment in developing countries.

Focusing on pediatric immunization in developing countries, thematic analysis was used to distill key concepts from 157 documents spanning health economics, clinical epidemiology and health financing. 11 key informants, researchers active in developing countries, were also interviewed to explore the production and use of evidence in public health decision-making.
Results showed a divergence between industrialized and developing nations in the emphases of methodological difficulties, in the general application of CEA, and the types of guidelines available. Explicitly considering donor funding costs and effects highlighted the need to specify an appropriate perspective and address policy-related issues of affordability and sustainability. Key informant interviews also revealed that opinion-makers, international organizations and the presence of local vaccine manufacturing have significant influence on decision-making. It is suggested that CEA could be more useful with a broadened reference case framework that included multiple perspectives, sensitivity analysis exploring differential discount rates (upper limits exceeding 10% for costs, declining from 3% for benefits) and supplemental reports to aid decision-making (budgetary and sustainability assessments).

This study has implications for improving health outcomes globally in the context of public-private collaborative health funding. Further research could explore defining an extra-societal (multi-country) perspective to aid in efficient allocation of immunization resources among countries.
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**ABBREVIATIONS AND ACRONYMS**

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACER</td>
<td>Average cost-effectiveness ratio</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Council on Immunization Practices, United States</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>AMC</td>
<td>Advanced Market Commitment</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette Guerin</td>
</tr>
<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technology</td>
</tr>
<tr>
<td>CBA</td>
<td>Cost-benefit analysis</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control, United States</td>
</tr>
<tr>
<td>CDR</td>
<td>Common Drug Review, CADTH</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis, and for this thesis, also cost-utility analysis</td>
</tr>
<tr>
<td>CHOICE</td>
<td>Choosing Intervention that are Cost-Effective (WHO)</td>
</tr>
<tr>
<td>CIDA</td>
<td>Canadian International Development Agency</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
</tr>
<tr>
<td>CMH</td>
<td>WHO Commission on Macroeconomics and Health</td>
</tr>
<tr>
<td>cMYP</td>
<td>Comprehensive Multi-Year Plan, UNICEF/WHO/GAVI</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Review and Dissemination, York University, United Kingdom</td>
</tr>
<tr>
<td>DAH</td>
<td>Development assistance for health</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life years</td>
</tr>
<tr>
<td>DARE</td>
<td>Database of Abstracts of Reviews of Effects</td>
</tr>
<tr>
<td>DCCP</td>
<td>Disease Control Priority Project</td>
</tr>
<tr>
<td>DFID</td>
<td>Department for International Development, United Kingdom</td>
</tr>
<tr>
<td>DOMI</td>
<td>Diseases of the Most Impoverished</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Surveys, World Bank</td>
</tr>
<tr>
<td>DTP3</td>
<td>Three doses of diphtheria-tetanus-pertussis vaccine</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization, UNICEF/WHO</td>
</tr>
<tr>
<td>EQ-5D™</td>
<td>EuroQol 5-Dimension, EuroQol Group</td>
</tr>
<tr>
<td>FSP</td>
<td>Financial Sustainability Plan, GAVI</td>
</tr>
<tr>
<td>GAVI Alliance</td>
<td>Global Alliance on Vaccines and Immunization</td>
</tr>
</tbody>
</table>
GCEA     Generalized cost-effectiveness analysis, WHO-CHOICE
GDP      Gross domestic product
GNI      Gross national income
GFATM    Global Fund to fight AIDS, Tuberculosis and Malaria
GSK      GlaxoSmithKline
Hib      Haemophilus influenzae type b
HIV      Human immunodeficiency virus
HPV      Human papillomavirus
HSS      Health System Services support, GAVI
HTA      Health technology assessment
HUI®     Health Utilities Index, Health Utilities Inc
ICER     Incremental cost-effectiveness ratio
IDRC     International Development Research Centre, Canada
IFFIm    International Finance Facility for Immunization
IHME     Institute for Health Metrics and Evaluation
IMF      International Monetary Fund
INAHTA   International Network of Agencies for Health Technology Assessment
INEGI    Instituto Nacional de Estadística y Geografía (National Institute of Statistics, Geography and Informatics), Mexico
ISPOR     International Society of Pharmacoeconomic and Outcomes Research
ISS      Immunization Services Support, GAVI
IPV      Inactivated polio vaccine
LMICs    Low and middle-income countries
LY       Life year
MAP      Multi-Country HIV/AIDS Program for Africa, World Bank
MDGs     Millennium Development Goals
MMR      Mumps, measles, rubella
NGO      Non-governmental organization
NHS – EED National Health Service, Economic Evaluation Database
NICE     National Institute for Clinical Excellence, United Kingdom
OECD     Organisation for Economic Co-operation and Development
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>OPV</td>
<td>Oral polio vaccine</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
</tr>
<tr>
<td>PEDE Project</td>
<td>Pediatric Economic Database Evaluation Project, Toronto Hospital for Sick Children</td>
</tr>
<tr>
<td>PEPFAR</td>
<td>U.S. President’s Emergency Plan for AIDS Relief</td>
</tr>
<tr>
<td>PSA</td>
<td>Probabilistic sensitivity analysis</td>
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<tr>
<td>SF-6D</td>
<td>Short Form 6D</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life years</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WPRC</td>
<td>Washington Panel Reference Case</td>
</tr>
<tr>
<td>YLD</td>
<td>Years of life lived with disability</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of life lost</td>
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1 CHAPTER ONE: INTRODUCTION AND BACKGROUND

Decision-making for the efficient allocation of health care resources in developing nations is complicated by an evolving landscape of international resources available for global health. Currently, while the poorest countries contend with very scarce locally-generated resources for healthcare, increasing and high profile funds flow in from a proliferation of external sources. In 2007, government expenditure on health as a percentage of all government expenditures was 8.7% in low-income countries compared to 17.2% in high income countries (World Health Organization, 2010f). Between 1990 and 2007, development assistance for health ¹, consisting of financial and in-kind contributions to low- and middle-income countries for health activities, increased from $US 5.6 billion to $US 21.8 billion (in 2007 US dollars), with the steepest rates of increase occurring from 2002 (Ravishankar et al., 2009). As a result, external sources of support are a significant budgetary resource for government ministries in many countries, and in 2007 accounted for 17.5% of total expenditures on health care in low-income countries (World Health Organization, 2010f). Although health care funding and support from donors, termed donor funding hereafter, has been a fixture of health ministries in developing nations for many decades, the unprecedented change in the last decade in the scale, donor composition and modes of delivery of that support raises questions for the accessibility, equity and economic cost of the programmes being supported and their impact on nascent and developing health care systems. Cost-effectiveness analysis (CEA), which quantifies the economic cost of health care interventions relative to the attendant health benefits, can be useful in guiding countries taking advantage of the recent global expansion in health care financial resources to make decisions that are economically efficient. Addressing the problem of resource allocation efficiency is particularly pertinent in developing nations, for the opportunity costs of even basic public health programmes can be high, counted in other needed and under-invested health interventions foregone or even foregone interventions in other sectors, such as in education. The selected

¹ Sources for development assistance for health include the officially recorded contributions from individual governments, international organizations like the United Nations, and loans and grants from development banks and private development foundations. In-kind contributions include donations of drugs, vaccines, other health-related inputs, technical assistance and training.
health and economic development indicators for a range of low and middle-income countries, as well as for Canada, included in Appendix 1 illustrate the context in which this thesis is set.

This thesis attempts to contribute to the field of health services research by exploring an enhanced framework for cost-effectiveness analysis in developing countries when donor funding is explicitly recognized as a resource. The chosen point of departure is the reference case introduced in 1996 by the United States Panel on Cost-Effectiveness Analysis, often referred to as the Washington Panel Reference Case (WPRC). The Panel had sought to standardize methodology and presentation of economic evaluation results to improve the quality of a rapidly increasing body of economic evidence (Gold, Siegel, Russell, & Weinstein, 1996; M. C. Weinstein, Siegel, Gold, Kamlet, & Russell, 1996). The WPRC is a structured set of methodological and operational recommendations originally proposed as a possible base-case scenario for broadly defined study designs and a possible base for comparative studies (Gold, Siegel, Russell, & Weinstein, 1996). Although in practice a formally estimated reference case is not usually included in CEAs, it continues to provide a conceptual framework from which current conventions, both implicit and explicit, for the conduct of economic evaluations in most industrialized countries has flowed. The main features of the WPRC as summarized by key members of the Panel are attached in Appendix 2, and a pared-down version that is reflective of current methodological emphases, as summarized by Drummond, Sculpher Torrance, O’Brien and Stoddart (2005), is included in Appendix 3.

The Washington Panel Reference case is thus fundamental to the field of economic evaluation, but it was formulated in the context of industrialized economies and mature health care systems. As the use of economic evaluation, and cost-effectiveness analysis in particular, has now spread worldwide, it is timely and appropriate to examine the Reference Case’s role in developing economies and forming health care systems. Thus, in this thesis suggestions are made for the enhancement of selected WPRC recommendations to take into account considerations for estimating costs, effects and uncertainty in the context of the recent rapid expansion of donor funding. The evaluation of childhood immunization programmes is highlighted. The intended audiences for such an enhanced reference case are primarily CEA producers and users concerned with policy-oriented economic evaluation in developing countries, particularly where
large commitments of resources are being considered for health care. Producers, such as health economists and health technology analysts in academic or government agencies, may find it helpful for demarcating boundaries in study design or determining comprehensiveness and relevance of study variables. Users, such as health care decision or policy-makers in developing countries, may use it to assess the appropriateness of externally generated CEA design and applicability of results to their own country. They may also find that an enhanced reference case could serve as a basis for the contextualization of existing studies for their own local health care environment, that is, to help in knowledge translation of economic evidence.

This thesis starts with a background description of cost-effectiveness analysis in both industrialized and developing countries, followed by the research question and objectives in Chapter 2. Chapter 3 explains the methods used in this research project. Findings are presented in Chapter 4 and are discussed in Chapter 5. Chapter 5 also includes the limitations of this thesis as well as some suggestions for future research. Appendices follow in the next section, including a glossary of terms used in this thesis in Appendix 13.

1.1 The use of cost-effectiveness analysis in industrialized countries

Cost-effectiveness analysis is an economic evaluation technique that compares costs and health consequences between two or more interventions, facilitating decision-making. The difference in net costs between two interventions is divided by the difference in outcome between interventions to obtain a ratio of incremental cost per unit of effect gained, most commonly expressed on a per person basis. When CEA ratios for a broad range of interventions and services are available, it is possible to rank them in a league table to prioritize and maximize health gain returns in a population. A crucial aspect of a CEA study is identifying the perspective, which in turn determines the scope of resource utilization on the cost side and, on the consequences side, the resource savings to be valued. Equally crucial is the setting of the temporal scope, or the time horizon, of the study sufficient for the capture of costs and benefits that flow from the intervention. For relevance to decision-making, costs and benefits are valued in the present day through the application of a discount rate to the stream of future costs and benefits. Accordingly, the choice of the discount rate has a profound impact on longer-term
interventions and on interventions for which the flow of costs and benefits occur at different times; the higher the rate, the more diminished are the future values.

The identification of the appropriate perspective depends on the broadness of the problem under study, taking into consideration not only those who gain health, but also those who pay for it (Gold et al., 1996). Commonly, a health sector perspective is taken. Here, the costs and savings pertaining to the health system alone are valued, including, for example, the costs of continuing care and the savings of avoided hospitalization or ambulatory treatment. From the patient’s narrower perspective, costs include all those borne through out-of-pocket payments, that is, that which are not covered or reimbursed through health insurance. In the broadest perspective, the societal, the costs accruing to the whole society are estimated regardless of payer, additionally taking into account the productivity losses of disablement or the productivity gains of a prolonged life. The societal perspective is that recommended for the reference case scenario. Below is a non-exhaustive sample of costs typically estimated in CEA, as demarcated by perspective:

**Table 1: Costs Demarcated by Perspective in Cost-effectiveness Analysis**

<table>
<thead>
<tr>
<th>Perspective</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health sector perspective</td>
<td>Fixed costs: overhead and administrative costs of health care facilities</td>
</tr>
<tr>
<td></td>
<td>Variable costs: hospitalization, medical personnel, in-hospital drug/vaccine consumption</td>
</tr>
<tr>
<td>Patient perspective</td>
<td>Out-of-pocket (non-insured) payments for drugs, medical devices and treatment/rehabilitation services; travel expenses; caretaker expenses; accommodation of health care/medical equipment in the household (e.g. construction of wheelchair ramps)</td>
</tr>
<tr>
<td>Societal perspective</td>
<td>Loss of patient work productivity or other time; loss of caretaker work productivity or other time; costs to other sectors (e.g. infection control in schools)</td>
</tr>
</tbody>
</table>
In industrialized countries economic (or opportunity) costs, the basic concept underlying resource valuation in cost-effectiveness analysis, are usually represented by financial prices, that is, the “sticker” or market price of the individual goods and services used in the intervention studied. For personnel costs, an accepted wage rate typical in the relevant industry is used. This practice rests on the assumption that markets are perfect and so financial prices faithfully reflect opportunity costs, even though health care markets are widely recognized as being imperfect, owing to monopolies of care providers or the one-sidedness of medical information for instance. However, the impracticality and difficulty in determining which financial prices should be adjusted, and when and how adjusted, means that standard practice among analysts is to simply use financial prices unless careful comparative cost studies show that there may be a demonstrated difference in CEA results (Drummond et al., 2005; Gold et al., 1996). Financial prices for medical costs are well documented in many jurisdictions given the concern with especially high-cost components such as hospital care. Third-party payers, including insurance schemes or governments, routinely collect and document cost information for management and decision-making, thus facilitating CEA estimation, particularly from a health sector perspective. For example, Ontario’s Ministry of Health and Long-Term Care maintains a standardized methodology and database of costs related to inpatient, day surgery and ambulatory care in provincially funded hospitals (Ontario Case Costing Initiative, 2010).

In studying immunization programmes, where a societal perspective is clearly indicated given the public health nature of immunization, opportunity costs of vaccines can be difficult to ascertain if they are not yet on the market or are still under patent. The market for pharmaceuticals and vaccines is often perceived to be highly distorted, resulting in financial prices that include a profit-making portion above the marginal cost (equivalent to the economic cost) that is partly attributed to the incentive (patents) offered by society’s desire for increasing health gains through drug innovation. Frequent price discrimination in the vaccine market also complicates ascertaining true economic costs. For example, governments that provide publicly funded vaccination to certain populations are usually offered a lower vaccine price than consumers who are not included in these populations. Analysts might use a price more reflective of its true opportunity cost, estimating it to be 20% to 60% of average sales prices, or if that is
deemed unrealistic, to declare their studies to be conducted from a “limited societal perspective” (Hay et al., 2010).

Outcomes or health consequences of an intervention are estimated as the denominator of the incremental cost-effectiveness ratio. They can be defined as “natural” units pertaining to specified health conditions such as the number of cases averted of an infectious disease or as units common to all health conditions, such as quality-adjusted life years (QALYs). When the QALY is used as the outcome measure, the evaluation technique is called cost-utility analysis. (In this thesis the term cost-effectiveness analysis is used to include cost-utility analysis.) QALY measurement allows the combining of disparate effects, adding averting the contraction of measles and the introduction of a fever together, for example. QALY measurement also explicitly recognizes both mortality and morbidity effects, say, reduction of childhood deaths as well as disability from blindness in the case of measles immunization. In estimating effectiveness of a specific intervention, the quantity of time lived in identified health states is weighted by the quality of life lived in a respective state, and then aggregated to form QALYs. The quality-of-life weights are numerical expressions of “preferences” or “utilities” that have been elicited from patients (represented by members of society) for different health states in either generic or specific disease conditions through standardized methods, commonly the standard gamble, time trade-off and the visual analogue scale methods (Drummond et al., 2005). Health states are valued on a continuum from perfect health to death, with perfect health weighted with “1” and death with “0”. Typically, researchers use “off the shelf” weights instead of surveying citizens afresh for each study. Two of the most commonly used measurement instruments are the EQ-5D™ (EuroQol Group, 2010) and the HUI® (Health Utilities Inc, 2010). These are both health state classification systems pairing multiple attributes of health states with preference scores. For example, the EQ-5D™ includes five attributes, or dimensions, (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) that have three levels each (no problems, some or moderate problems, severe problems (EuroQol Group, 2010). Valuing of the health states is performed with visual analogue rating scales (often described as a “thermometer” scale with best health states at the top). Valuation in the HUI® systems (two variants, HUI2 and HUI3) are based on standard gamble (choices between two health state alternatives weighted by their respective probabilities of occurrence). Health attributes include
vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition. Within these attributes three to six levels, descriptively detailed, are scored on a best to worst scale. For example, in the HUI3 (Health Utilities Index Mark 3), the “Vision” attribute Level 1 is described as “Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.” Level 6 is described as “Unable to see at all” (Health Utilities Inc, 2010). In deciding which measurement system to use, including other well-known systems like the SF-6D (Short Form 6D), Drummond et al. (2005) suggested researchers consider the instrument’s credibility as well as its appropriate representation of attributes and their levels relevant to the patient population being studied. In its manual for technology assessment, NICE recommends the use of the EQ-5D, with the special consideration in the case of pediatric populations for using an alternative validated health-related quality-of-life instrument like the HUI2 (NICE, 2008, p. 39).

The QALY outcome measurement is recommended by the WPRC to allow comparisons across studies and is the most commonly used measurement for broadly based interventions. However, its use is sometimes controversial among theorists and methodologists. Debates include the economic theoretic foundations in defining and valuing utilities (Birch & Donaldson, 2003; Brouwer & Koopmanschap, 2000; Culyer, 1989; Gafni, 2006) the descriptive ability of QALYs to accurately capture patient preferences (Culyer & Wagstaff, 1993; Dolan, Shaw, Tsuchiya, & Williams, 2005) relative merits of competing outcome measures (Chapman et al., 2004; C. Evans, Tavakoli, & Crawford, 2004) and significantly, the ethical considerations embodied by the valuing of life and disability for various patient groups (Gold, Stevenson, & Fryback, 2002; Sassi, 2006; Wagstaff, 1991).

In a direct comparison of the use of unadjusted life-years (LYs) as an outcome measure against QALYs for the same interventions in published studies that used both measures, Chapman et al. (2004) found that the quality adjustment did not significantly alter the cost-effectiveness for the majority of 140 pairs of interventions. They suggest that the extra cost of obtaining quality of life information may thus not be warranted in many cases. However, they found that in certain interventions, such as those addressing chronic conditions, palliative care and long-term negative sequelae, quality adjusting caused the cost-effectiveness ratio to cross either above or
below a widely held threshold of $50,000 per LY or per QALY in 14 cases out of 173 pairs and above or below $100,000 per LY or per QALY in another 11 cases. Including the cases where the intervention became either dominated or not dominated when quality adjustment took place, quality adjustment made a difference to the threshold (or a decision rule) in a total of 32 cases (18.5% of pairs). Drummond et al. (2005) also indicate the use of QALYs when quality of life is the main health outcome of an intervention and further recommend the use of QALYs in a limited budget situation, when prioritizing choices must be made between interventions to adopt, to maintain and to discard.

To clarify the conditions under which to use QALYs, M. Weinstein, Torrance, and McGuire (2009) oriented the methodological debates in terms of objectives for health care policy-making. They recall and support the original intent of QALYs in meeting the objective of policy-makers to maximize health benefits under a constrained budget. For other policy-maker objectives (e.g. equity, politics) methodological controversies for using QALYs, and indeed, the incremental cost-effectiveness ratio for efficient allocation of resources, continue (Donaldson, Currie, & Mitton, 2002).

Nevertheless, using cost-effectiveness analysis (including cost-utility analysis) to help inform health care policy and decision-making has become increasingly common in industrialized countries over the last 20 years. It is considered a tool of payer decision-making and health technology assessment, and is the backbone of the field of pharmacoconomics. Various countries in Europe and Australia use it as a criterion for pharmaceutical and health care product approval. The most extensive, explicit and influential use of CEA for policy and decision-making is found at the UK National Institute for Clinical Excellence (NICE) of the National Health Service (NHS), which provides broad-based health care guidance for government, practitioners and patients alike (National Institute for Clinical Excellence, 2010a). NICE incorporates economic evidence into all its areas of work, and CEA studies are key to its recommendations of technologies for public funding. According to S. Walker, Palmer, and Sculpher (2007), NICE technology appraisals are comprised of four steps: 1) Scoping, or the establishment of the appraisal framework; 2) Assessment, which is itself two parts - the systematic review of all clinical and economic evidence, and an economic evaluation that
synthesizes this information; 3) Appraisal, or the formulation of a decision based on cost-effectiveness, clinical evidence, clinical need, technical specifications (of products, drugs etc.) and other factors, and which, when formalized in the Appraisal Consultation Document, may be commented upon by all stakeholders; and 4) Appeal, or a formal channel for stakeholders to appeal the decision. Cost-effectiveness acceptability rests on the ICER being below the NICE threshold range of £20,000 to £30,000 per QALY (S. Walker et al., 2007). Decision-making for new technologies and interventions is thus not only informed but also framed by CEA. For the implementation of its national level guidance, that is, formal recommendations based on integrated clinical guidelines and cost-effectiveness evidence, NICE provides decision-making tools to regional health authorities that must make decisions on the introduction, elimination and delivery of programmes at the local level. A downloadable costing template to assess and minimize the financial impact of its recommendations for the uptake of new immunization programmes is available on the NICE website, for example (National Institute for Clinical Excellence, 2010b). Similarly, cost statements describe the resource implications for its recommendations, with suggestions on the contextualization of the implications at the local level.

Iliffe (2007) cited the great technical capacity of NICE. The Institute is able to modify CEA methodology to meet criticisms and challenges, but it also has the managerial capacity to benefit from the wide inclusion of multidisciplinary stakeholders in the decision-making process, including patient advocacy groups and industry. Iliffe also points, however, to patient complaints of the inadequacy and inequity of using the QALY (resulting, for example on greater value placed on treating patients with more severe diseases), the focus on costs to the NHS rather than to the patient and the use of an inappropriate threshold, among others. The concept of a cost-effectiveness threshold is generally controversial, but its explicitness and high profile at NICE garners concerns that it may promote dis-investments of established technologies that may be more effective and the adoption of financially (budget-wise) unsustainable technologies (Birch & Gafni, 2002; Iliffe, 2007; S. Walker et al., 2007). Using a range of values for the threshold rather than a single value has also been concluded to yield less health improvement, and it has been suggested that it should therefore should be replaced with a threshold near the lower end (currently £20,000) (McCabe, Claxton, & Culyer, 2008). This threshold should be
periodically reviewed, however, and take into consideration budgetary implications as well as a mechanism for dis-investment of previously approved programmes.\textsuperscript{2}

In Canada, the Canadian Agency for Drugs and Technology (CADTH) provides formalized recommendations and guidelines (CADTH, 2006) for the voluntary integration of CEA into evidence for third-party insurers at various levels of jurisdiction as well as the mandatory pharmacoeconomic studies required with submissions for new drug inclusions in government funded drug plans or formularies. Formulary decisions are made by CADTH under the Common Drug Review (CDR). Once a submission is filed, a CDR team of experts is convened to compile and systematically review information gathered through the submission, literature searches and solicited patient group input. Reviews, after incorporating the drug manufacturer’s response, are considered by a CADTH body, the Canadian Expert Drug Advisory Body, sometimes along with supplemental advice or information. Final inclusion recommendations are made by the Advisory Body to the relevant drug plan(s) and drug manufacturer after an opportunity is allowed to the plans to request clarification and the manufacturer to request reconsideration (CADTH, 2010).

In the United States, explicit use of CEA by government and payer decision-makers is far less extensive, but the rise in CEAs published in high-impact medical journals suggests that they do influence decision-makers (including private insurers). A Vaccine editorial cited a study assessing 39 reviews of over 3000 CEAs in the health field published or undertaken in the 1990’s alone (Spier, Jefferson, & Demicheli, 2002). With a stated aim of assisting policy-makers in resource allocation decisions, the Tufts-New England Medical Center maintains a database of over 2300 cost-utility studies and a league table of CEAs complying with the Washington Panel Reference Case (Center for the Evaluation of Value and Risk in Health, 2010).

\textsuperscript{2} The concern for the potential dis-investment of more cost-effective, previously approved programmes arises from the implicit acknowledgment that the recommendations are based on the constant budget of the NHS. Therefore, in order to introduce a new programme, an older one must be removed. An additional issue then arises in that it is the regional health authorities that make the decision for dis-investment, sometimes with insufficient evidence and tools upon which to base the decision. NICE recognizes this last issue in its provision of costing statements and templates.
Although cost-effectiveness analysis is recognized as a valuable input into health care decision-making, the extent to which it is actually used by decision-makers is unknown. The lack of consistency in its execution, reporting and interpretation as well as suspicion of industry-sponsored studies detract from its value and impede fuller integration into decision-making (Jefferson, Demicheli, & Vale, 2002; McGregor, 2006; Neumann, 2005). Its progressive, systematic integration into priority-setting at the national or international level remains hampered by the limited applicability of results outside the health care jurisdiction in which data were gathered. Sculpher and Drummond (2006) have suggested that to increase the technique’s generalizability, and therefore its potential as a major input into public policy-making, decision-makers and analysts must together streamline and harmonize CEA methods and guidelines across jurisdictions.

1.2 The use of cost-effectiveness analysis in developing countries

The lack of access to health care decision-making tools and information in low and middle-income countries (LMICs) was in the past characterized by the shortage of good quality cost-effectiveness studies specific to their own national epidemiologic and socio-economic situation (Iglesias, Drummond, Rovira, & Group, 2005; Mulligan, Walker, & Fox-Rushby, 2006; D. Walker & Fox-Rushby, 2000). Walker and Fox-Rushby (2000), analyzing economic evaluation studies of communicable disease interventions in developing countries from 1984-1997, deemed 107 review-worthy, of which 26 targeted vaccine preventable diseases. Another study examining non-communicable diseases found that only 32 economic evaluations aimed at LMICs were published between 1984 and 2003, and the general quality was poor, with many studies so opaque that details could not be assessed (Mulligan et al., 2006). Given this shortage, the poor generalizability and transferability of CEA was especially problematic since data and analytical constraints in LMICs could not be overcome by sharing data or results from industrialized countries. Poor generalizability is a widely acknowledged weakness that

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3 The World Bank defines low-income countries as those where 2009 GNI per capita was $995 or less, lower middle-income countries where GNI per capita was between $996 and $3945, and upper middle-income, between $3946 and $12,195.
continues to generate commentary and research even in industrialized countries where these constraints are less severe and health systems are more similar (Sculpher & Drummond, 2006).

Since the mid-1990’s, however, the World Health Organization and the World Bank have taken the lead to re-tool and refine CEA methodology for specific application to developing countries and to coordinate large scale efforts in producing and providing CEA evidence for policy and decision-making. The most important methodological developments include the formulation of the DALY (disability-adjusted life year) outcome measure introduced in the 1993 World Development Report (World Bank, 1993) and the sectoral approach to CEA developed by the WHO. The DALY is described immediately below and the sectoral approach (also called generalized CEA) in the next section.

The DALY was originally conceived to measure the population-wide burden of disease in developing countries and also as the measure of effectiveness in cost-effectiveness studies (Murray & Acharya, 1997). DALYs are a composite measure of health effects, composed of the elements of mortality (years of life lost or YLL) and morbidity (years of life lived with disability or YLD). In contrast to QALYs, full health is valued at “0” and death at “1” in the DALY weighting system. DALYs focus on the degradation of healthy life, summing years of life lost and years lived with disability, so a desired goal of interventions is to avert or minimize DALYs. In cost-effectiveness analysis it is desirable to maximize DALYs-averted relative to costs. Drummond et al. (2005, p.187) point out the most important differences between QALYs and DALYs:

- Life expectancy of QALYs differ according to the intervention while DALY life expectancy is constant across interventions, equal to the highest national life expectancy (Japan)
- In adjusting life years with weighting, patient and community preferences underlie valuation of QALY weights while health care experts’ opinions underlie DALY weights
- QALY weights can take on any value between 0 (death) and 1 (full life), implying a continuum of health states while DALY weights take on only 7 values between 0 and 1, implying nine health states including death and full life
DALYs are additionally weighted by age, with lower weights given to the very young and the elderly

The underlying values of the DALY, expressed partly through the above differences, were criticized for being discriminatory, inadequately capturing burden of disease and being technically unsound (Anand & Hanson, 1997; Arnesen & Nord, 1999; Barker & Green, 1996). Murray and Acharya (1997) countered earlier criticisms with an argument that the criticisms also applied to QALYs, and sought to clarify the motivation and principles of the DALY. The authors stated that an updated version of the DALY incorporated disagreements with disability-weighting (by iteratively refining their preference elicitation with more diverse groups of participants), but stood by their use of age-weighting (including an argument that young adults contribute to the health and well-being of children in their care as well as to the productivity and well-being of society as a whole) (Murray & Acharya, 1997). Musgrove (2000) concluded that some DALY criticisms are founded, but that some stem also from misinterpretation by critics and misapplication by analysts.

Analysts may handle disputed aspects of the DALY through sensitivity analysis by, for example, removing age-weighting altogether or applying a 0% discount rate to neutralize age-related impacts (D. B. Evans, Edejer, Adam, & Lim, 2005). If analysts make adjustments to account for differential assumptions and impacts, the question arises whether there is a convergence in QALY and DALY weighting and their results. One researcher found that even when age-weighting, discounting and life expectancies were made equivalent, DALYs averted were systematically smaller than QALYs gained for the same intervention (Airoldi, 2007). In addition to the criticisms mentioned above, Arnesen and Kapiriri (2004) point out that analysts found the DALY technique “mystical” and recommended more transparency for both analysts and policy-makers who might use the results. Therefore, as interest gains in using the DALY, so have attempts made to more clearly delineate the differences and implications for using the QALY versus the DALY (Gold et al., 2002; Sassi, 2006) and to provide criteria and instructions for the calculation of DALYs (Fox-Rushby & Hanson, 2001).
In practice the DALY is still used predominantly for analysis pertaining to the international sphere and developing countries. The Global Burden of Disease Study, the originating and main ongoing motivation for development of the DALY, relies on DALYs to express the health impact and comparative importance of major diseases and types of injuries worldwide and to express risk factors of ill health. Its original 1990 estimates show that the five top-ranking diseases in terms of DALY accrual and their global share of the DALY burden were lower respiratory infection (8.2%), diarrhoeal disease (7.2%), perinatal conditions (6.7%), depression (3.7%) and ischemic heart disease (3.4%) (Lopez, 2005). The risk factor malnutrition alone contributed to 15.9% of global DALYs. New estimates of disease burden based on revised DALY weighting is anticipated for its 2010 report (Global Burden of Disease Project, 2010).

Related to the Global Burden of Disease Study, the multi-institution Disease Control Priority Project (DCCP) conducted CEAs using non-age weighted DALYs with regional life expectancies to formulate a database of results for interventions that address disease burdens particular to developing countries (Jamison et al., 2006). This work followed up and updated that initiated by the Project in 1996 and by the WHO Commission on Macroeconomics and Health (CMH) in 2001 (Sachs & Commission on Macroeconomics and Health, 2001; World Health Organization, 2010d) to identify and recommend “best health buy” interventions, based on the most DALYs averted at the lowest cost. Of the ten best buys, vaccination against childhood diseases and monitoring children’s health to prevent or treat pneumonia, diarrhea and malaria top the list. The DCCP maintains ongoing research and updates of its CEA database, centered on the use of CEA as a health care and development decision-making tool (Disease Control Priorities Project, 2010). In applying standardized, global methodologies for the calculation of disease burdens and estimation of cost-effectiveness (based on WHO-CHOICE methodology, discussed in the next section), international and regional comparisons may be made. Furthermore, recognizing that national income levels greatly affect the pattern of resource use, epidemiological profiles and price levels, the DCCP, WHO-CHOICE and other international organizations are united in promoting CMH’s recommendation to use cost-effectiveness thresholds based on the GDP of the country studied. Interventions that are less than the GDP per capita are termed “highly cost-effective”; those that are between one to three
times the GDP per capita are “cost-effective”; and those that are more than three times the GDP per capita are considered “cost-ineffective” (Jamison et al., 2006).

Although these efforts initiated and supported by the large health-related international organizations have greatly advanced the use of CEA in or for developing nations, making economic evidence as well as the techniques themselves accessible through publications and websites, it is still relatively underused by local policy and decision-makers and local researchers and analysts. Findings from the key informant interviews conducted for this thesis highlight this (discussed in Section 4.6.2). Cost-effectiveness analysis is rarely seen as a standard policy-making tool in developing countries; a review of health policy-making tools conducted by the WHO gives it small recognition (Liu, 2003). Most of the analysis conducted for the Global Burden of Disease and Disease Control Priority projects were done, and continue to be done, by researchers specialized in developing countries but based in industrialized countries. The WHO and World Bank work remains relatively unknown to the majority of CEA theorists and practitioners based in industrialized countries, who might otherwise assist in advancing methodologies and applications oriented towards developing countries, but are unfamiliar with the problems of using this analytical tool outside their own health systems. Nevertheless, partly due to the strong focus on cost-effectiveness at the World Bank, WHO and other international organizations, decision-makers in the international arena are increasingly using CEA evidence for both health and non-health issues. For example, donors use cost-effectiveness as an input for making strategic decisions on aid priorities (e.g. in choosing whether to support vaccine introduction) or for debt relief (e.g. assessing fiscal health through government support for efficient immunization programmes) (Fairbank, Makinen, Schott, & Sakagawa, 2000; Radelet & Siddiqi, 2007).

1.3 The WHO-CHOICE Project

The ongoing CHOICE (Choosing Interventions that are Cost-Effective) project based at the WHO is currently the largest effort focused on CEA methodology and application for developing countries. It aims to develop and disseminate CEA methods and results that can be
used with country-specific adaptation within specific regions, thereby eliminating the
duplication of efforts by LMICs that have limited resources and capacity (Raymond C.
Hutubessy, Baltussen, Torres-Edejer, & Evans, 2002; R. C. Hutubessy, D. Chisholm, & Torres-
Edejer, 2003; Tan-Torres Edejer et al., 2003).

WHO-CHOICE methodology for CEA, called generalized cost-effectiveness analysis, was
developed to allow broad-based decision-making and priority-setting at the national level, as
opposed to conventional CEA (described in section 1.1.1), which focuses on the patient level. Its
developers identified four shortcomings associated with conventional CEA that prevent it from
helping to achieve better resource allocation in the health (R. C. Hutubessy et al., 2003; Murray,
Evans, Acharya, & Baltussen, 2000). First, despite the theoretical underpinnings that could
allow the achievement of the highest level of population health with the least resources
(allocative efficiency), conventional CEA is constrained by its incremental approach to address
technical efficiency. Second, current misallocations of resources are not identified as the focus
is on new interventions, which are compared to existing (and possibly inefficient) interventions.
Third, the data and technical requirements for making broad, allocative decisions are lacking.
Studies using conventional CEA are so context-specific they cannot be generalized, which is
detrimental especially to developing countries where data and technical limits are even more
acutely felt. Finally, there are no international methodological guidelines for enhancing
allocative efficiency.

The approach used by WHO-CHOICE simultaneously analyzes multiple interventions within
the health sector. The authors’ term “generalized cost-effectiveness analysis” (GCEA) indicates
its broader application compared to conventional CEA, which the CHOICE authors call
“intervention mix constrained CEA” (IMC-CEA) (Tan-Torres Edejer et al., 2003). In IMC-CEA
the intervention options open to decision-makers are constrained by the interventions already in
place, that is, the counterfactual for CEA is the current intervention or practice, and analysis is
incrementally built upon it. In contrast, the GCEA used by WHO-CHOICE takes as its
counterfactual the null set of interventions, a health sector in which all interventions
theoretically cease to exist at the point of analysis. Every feasible intervention could then be
considered for introduction, and old interventions can be re-evaluated. Consequently, average
costs and benefits are estimated instead of marginal (incremental) costs and benefits. Thus, by using a null set of interventions as a starting point, the analysis is shifted from intervention-to-intervention to a mix of interventions, moving away from technical to allocative efficiency. Furthermore, the identification of current inefficient interventions as well as new efficient interventions is enabled.

To overcome data limitations in developing countries, WHO-CHOICE developers and analysts established and maintains regional databases of costs and effectiveness information as well as developed tools to collect relevant primary data. These include a template (CostIt) for the standardized, consistent collection of data pertinent to cost-effectiveness analysis. The Project aims to overcome technical capacity constraints for conducting CEAs, too. For example, in estimating health personnel costs, Caribbean countries may use pre-collected salaries standardized for their WHO region, or adapt them through a CHOICE-designed “contextualization tool”. Datasets and tools, including the CostIt template and epidemiological modeling software (PopMod), along with CEA results for a limited number of interventions, are available online and are supported by WHO technical staff (World Health Organization, 2010b).

World Health Report 2002 first presented selected summary results generated from the WHO-CHOICE Project for 42 interventions, focusing on interventions addressing main risk factors according to burden of disease defined by DALYs. There was a wide scope of risk factors represented ranging from child under-nutrition to blood pressure to unsafe sex and HIV/AIDS to unsafe water, sanitation, hygiene. Clusters of cost-effective interventions were presented for each risk, discussed for selected (and relevant) WHO epidemiological regions. For example, in addressing unsafe water, sanitation and hygiene, the interventions studied included disinfection at point of use and enhanced low-tech solutions for improved water supply and sanitation. Interventions were not evaluated in the North American and European regions, however, as this risk factor was not high in these regions (World Health Organization, 2002). Currently, updated and expanded summary cost-effectiveness results by region and disease/risk factor are available through the WHO website (World Health Organization, 2010c).
WHO-affiliated researchers also published a series of studies that used generalized cost-effectiveness analysis to identify cost-effective interventions consistent with strategies to reach the Millennium Development Goals (MDGs). D. B. Evans et al. (2005) set out the assumptions, choice of interventions and costing methods for this series, which recommended artemisinin-based combination treatments to address malaria in sub-Saharan Africa (Morel, Lauer, & Evans, 2005), zinc and vitamin A fortification and measles immunization to address global child health (Tan-Torres Edejer et al., 2005) and mass media campaigns, interventions for sex workers, and treatment for sexually transmitted disease infections to address HIV/AIDS in lowest-income regions (Hogan, Baltussen, Hayashi, Lauer, & Salomon, 2005). Adam et al. (2005) studied 21 interventions in various combinations to improve maternal and neonatal health in sub-Saharan Africa and South East Asia.

Aside from WHO researchers, there has been limited use of the GCEA methods by other researchers in the industrialized world. Various researchers have used WHO-CHOICE databases, however, including those estimating cost-effectiveness of rotavirus immunization in Asia (Fischer et al., 2005; Podewils et al., 2005). It is unclear yet whether there will be substantive uptake of the WHO-CHOICE technique by LMIC analysts, although recently a group of interventions preventing cardiovascular disease in Argentina were studied (Rubinstein, Garcia Marti, Souto, Ferrante, & Augustovski, 2009).

1.4 Cost-effectiveness analysis of pediatric interventions

Whether in developed or developing countries, pediatric interventions is a neglected focus in economic evaluations. The Pediatric Economic Database Evaluation (PEDE) project based at Toronto’s Hospital for Sick Children revealed substantial deficiencies in methodology, reporting and coverage areas for studies based predominantly in industrialized countries. Particularly, uncertainties were very poorly addressed. In 52% of the studies no sensitivity analysis were performed and only one-way analysis performed in another 44% (Ungar & Santos, 2005). A review of QALY estimation in pediatric studies found considerable variation in the method of its calculation and underdevelopment of child-specific health state measurement and expressed
disappointment that guidelines provided by the Washington Panel reference case have not been met (Griebsch, Coast, & Brown, 2005). In addition to falling below established quality guidelines, pediatric studies generally do not explicitly address the distinctiveness of children compared to adults. Keren, Pati, and Feudtner (2004) discussed several differences between adults and children that, when taken into consideration, might affect cost-effectiveness results and thus require addressing: distinct biology; difficulty in assessing child health values and utilities; dependency on others; development, interventional timing and impact; delay to key outcomes; duration of dependency on others; diverse forms of productivity; dissimilar past opportunities to life experience; disparities in socio-economic status; and disenfranchisement from legal and political redress.

There are few studies directly comparing CEAs for children and adult populations, but a comparison of 35 pediatric and 491 adult studies in the U.S. found that they are largely methodologically undifferentiated (Ladapo, Neumann, Keren, & Prosser, 2007). These authors concluded that the quality of the pediatric studies were similar to the adult studies, according to their quality scoring. Like Ungar and Santos (2005) and Griebsch, Coast, and Brown (2005), however, they found that authors in both groups frequently failed to mention methodological items like the discount rate used or sources of preferences. The main difference found between the two groups of studies was that the authors’ assumptions or expert opinions were significantly more often the source of preference in quality-of-life weighting in pediatric studies. Ladapo, Neumann, Keren, and Prosser (2007) also selectively explored whether the concerns for possible divergence or degradation of CEA results outlined in Keren, Pati, and Feudtner (2004) were borne out, but in their judgment CEA ratios did not reflect respective methodological choices, such as the different time horizons used.

The valuation of health costs and benefits to children is challenged by their epidemiological and cognitive differences to adults. Children’s life spans and therefore time horizons are longer so issues of the adequate capture of future costs and discounting become more acute, especially since preventative interventions predominate for children. Children’s biology differ from adult’s, too, so that interventions developed for and/or tested on adults, say, drugs, may have different effectiveness. They may also have unintended negative impacts, as Keren, Pati, and
Feudtner (2004) points out, citing the decrease in cost-effectiveness for dual air bags in cars given their fatal deployment on front-seat children passengers.

Cognitive differences contribute to the issues concerning the elicitation of children’s preferences in measuring health status and subsequently to weight effectiveness measures. Parents’ and caregivers’ preferences often stand as proxies for very young children, but it is not clear their preferences are the same as children’s or whose preferences are more important (Keren, Pati, & Feudtner, 2004; OECD, 2006). Generic utility instruments derived from adult instruments or those non-validated for children, e.g. the EQ-5D, may also degrade measurement of health states. Furthermore, as childhood development is so rapid and divergent among children, a common set of dimensions may be hard to assign to each age group, so that using fixed health states are inadequate (Petrou, 2003). Contingent valuation methods, such as discrete choice experiments to derive willingness-to-pay for cost-benefit analyses, are inappropriate for application to children as these methods require a grasp of monetary values, time horizons and health states beyond the experience and comprehension of children, especially younger ones (Ungar & Gerber, 2010). Substantial work is continuing in pediatric outcome measurement, however. In a literature review of current quality-of-life measurement instruments for children, Solans et al. (2008) found that rapid development has been taking place, with 51 new instruments published between 2001 and 2006 meeting their quality and inclusion criteria. They note that the multiplicity of dimensions captured in these questions may reflect attempts to capture health states rapidly evolving apace with child development.

Unfortunately no similar large-scale quality reviews for pediatric interventions focused on developing countries have been conducted. However, given the increasing use of economic evidence in global health, such as in prioritizing strategies for achieving the Millennium Development Goals for child health (Tan-Torres Edejer et al., 2005), such a review is warranted.
1.5 Cost-effectiveness analysis of pediatric immunization in developing countries

CEAs of vaccines set in developing countries are relatively few compared to those set in industrialized countries (Beutels, Doorslaer, Damme, & Hall, 2003). Kim and Goldie (2008) found that of the 276 studies surveyed in their study, published between 1976 and mid-2007, only 43 were set in low- and middle-income countries, with another three set worldwide. Nevertheless, studies of immunization programmes form the bulk of economic evaluations in developing countries. In the 1980’s the cost-effectiveness of the vaccines and the programmes against measles, diphtheria, pertussis, tetanus, tuberculosis and polio (the vaccines used in the traditional Expanded Programme on Immunization (EPI) put into place by UNICEF/WHO) was firmly established (Brenzel, 1990; Brenzel & Claquin, 1994; Mills & Thomas, 1984). After two decades of coverage rate gains worldwide, the 1990’s saw stagnation and decline in coverage rates due to shrinking donor assistance and local economic and social upheavals, including the AIDS epidemic. Between 1990 and 2000 DPT3 rates in the Central African Republic plunged from 82% to 29%, contrasting starkly with the 70% global average (Davey, 2002). Unequal distributions of coverage also persisted or worsened within countries. For example, in Niger, 50.9% of children in the richest quintile were fully immunized compared to 4.6% of those in the poorest quintile (Gwatkin & Deveshar-Bahl, 2001).

The promotion of economic evidence by the World Bank and WHO, as described in Sections 1.2 and 1.3, lead to a substantial increase in awareness and feasibility in using CEA as a decision-making tool, reflected also using CEA results to encourage national governments and donors to continue or resume supporting immunization, and ultimately to improve coverage and distributions of coverage. Renewed efforts have been made to assess the cost-effectiveness of immunization to highlight its value to both health and economic development. CEAs were also used to inform potential additions to the core EPI programmes. These include vaccines against Haemophilus influenzae B (Hib) and hepatitis B, which are widely used in industrialized countries but underutilized in developing countries, and new or potential vaccines for HIV and dengue fever (Andrus, Tambini, di Fabio, & Periago, 2004; Bos & Postma, 2001; Limcangco, Armour, Salole, & Taylor, 2001; Shepard et al., 2004). These studies focus on cost, as these

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4 Three doses of the diphtheria-pertussis-tetanus vaccine, a WHO/UNICEF proxy for full coverage.
vaccines are more expensive than the traditional EPI vaccines and would also require additional storage and possibly new delivery mechanisms. Griffiths, Hutton, and Pascoal (2005) estimated that the addition of hepatitis B vaccine combined with the DTP vaccine to the routine schedule in Mozambique in 2001 increased the cost of immunization services by 56%, with the cost of vaccines accounting for about a third of the increase. They estimated a cost-effectiveness ratio of US$47 per DALY averted for the combined vaccine, and a ratio of US$19 per DALY averted for a monovalent (uncombined) hepatitis B vaccine, making the intervention moderately cost-effective according to WHO thresholds that are based on national income per capita. The discrepancy between the two modes of delivery, however, poses a challenge for decision-making.

For the vaccines still in research and development, like the malaria vaccine, detailed costing of all the known characteristics of the vaccine and its delivery forms a first step towards a full cost-effectiveness study (Hutton & Tediosi, 2006). Because new vaccine prices are unknown and subject to negotiation between manufactures and the international organizations that provide vaccines to developing countries, Hutton and Tediosi analyzed comprehensively the marginal costs to the entire immunization services using a range of plausible prices from $1 to $10 a dose. At the highest price level, the EPI programme including malaria would exceed the current EPI budget in Tanzania. As it is likely that other new vaccines may be similarly costly, detailed costing exercises for them would also be in order. For example, Berndt et al. (2007) used estimates of $15, $13 and $14 per person immunized for the malaria, tuberculosis and HIV vaccines (vaccine plus delivery costs) to estimate cost-effectiveness in a variety of countries in support of the proposal for the Advanced Market Commitment programme.

1.6 Cost-effectiveness analysis of rotavirus immunization

The introduction of the rotavirus vaccine has been a major confluence of interest for donors, international organizations and developing countries in recent years due to its promise of

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5 The six antigens are BCG (Bacille Calmette Guerin) against tuberculosis; DPT against diphtheria, pertussis, tetanus; measles; and OPV (oral polio vaccine) against poliomyelitis. They are all delivered in the first year of life.

6 In this study the authors assumed that adults would also be immunized and that two doses per person is needed.
reducing a heavy burden of pediatric coupled with its high cost – a situation in which the careful weighing of policy options could be helped by economic evaluation.

The burden of rotavirus-induced gastroenteritis is tremendous and worldwide. Almost every child in the world has had at least one episode by age 5, resulting in 25 million clinic visits and 2 million hospitalizations per year (Parashar, Hummelman, Bresee, Miller, & Glass, 2003). Of the resulting 400,000 annual deaths, 82% occur in developing countries, where the risk of dying from rotavirus disease is 1 in 205 in the lowest income group. Because its burden is global, rotavirus disease has received keen attention from vaccine producers and medical researchers of both industrialized and developing countries. Therefore, the 1999 withdrawal of the first licenced rotavirus vaccine (Rotashield™) after reported intussusception only a year after its recommended adoption in US routine programmes spurred the development of new vaccines. Rotateq™ and Rotarix™, made by Merck and Glaxo-Smith-Kline respectively, were licensed in 2006 (Glass & Parashar, 2006; Kamal-Uddin & Croft, 2006; Ruiz-Palacios et al., 2006; US Food and Drug Administration, 1999; Vesikari et al., 2006). Rotateq™ is a live pentavalent human-bovine reassortant vaccine that requires delivery in three doses, while Rotarix™ is a live attenuated human monovalent vaccine requiring only two doses for good immunogenity. It is significant to note that Rotarix™ trials took place in Latin America and the vaccine was launched in Mexico, a departure from the usual launch of major pharmaceuticals and vaccines in industrialized countries. This may give a more realistic, accurate idea of its effectiveness in the population for which it is targeted. Efficacy was lower for Rotarix™ than for Rotateq™, 85% versus 98%, and this could be due to the less-healthy population in the Rotarix™ trials set in middle-income countries compared to the healthier population of the Rotateq™ trials set in Europe (Glass & Parashar, 2006). A domestically-produced vaccine is currently licenced in China (Mohan, Kulkarni, Glass, Zhisheng, & Atreya, 2003) and three others are in clinical trials in India under the supervision of a local producer (Jaffe, 2005).

The promise of reducing a major source of global childhood morbidity and mortality suggests that the cost-effectiveness evidence base, currently very small, will be an increasing focus for researchers. In reviewing the earliest CEAs of rotavirus immunization (including that for the withdrawn Rotashield™ vaccine), D. Walker and Rheingans (2005) found persistent problems
of inconsistency in the application of methodology, which resulted in non-comparability of the eight studies. For example, three of the eight studies did not specify the discount rate used, one stated that none was used, and the remaining used either 3% or 4%. The methods for collecting productivity costs also varied from data gathered at clinical trials to general assumptions being made about work time lost. The reviewers nevertheless thought this early body of economic evidence was reasonably good and provided some worthwhile models that could be applied and refined in future studies. They noted that although rotavirus immunization might be cost-effective in a variety of country settings, as indicated by the reviewed studies, the issue of affordability might prove to be a barrier not easily overcome without external support.

Economic studies set in developing countries anticipating the introduction of rotavirus vaccines have been more recently completed, some benefiting from guidance from the WHO rotavirus-specific guidelines for estimating economic burdens (World Health Organization, 2005) and regional data from the WHO-CHOICE project. Fischer et al. (2005) studied the cost-effectiveness of universal rotavirus immunization with a range of vaccine prices ($1 - $20 per 2-dose regimen) to determine the price at which the intervention would be cost-effective in Vietnam according to WHO standards. The authors estimated that routine immunization would be cost-effective at $40 per DALY averted for vaccine prices up to $4.52 per course. As found in the earlier studies mentioned above cost-effectiveness was highly sensitive to vaccine price. In the Fischer study, the investigators fielded-tested the then draft rotavirus burden guidelines, specifically for the collection of patient level data for extrapolation to the national level in Vietnam. The authors, however, did not outline the assumptions made in their modeling or DALY calculations. Nor did they specify a discount rate, time horizon, or analytical perspective.

Isakbaeva et al. (2007) found that routine rotavirus immunization in Uzbekistan would be cost-effective for a vaccine price between $2 and $25 per child. The health burden in terms of deaths, hospitalizations and DALYs was estimated, as was the economic burden in terms of hospitalization costs and intervention costs. Universal immunization of the 2004 birth cohort would avert 353 or 1144 deaths, depending on the two different published under-5 mortality rates for Uzbekistan. Mortality rates have the most influential impact on the cost-effectiveness ratio; vaccine price is the next most influential. The authors had also followed the WHO
rotavirus economic evaluation guidelines, mainly for the estimation of costs. However, although WHO-CHOICE regional data for hospital bed costs were available, they used their own Uzbekistani-specific data as they felt the domestic data were more realistic. Isakbaeva et al. (2007) were much more complete and transparent in presenting their study, providing details about methods, assumptions and parameter values.

Podewils et al. (2005) performed a regional study of the incorporation of rotavirus immunization into the EPI programmes of Asia. This study estimated the health burden (in DALYs), the economic burden (in medical costs) and the cost-effectiveness (cost/DALY averted and cost/death averted), stratified by low, middle and high national income countries, from the health system perspective. A range of vaccine prices from $2 to $60 per 2-dose course was used in the modeled 5-year study of a single birth cohort. Using the WHO cost-effectiveness standards by national income level, routine immunization would be cost-effective at $43.18 per course, $100.50 per course and $77.98 per course for the low, middle and high income groups respectively. Sensitivity analysis tested only a small group of variables, which surprisingly did not include variations in vaccine price. Cost-effectiveness was influenced by the rate of hospitalization, the rate of inpatient visits and hospitalization costs, but in varying degrees according to income group. Rotavirus immunization would reduce death and hospitalization by 62%, 74% and 85% for the low, middle and high-income groups respectively. The authors provided a high level of details regarding study design, parameter values and assumptions.

Rheingans, Constenla, Antil, Innis, and Breuer (2007) selected eight countries in Latin America of differing geographic and economic settings to study the variation of health and economic burden among them. They used various sources of data: other regional studies, surveys of health facilities, WHO-CHOICE per diem/per visit costs for facilities and physician interviews. Other economic costs were retrieved from a prospective rotavirus gastroenteritis surveillance study. Sample size recommendations were used from the WHO rotavirus economic evaluation guidelines. This study examined the economic burden in terms of medical and non-medical costs and the health burden in terms of DALYs lost. Health burdens were highest among the lower-income countries while economic burdens were highest among the higher-income countries. Health burdens were highly sensitive to outpatient visits for diarrhea in all countries.
The economic burden of higher income countries like Argentina and Chile were most sensitive to the direct medical costs from hospitalization. The authors in this study were also very transparent and detailed about the design, parameters and assumptions used.

The CEA studies discussed above (except Rheingans et al. (2007)) have not been systematically examined for quality, but compared to those reviewed by D. Walker and Rheingans (2005), showed more adherence to established guidelines with the exception of Fischer et al. (2005). Noteworthy is that two claimed analysis from a societal perspective but did not include any productivity costs pertaining to caregivers, children or otherwise. None of the studies accounted for herd immunity. All included economic and health burden studies to add valuable supplemental information for decision-making.

Highly diverse in geographical setting and study design, the studies above underline the difficulties of generalizing economic results. The variations in these studies stemmed from the unknown eventual price of the rotavirus vaccine, the local cost setting, local efficacy and the local mortality rate. It can be observed, however, that critical to vaccine introduction are averted medical costs in higher income countries and the number of averted inpatient/outpatient visits in lower income countries. Affordability may be equally or more important than cost-effectiveness in most of the countries in these studies. All of the CEA studies showed cost-effectiveness for a large range of vaccine prices, but even at the low end of the price range ($1-10), the price is several times the price of the traditional EPI vaccines in developing countries. Perhaps the most valuable aspect of these studies is their establishment of the problem in terms of health and economic burdens from rotavirus gastroenteritis.

It should also be noted that malnourishment may reduce the efficacy of vaccines and thus the effectiveness of vaccine programmes. Comparing well-nourished and malnourished infants in Brazil, Mexico and Venezuela, Perez-Schael et al. (2007) found that malnourishment did not significantly affect Rotarix™ vaccine efficacy against severe rotavirus gastroenteritis (74% and 73% for the respective well-nourished and malnourished groups). The impact of nutritional status will be addressed in other ongoing trials.
1.7 Donor funding of health and immunization in developing countries

External funding for health, variously called development assistance for health, is one of the three main sources of health financing in developing countries, the other two being domestic public financing (taxation, user fees) and private financing (out-of-pocket payments, private insurance). The degree of external funding varies widely from country to country, with external sources as a proportion of all health expenditures accounting for as little as 1.2% in El Salvador to as much as 60.8% in the Solomon Islands in 2004 (World Health Organization, 2006b).

Almost without exception, however, immunization in developing countries has traditionally been heavily funded by external sources, due to immunization’s central role in public health and its established relative cost-effectiveness. Vaccines and other vaccine-related inputs (e.g. syringes, cold chain equipment) as well as operations support (e.g. training) and related health education have been priority items of assistance for donors. For the purpose of this thesis, donor funding is defined as a subset of external funding. It is distinguished from external funding in that it is a grant; it is not a loan or part of a debt-forgiveness programme. However, in referencing sources, the distinction may not be clear, as donors, governments and relevant international organizations that report external funding sometimes do not make this distinction themselves.

Donors in global health range from the purely public to the purely private, as shown in Figure 1 below.
Figure 1: Donors in Global Health

Bilateral donors are governments that provide government-to-government assistance, usually through a national agency such as CIDA, DFID or USAID. Multilateral donors consist mainly of the United Nations system, and include organizations such as the UNICEF and the WHO and the development banks (e.g. the World Bank, the Asian Development Bank). Country assessments to the United Nations fund the multilateral donors’ programmes while member dues and capital markets fund the development banks. In the past these bilateral and multilateral donors dominated the provision of global healthcare. Private commercial donors include pharmaceutical companies such as Merck, which provides Metizan™ to combat onchoceriasis
(river blindness) in Africa and Latin America. Private philanthropists are mainly foundations, among which the largest are the Rockefeller Foundation and the Bill and Melinda Gates Foundation. Non-government organizations include faith-based organizations, local grass-roots or community initiatives, and large international organizations like Rotary International, which concentrates in donating polio vaccine and Save the Children, which operates comprehensive child health programming.

While donors have in the past joined forces to share expertise or deliver various components of a particular project, the trend toward private-public partnerships in the health sector has resulted in even more combinations of the donors outlined. One of the most significant changes in DAH has been the formation of supranational global health funds that are comprised of the traditional important bilateral and multilateral donors, the largest private foundations and the largest multinational drug companies as well as institutional healthcare research and development institutes. Two of the most prominent of the global health funds are the GAVI Alliance and Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

Because external health funding is so important to developing countries, substantial changes in the funding environment have attracted the attention of development economists and political scientists. The environment is now characterized by a proliferation of private sector entities, such as foundations and non-profit organizations, various disease-specific funds and initiatives, and innovation in funding partnerships and mechanisms, all in about ten years. Globally, development assistance for health (DAH) rose from US$2.5 billion in 1990 to US$14 billion in 2005. The share provided by new partners like the Bill and Melinda Gates Foundation and the GAVI Alliance (also known simply as GAVI), operational only since the early 2000’s, accounted for almost 13% of the total in 2005 (World Bank, 2007). The Institute for Health Metrics and Evaluation (IHME) reported that as of 2007 DAH amounted to US$22 billion, with GAVI accounting for US$900 million (Institute for Health Metrics and Evaluation, 2010).

While successful in mobilizing large-scale resources and raising international awareness of relatively unknown problems, the narrow focus of some of the initiatives on specific diseases or disease groups (particularly the GFATM) as well as the magnitude of their funding and prominence of their activities raise questions of their influences on national health objectives and priorities, long-term financial and operational sustainability for the supported programmes.
and distortions of local resource allocation (Caines, 2005; Garrett, 2007; Schiffman, 2006; Waddington, 2004; Widdus, 2003). For example, during the expansion of funding between 1990 and 2005, the share of DAH allocated to primary health care dropped from 28% to 15% (World Bank, 2007). These are especially relevant concerns for the lowest income countries and the most donor-dependent health systems, such as Cambodia where donor expenditures were greater than government expenditures for health in 2003 (Michaud, 2005).

In the field of immunization, GAVI has become a major international coordinator of funds for new and continuing immunization efforts. On its board, it counts representatives from national governments, research and technical institutes, vaccine industry representatives from both industrialized and developing nations, civil society organizations, the Bill and Melinda Gates Foundation, WHO, Unicef, and the World Bank Group (GAVI Alliance, 2010a). GAVI receives donations from national governments and private foundations, with the largest contribution to date coming from the Bill and Melinda Gates Foundation. Since GAVI’s inception in 1991 to July 2010, the Foundation has contributed US$1.6 billion out of total cash donations of US$10.6 billion (GAVI Alliance, 2010b). Additional funds flow periodically to GAVI for re-disbursement from two other financing vehicles (GAVI Alliance, 2010a). The International Financing Facility for Immunization (IFFIm) raises funds through private investment markets for GAVI activities in developing countries and the Advance Market Commitment (AMC) programme funnels public and private contributions through GAVI to purchase future supplies of vaccines from vaccine manufacturers at a pre-agreed to price (Berndt et al., 2007; GAVI, 2010a).

As of December 2009 GAVI has disbursed US$2.2 billion to lowest-income countries in cash, vaccines and vaccine services support. The largest recipients have been Bangladesh (US$102 million), the Democratic Republic of Congo (US$140 million), Ethiopia (US$207 million), Kenya (US$128 million); Pakistan (US$195 million); Uganda (US$113 million) (GAVI Alliance, 2010c). A recent evaluation of the progress of immunization in Africa attributes the greatly improved coverage rates for all vaccines (but especially for DTP3) from 2001 to 2005 partly to the unprecedented support of GAVI and other donors. However, it also identifies a need for a longer-term approach for sustainable programming (Arevshatian et al., 2007). Despite
improvements in coverage, immunization will continue to be a priority for international assistance given the large burden of disease attributed to vaccine-preventable diseases (Brenzel, Wolfson, Fox-Rushby, Miller, & Halsey, 2006). Several new single and combination vaccines targeting developing countries are already in the R&D “pipeline”. Vaccines for dengue fever, meningitis, Japanese encephalitis, cholera, shigellosis, DPT-HepB-Hib-MenA/C are all in phase II or III trials as of 2006 (World Health Organization, 2006a). Funding required of GAVI and other donors for the vaccines most likely to be introduced in the period between 2004-2014 is projected to be a cumulated US$ 4 -18 billion (Peny, Gleizes, & Covilard, 2005).

1.8 Summary and conclusions

In this chapter the fundamental elements of CEA were laid out, highlighting the importance of the analytical perspective, the difference between financial and economic prices, and the definition and application of the outcome measure, the QALY. The use of CEAs is firmly integrated as a decision-making aid in the National Institute for Clinical Excellence, which guides medical practice in the United Kingdom. In Canada, CEAs are formally required for applications of drug inclusion in provincial formularies. While there is no formalized integration of CEA in American government agencies, there is nevertheless profuse generation of economic evaluation evidence. CEA has also been increasingly used in developing countries, given impetus by an emphasis on the economic aspects of health and healthcare by the World Bank and the WHO. The DALY, developed and supported by these organizations, has become the most commonly used outcome measure for CEAs set in developing countries. A variant method of CEA, generalized cost-effectiveness analysis, that aims to assist priority-setting among multiple intervention choices also distinguishes the practice of CEA in developing countries as opposed to that in industrialized countries. A focal point of CEA activities is the WHO-CHOICE project that provides data, technical and analytical support for the evaluation of healthcare projects globally, but especially for developing countries.

Issues pertaining to economic evaluation of pediatric immunization were also discussed. The controversy of constant and non-differential discounting of costs and effects has particular
relevance for preventative interventions administered in childhood, as the time span in which benefits could accrue is longer than for adults. The developmental characteristics of children also warrant special attention to the appropriate elicitation of preferences for outcome measurement. Almost all CEAs for child health in developing countries examine preventative interventions, most often immunization. Methodological deficiencies may not have been pertinent in the past when vaccine prices were exceedingly low compared to those in industrialized countries, but new and underutilized vaccines that are several times more expensive than the ones in current use have now been widely promoted. The cost of these vaccines, the global uncertainly of vaccine supply, and the need for additional resources to rapidly improve immunization coverage rates motivated the formation of the GAVI, which has been instrumental in mobilizing and channeling donor funds to the poorest developing nations to support immunization programmes.

Of relevance to this thesis, is the observation that the impact of issues of donor funding on CEA estimation has not been studied. For instance, the length of time of donor commitment for a certain programme has implications for the time horizon chosen for a CEA study and introduces uncertainty that might not be captured by the conventional variables tested in sensitivity analysis. As another example, GAVI indirectly influences the availability of vaccines from manufacturers through its pivotal role in the IFFIm and AMC initiatives. GAVI also influences the demand for vaccines through its assurance to eligible developing countries of funding stability. GAVI activities have an indirect, as yet unknown, impact on the eventual market price of vaccines and subsequent unit costs of immunization programmes. In theoretical terms the implications for cost-effectiveness analysis is that the opportunity cost that underlies valuation of the intervention becomes increasingly complicated to ascertain. In practical terms, decisions made without proper valuation and costing result in health programmes that are domestically unsustainable and that may improve health outcomes for some segments of the population at the expense of others.

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7 GAVI is also currently negotiating rotavirus vaccine prices on behalf of Vietnam. Personal communication of key informant.
CEA evidence is increasingly used to inform donor funding for immunization (Shepard, Walsh, Kleinau, Stansfield, & Bhalotra, 1995). A study on the cost-effectiveness of pneumococcal conjugate vaccine is a case in point. It was funded by GAVI, set in the countries eligible for GAVI support in 2005 and used GAVI-supplied cost data from those countries (Sinha, Levine, Knoll, Muhib, & Lieu, 2007). CEA’s role and contribution to the development of health systems in developing countries need more study, especially when multiple objectives motivate the analysis and when allocations of resources cross national boundaries as they do for immunization programmes. For developing countries a wider focus for CEA is not only relevant but also crucial, for allocations of resources for child health may have far-reaching positive impacts on economic growth through improved adult health and productivity (Belli, Bustreo, & Preker, 2005; Bloom, Canning, & Weston, 2005). Additionally, economically transitioning countries may find that decision-making tools developed in a stable, industrialized country context cannot adequately address the many unique issues resulting from rapid epidemiological, economic and social change.
CHAPTER TWO: RESEARCH QUESTION AND OBJECTIVES

As the demand for economic evidence to support wise health care decision-making grows, cost-effectiveness analysis is becoming increasingly important in both industrialized and developing countries. However, wider application of the mounting evidence produced by researchers and analysts in industrialized countries to developing countries is prevented not only by the lack of generalizability inherent in the technique, but also by an incomplete understanding of the context in which decision-makers in developing country health systems work. The shortcomings are accentuated when CEA is applied to pediatric immunization, for methodological issues concerning the pediatric population are still unresolved even in industrialized nation settings.

By incorporating an important element of the health system financing of the lowest income countries, substantial donor funding for fundamental health services, CEA might better serve local health objectives. The integration of additional, expensive vaccines such as rotavirus vaccine into the routine immunization schedule suggests that developing countries will continue to require donor assistance to procure supplies and increase operational capabilities and capacities. In order for developing countries to benefit from the current renaissance of the global vaccine industry to address their particular burdens of disease, continued substantial external assistance is required. Thus, not only governments deciding on sustainable interventions but also donors concerned with aid effectiveness may see a need for a CEA reference case incorporating donor funding issues such as vaccine uptake and financial sustainability.

Research Question: How can methods of cost-effectiveness analysis (CEA) of pediatric immunization programmes be improved for use in developing countries?

Research objectives:
1. To identify the methodological and practical limitations of conventional CEA when used in developing countries, particularly for pediatric interventions;
2. To identify guidelines and recommendations for CEA methodology and application specific to developing countries;
3. To identify the impacts of donor funding on the selection and estimation of costs, outcomes and the measurement of uncertainty for cost-effectiveness analysis;
4. To identify elements of the Washington Panel Reference Case that might be enhanced for better application in developing countries; and
5. To better understand the decision-making environment in developing countries.
3 CHAPTER THREE: METHODS AND DATA

The research methods comprise of a thematic analysis of a data set of multi-disciplinary literature and semi-structured key informant interviews. This chapter begins with a graphical depiction of the organization of the research project and the relationship of the research objectives to one another, below in Figure 2. A description of the thematic analysis follows in Section 3.1 starting with a definition of terms, rationale of the analytical approach, and a summary of the individual steps of the thematic analysis in Table 2.

Section 3.1 proceeds with a fuller description of each step of the thematic analysis. In Section 3.1.3 Step I is described, including the details for the literature search, formation of the Data Set for the thematic analysis and the development of a priori codes. The inclusion criteria for the Data Set are summarized in Table 4 and the a priori codes are set out in Table 5.

This section includes a description of the concepts motivated by the research objectives and which underlay the codes. A description of data extraction through coding of the Data Set (Step II) follows in Section 3.1.4. The decisions and choices made in coding the Data Set are explained here, including the questions used to query the Data Set while reading and coding. Step III, the development of themes, is described in Section 3.1.5. The capture of the themes and sub-themes and their synthesis is described in Section 3.1.6 and the matching of the themes to the relevant sections of the Washington Panel Reference Case is described in Section 3.1.7.

The last section of this chapter, Section 3.2, is devoted to the Key Informant Interviews. The key informant sampling method is laid out and processes of interviewing and data analysis are detailed.
Figure 2: Research Objectives and Study Flow

Objective 1
Identify limitations of CEA

Objective 2
Identify guidelines

Objective 3
Identify funding impacts

Objective 4
Identify enhancements of the WPRC

Objective 5
Understand the decision-making environment in developing countries

Focus of thematic analysis
3.1 Thematic analysis (Objectives 1-4)

3.1.1 Overview and definitions

To reach Objectives 1 to 3 thematic analysis was employed, an analytical method often used in qualitative research. There are varying perspectives and a richness of approaches among qualitative researchers in regards to the application of methods and techniques, often with overlapping processes and similarities in terms. An uncomplicated version of thematic analysis as described by Braun and Clarke (2006) is used in this thesis, and the data is defined as follows:

- Data Set – the selected body of documents culled from the literature search
- Data Item – the individual papers, reports, chapters, documents forming the Data Set
- Data Extract – a coded portion of a Data Item that expresses an idea of interest to the research question
- Theme – a synthesis of ideas revealed by examination of and reflection on the Data Extracts

3.1.2 Analytical approach

Thematic analysis is distinguished by its accessibility to researchers and its theoretical flexibility (Braun & Clarke, 2006). That is, it is not bound by rigidly applied techniques and is not necessarily operationalized from a theoretical position. However, it employs processes similar to other qualitative methods that searches for and describes patterns: reading, coding, data reduction, and synthesis. In this thesis it is distinguished from other methods by adhering to the clear definition and process described by Braun and Clarke, who acknowledge that it has been a poorly demarcated although widely used method. Its strength is that it is extremely flexible and can be applied to a large diversity of data and in a widely varying analytical depth. Its weakness is that, being poorly demarcated, its application can be haphazard. In this thesis, thematic analysis was applied in as deliberate, consistent and systematic a manner as possible.
Assumptions, guiding analytical questions and decision process are discussed below to allow the reader to assess the rigour with which the themes were developed.

A theme, according to Braun and Clark, “captures something important about the data in relation to the research question, and represents some level of patterned (italics theirs) response or meaning within the data set” (Braun & Clarke, 2006, p. 82). Understanding and constructing themes is an iterative and dynamic process of analysis that summarizes the “informational content” of the data (Crabtree & Miller, 1992).

In this thesis more emphasis was placed on the informational content than on the meaning of the data. Our organization and description of the data and themes could also be termed “systematic qualitative description”, following Sandelowski (2000). This approach does not strive for in-depth interpretation, but stays close to the surface meaning of the data. According to Sandelowski, fundamental qualitative description is less interpretative than some other qualitative approaches such as grounded theory, phenomenology or ethnography, but is nevertheless more interpretative than quantitative description. This approach was considered the most appropriate to answer the research questions for the following reasons: 1) the documents selected are mainly of a technical nature and do not require substantial interpretation 2) the breadth of the inquiry required a synthesis of broad themes and a comprehensive summary 3) the answers to the research questions have a practical purpose, having particular relevance to practitioners of CEA and to policy makers, and therefore do not require re-representation in terms of other abstract ideas, theories or systems of thought and 4) much of the text examined was based on or derived from quantitative information.

Braun and Clarke (2006, p. 87) outline the phases of thematic analysis as follows:

   Phase 1: Familiarizing yourself with your data
   Phase 2: Generating initial codes
   Phase 3: Searching for themes
   Phase 4: Reviewing the themes
   Phase 5: Defining and naming themes
   Phase 6: Producing the report
Following this guideline, the following steps shown in Table 2 were taken in the thematic analysis. Braun and Clark’s Phases 1 and 2 were collapsed into the first step, as, from the preliminary literature search done to refine the research question, some themes had already started to emerge. It is important to note that Steps II, III, and IV are iterative and repetitive.

**Table 2: Steps of Thematic Analysis**

<table>
<thead>
<tr>
<th>STEP</th>
<th>DESCRIPTION</th>
<th>KEY OBJECTIVE</th>
<th>MAIN OUTPUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step I – Anticipatory Data Reduction</td>
<td>Develop <em>a priori</em> codes; broadly scan Data Set for exclusions; categorize Data Items according to research objective; summarize Data Items; flagging influential data; note ideas and concepts for code development</td>
<td>Establish pathways to address research question and operationalize research objectives</td>
<td>Data Set and <em>a priori</em> codes</td>
</tr>
<tr>
<td>Step II – Data Extraction</td>
<td>Read Data Items, identify relevant Data Extracts with <em>a priori</em> codes; identify other, non-anticipated Data Extracts</td>
<td>Identify and assemble Data Extracts</td>
<td>Code structure and definitions</td>
</tr>
<tr>
<td>Step III - Development of Candidate Themes</td>
<td>Collate coded Data Extracts, look for patterns within and between categories of Data Items</td>
<td>Identify patterns and relationships of Data Extracts</td>
<td>Collation table of Data Extracts and identified themes and sub-themes</td>
</tr>
<tr>
<td>Step IV – Synthesis and Review of Themes</td>
<td>Check thematic consistency, between categories and between sub-themes to major themes.</td>
<td>Confirm validity of themes</td>
<td>Thematic maps of relationships and reviews</td>
</tr>
<tr>
<td>Step V – Mapping of themes to Reference Case</td>
<td>Relate themes and sub-themes to specific recommendations</td>
<td>Extend theoretical framework</td>
<td>Identified areas of discussion for enhancing WPRC</td>
</tr>
</tbody>
</table>
3.1.3 **Step I - Anticipatory data reduction**

The activity in Step I is called “Anticipatory Data Reduction” following Miles and Huberman (1994), as it is a better description than Braun and Clarke’s “Familiarizing yourself with your data” (2006). This step was composed of scanning all the retrieved literature to cull for a Data Set and to develop *a priori* codes.

**ESTABLISHING A DATA SET**

The Data Set for analysis was established through a literature search, selection of potentially relevant papers through abstract review, and then selection of a final Data Set through reviews of the full papers.

In the literature search a purposeful technique, maximum variation sampling, was employed to obtain as broad a selection of documents as possible from diverse sources.

The following data sources were used:

1. Multi-level search of major broad-based databases: EconLit, EconPapers, International Bibliographies of the Social Sciences, Medline, Popline, Embase, the Cochrane Library, CINAHL

3. Published guidelines for cost-effectiveness analysis: formal guidelines from organizations specialized in CEA and health technology assessment (the Canadian Agency for Drugs and Technology (CADTH), National Institute for Clinical Excellence (NICE), British Medical Journal Economic Evaluation Working Party); from the World Health Organization; for journal authors and reviewers; reviews and comparisons of guidelines, with reference to developing countries

4. Published guidelines for model-based study designs authored by individuals or organizations having global reach (e.g. the International Society for Pharmacoconomics and Outcomes Research (ISPOR))

5. Websites and publication repositories of relevant international organizations concerned with global and/or child health: WHO/Pan American Health Organization, UNICEF, World Bank Group, Canadian International Development Agency (CIDA), International Development Research Centre (Canada) (IDRC), United States Agency for International Development (USAID), UK Department for International Development (DFID), Rockefeller Foundation, Albert B. Sabin Vaccine Institute, Global Alliance for Vaccines and Immunizations, Roll Back Malaria, Multi-Country Evaluation of Integrated Management of Childhood Illness (multiple organizations)

6. Websites and publication repositories of relevant research and policy institutes: CADTH, NICE, Centre for Global Development (Washington, DC), London School of Hygiene and Tropical Medicine, University of York (Center for Health Economics)

7. Hand searches from references of publications

Although the publications of categories 4-6 may not be peer-reviewed, to have omitted them would have been a loss of rich information, as these sources are the main actors in the field of
global child health and the development and application of economic techniques for developing countries.

All databases were predominantly searched electronically, through both protocol and non-protocol methods as summarized below in Table 3.

**Table 3: Databases Search Methods**

<table>
<thead>
<tr>
<th>SEARCH ENGINE</th>
<th>DATABASE</th>
<th>SEARCH BY</th>
</tr>
</thead>
<tbody>
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<td>Ovid</td>
<td>Major Medical (Medline, Embase, CINHAL, IPA)</td>
<td>MeSH terms, Emtree terms, keywords</td>
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<tr>
<td>Ovid</td>
<td>Cochrane</td>
<td>Key words</td>
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<tr>
<td>CRD proprietary</td>
<td>NHS-EED, DARE, HTA</td>
<td>MeSH terms</td>
</tr>
<tr>
<td>Scholar’s Portal</td>
<td>EconLit, Social Science Abstracts</td>
<td>Key words</td>
</tr>
<tr>
<td></td>
<td>LILACS – Latin American and Caribbean Health research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SciELO (Scientific Electronic Library Online) focus on developing countries</td>
<td></td>
</tr>
<tr>
<td>Hand (paper and electronic)</td>
<td>References (including references of references), websites of umbrella and individual organizations (e.g. policy.com, CEARegistry.com); personal contacts</td>
<td>Key words, various</td>
</tr>
</tbody>
</table>

Appendix 4 lists the controlled vocabulary used for the major medical databases, the Centre for Reviews and Dissemination Databases, and the EconLit database. They include MeSH and Emtree search terms as well as the English thesaurus terms for EconLit. Samples of the search
strategies are included in Appendix 5. The protocol-based strategy was developed with assistance from the head librarian at the library of the Hospital for Sick Children in Toronto.

Limits for the search of the medical databases were: Full-text; 1950-2007; Humans 0-18 years; English-language. A second search of the medical databases by key words was also necessary to capture the following relevant concepts for which there are no subject headings: preference valuation, benefit incidence analysis, risk analysis, risk-adjusted discounting, priority setting, vaccine market, vaccine economics, and health financing. Then a third search combining the most productive MeSH-based search with a Boolean connector to the most productive key words was subsequently conducted. In two latter searches the search period was shortened to 1970-2007 from the initial search of 1950-2007. It was decided after the initial search that papers prior to 1970 were not relevant in respect to this thesis as cost-effectiveness analysis was really only in its infancy then.

The protocol-based search yielded 900 abstract and citations. An Ovid Auto-Alert for Medline was also maintained until December 31, 2008; 26 new abstracts were generated from this period.

Because of the complexity and interdisciplinary nature of the research question, a significant portion of the literature search depended on non-protocol searches. This included keyword searching of grey literature databases (e.g. World Health Organization publication databases) and a manual searching in a “snowball” approach (references of references). The limits of the keyword searches were the same as for the protocol searches, i.e. Full-text; 1970-2007; Humans 0-18 years; English-language. This search yielded 148 more abstracts and citations. For questions of a broad nature like the research question of this thesis, a snowball approach can yield substantially more sources, more efficiently and more effectively than a strictly protocol-based approach, according to Greenhalgh and Peacock (2005). The manual-search took place after promising publications were downloaded or references from search engines were exported. This search yielded 11 more distinct abstract and citations.

In total, the protocol-based and non-protocol searches yielded 1084 abstracts and citations.
All abstracts and citations, including those from grey literature, were imported or hand-entered into EndNote X1, which was used to store, manage and annotate all the literature used in this thesis. An initial quick check of abstracts eliminated duplicates (including those missed by the automatic function because of variations in citation formatting by the various data vendors) and those that clearly had little relevance to the research question (e.g. rabies vaccine research for developing countries). The remaining abstracts were scanned for confirm conformity with the research question and Research Objectives 1 to 3. Promising full texts were downloaded and then re-checked for inclusion criteria. Table 4 below details the inclusion criteria.

The reader is first reminded of the relevant objectives pertaining to the Data Set selection:

Objective 1: Identify imitations of CEA for developing countries
Objective 2: Identify CEA guidelines for developing countries
Objective 3: Identify potential donor funding impacts on CEA estimation
<table>
<thead>
<tr>
<th>Objective</th>
<th>Broad concept</th>
<th>Narrow concepts – Inclusion Criteria</th>
</tr>
</thead>
</table>
| Objective 1 | CEA methodology | Mention of developing country (either individual country or developing countries as a whole) +  
- Mention of any CEA challenges  
- Mention of CEA methodology  
- Mention of CEA immunization  
- Mention of CEA generalizability  
- Rotavirus immunization  

CEA application | Mention of developing country (either individual country or developing countries as a whole) +  
- CEA for policy-making  
- CEA for decision-making  
- Rotavirus immunization |
| Objective 2 | CEA guidelines | Mention of developing country (either individual country or developing countries as a whole) +  
- Immunization specific guidelines  
- Costing guidelines  
- Public health programming guidelines  
- CEA guidelines developed for aspects of developing countries health systems  
- CEA guidelines claiming to have global application  

CEA guidelines | Editorial guidelines for publishing CEAs pertaining to  
- Costing  
- Discounting  
- Uncertainty  

Guidelines from major government CEA/HTA agencies pertaining to  
- Costing  
- Discounting  
- Uncertainty |
| Objective 3 | Donor funding | Mention of developing country (either individual country or developing countries as a whole) +  
- Donor fund/financing of immunization  
- Donor fund/financing of vaccines  
- Donor funding successes/problems in |

46
In total, 157 full texts (journal articles, working papers, book chapters, reports, editorials) were designated as the Data Set. The individual texts are termed data items in this thesis, and they are listed in Appendix 7: Data Set.

**DEVELOPING CODES**

In coding the data items in our Data Set, that is, systematically identifying, marking and naming relevant concepts and ideas, a start was made with an *a priori* list. Miles and Huberman (1994) calls this a “provisional “start list” …. [that] comes from the conceptual framework, list of research questions, hypotheses, problem areas, and/or key variable that the researcher brings to study,” (Miles & Huberman, 1994, p. 58). This directed approach was taken because its main strength is to extend theoretical frameworks, rather than to develop new theories (Hsieh & Shannon, 2005). In this thesis the *a priori* list was largely developed through the preliminary literature review for the development of the research question and objectives. The concepts that underlie the *a priori* codes are described below.

- **Objective 1**: To identify the methodological and practical limitations of conventional CEA when used in developing countries, particularly for pediatric interventions

The concepts included:

CEA methods, transferability, generalizability, international prices, costing of non-traded goods, data availability, appropriate expression of preferences, appropriate discounting rates, time horizons, value to decision-makers, barriers to use in developing countries, technical efficiency vs. allocative efficiency, issues of children’s developmental stage, ethical issues in regards to children
• **Objective 2:** To identify guidelines and recommendations for CEA methodology and application specific to developing countries

The concepts include:

Guideline development and appropriateness for developing countries, specific guidelines/recommendations for developing countries, developing countries practice/use of evidence

• **Objective 3:** To identify the impacts of donor funding on the selection and estimation of costs and the measurement of uncertainty for cost-effectiveness analysis

The concepts include:

Health financing strategies for developing countries, financial sustainability of donor-supported programmes, impact of aid on health, trends in donor funding (amount and area), health budgeting risks, health accounts, effectiveness of health aid, economic evaluation of health aid, vaccine economics, costing of vaccine and vaccine-related products, adjustments for uncertainty, sensitivity analysis, risk adjustments, GAVI funding and programming, priority-setting and decision-making

The *a priori* codes were very descriptive, directly representing the concepts of the research objectives. At the broadest level, and used on the first scan of the data items, they served to categorize the data items into the three groups that represented the main concepts of the objectives themselves (LIMIT, GUIDE, FUND). The other *a priori* codes represented concepts that were related to these main concepts. Below, Table 5 lists these *a priori* codes.
An independent researcher was asked to code two data items using this set of *a priori*. The researcher was also given the research objectives with their relevant concepts, as described above, and asked to suggest other codes that might be useful in capturing these concepts as he read the data items. There was high agreement (87%) with the coding that was performed by this author with the same two data items, but that was not unexpected as the codes represented very little latent meaning. Nevertheless, the independent researcher was able to help point out where more clarity was required in creating code names and in subdividing larger concepts into logical sub-concepts.

These changes were eventually augmented with additional codes that captured concepts that were deemed relevant. Some of the *a priori* codes were also modified or deleted when they proved unimportant (dead ends, less relevant) in subsequent analysis. The final set of codes is included in Appendix 6.

Data items were first scanned and flagged with the above three codes to sort and categorize into the three main groups corresponding with the objectives and by extension, the main concept groups. For data items with abstracts (like journal articles) or clear introductory sections, these
sections were also read and relevant data extracts (segments of text) were identified (i.e. highlighted with marker) with the *a priori* codes. After all the data items were sorted into three groups, data items were then re-read, group by group, and coded by hand, with codes that emerged from the reading noted directly on front page of the data item. Data items were also briefly summarized for pertinent information, remarks and observations. Additionally, as reading and coding proceeded, memos were made as themes (recurrent patterns of concepts) were noted.

The codes pertaining to each data item were stored in a customized field of the data items’ bibliographic information through the reference manager EndNote X1. Additional fields were used to record salient points and research notes. These fields were manipulated to manage the information as thematic analysis proceeded. A bibliographic style was customized to allow the viewing and printing of research notes.

The thematic analysis was conducted by reading, writing and reviewing memo notes, re-examining data extracts (coded portions of texts), and reflecting. This occurred iteratively. In the next three sections some of the underlying process is explained.

### 3.1.4 Step II – Data extraction

Our approach to data extraction through coding is “theory-driven” (Braun & Clarke, 2006), being highly influenced by specific questions already in mind. Thus, only for a limited amount of the data content was coded, only enough to capture the question in mind. The reader is reminded that coding sought to identify the “semantic content” (Braun & Clarke, 2006, p. 88) of the Data Set, and not to search for “latent”, or underlying, meaning. In this section some of the decision-making and the choices made in coding the data items, the individual documents making up the Data Set, are described. The initial assumption is that all data items were equally important.
CATEGORIZATION OF DATA SET

The Data Set was sorted into three groups corresponding to the three first research objectives. These three groups formed the initial grouping of data items and remained the top thematic level since they embodied the concepts that guided the deductive analysis. However, as coding and re-coding proceeded, some of the sorted data items were judged to also offer insights into the questions raised by the other research objectives and so were then reassigned or put into two or all groups. Thus the groupings of the Data Set overlap. The relationship is shown in the Results chapter below.

CODING – IDENTIFYING DATA EXTRACTS

Coding is part of the process of analysis (Miles & Huberman, 1994), serving to organize the data into meaningful units for description and interpretation. In iterations of coding the units can be broken up, rearranged, or reassigned with other codes. It is subject to the judgment of the researcher, but is not haphazard. Below the questions that guided the decisions for whether a piece of text should be coded, that is, be included as a data extract, are outlined.

Objective 1 – Identifying limitations of CEA for developing countries

This group of data items relating to methodological limitations is the largest and it was the first coded. Many of these data items do not have developing countries as their main focus, but were chosen because they mentioned developing countries or explicitly purported to speak to the methodological issues on a global basis. It is important to note that the observations gained from coding of data items in this group gave shape to subsequent, additional questions that informed the coding of the other two groups of data items (guidelines and donor funding).

Within this group, sub-groups were formed, reflecting a categorization, re-organization, collation or emergence of sub-themes. These groups thus represent an intermediate step of analysis.

a. Main methodological issues in CEA
Some of the questions that informed the coding (the selection of text to code, the assignment of the code name, the revision of codes) of this sub-group were:

- Does “cost” refer to opportunity or financial cost?
- Does “costing” refer to valuation (assigning an opportunity cost) or to gathering average financial costs?
- Is the DALY discussed as the original or adjusted (post-2003) formulation?
- What is the relevance of the issue to developing countries?

b. Main methodological issues in CEA of communicable diseases

The data items in this sub-group were selected because they included diseases with relatively heavy burdens of mortality and morbidity in developing countries, were prevalent in children and were vaccine preventable. Because of the dominance of HIV/AIDS in recent global health research and funding efforts, some of the data items with this focus were included if there was significant discussion of CEA methodology. Some of the questions that guided the coding of the Data Items were:

- If the disease focus is HIV/AIDS, were methodological aspects being presented in common with diseases of more traditional focus (e.g. measles)?
- Are the methodological issues mentioned common to all communicable diseases?
  - If not, are they common to communicable diseases prevalent in developing countries?

c. Main methodological issues in CEA of immunization

Many of the data items in Group (c) were also placed in Group (b) above, but had as their main focus immunization rather than other preventative interventions such as sanitation and health education. Some of the questions that guided the coding were:

- Are discussed issues unique to vaccine-preventable diseases or common to communicable diseases?
• Is this disease treated by routine immunization in the developing world? (e.g. varicella is not included in routine immunization, but the vaccine is privately and widely available)
• Is this a disease of current interest to donors? (for cross-referencing to Objective 3)

d. Main methodological issues in pediatric economic evaluations

These Data Items included discussions on general considerations of age, including age-weighting, as well as specific issues for pediatric immunization. The questions used in coding included:
• Are discussed issues relevant for children of developing countries?
• How are these issues different for children under 5 years old?

e. Development of generalized CEA for developing countries

These data items concern an alternative technique of CEA that is by its authors’ definition a correction of some of the larger methodological problems for developing countries (Tan-Torres Edejer et al., 2003). Therefore, there is explicit mention of limitations. The coding questions pertaining to this sub-set of data items, which are all written by the same authors of the technique, relate to the generalizability of the mentioned issues.
• How important are the limitations to the authors?
• Are these limitations also mentioned by other researchers?
• How have other researchers dealt with the same limitations?

f. Issues of developing country health sectors (epidemiological/economic situations, health system structures)

This set of data items relates to the setting in which the cost and effectiveness of interventions might be calculated. The questions informing the coding reflected the constraints that might affect the effectiveness of an intervention, regardless of the measure used.
• What kind of health system is discussed? Universal coverage, public/private mix?
- What factors are important to health care costs/effectiveness? (income level, geographic location, clinical practices (e.g. immunization scheduling)?)
- What factors (e.g. preferences, values, data availability) are important to calculation of the QALY, DALY?

g. Adjustments made in CEA to accommodate local, developing country contexts

The Data Items in this sub-group provide explicit suggestions or examples for adjustments (mostly for costing) made for the developing world context, even if there is no explicit discussion of methodological issues. Some of the questions guiding the coding include:
  - Are these ad-hoc adjustments or have other analysts made the same adjustments?
  - What is the rationale for the adjustment?
  - Are these adjustments discussed in the Washington Panel reference case as alternative techniques?

h. Direct identification of main methodological issues in CEA for LMICs

These were the most straightforward data items to code, as the authors explicitly identify methodological issues. Although coding required fewer auxiliary questions, a few questions guided the relevance of the data extract.
  - Are these issues still current? Are they now resolved? If so, how?
  - Are they issues related to the quality of the CEA conducted rather than to the methodology?

**Objective 2 – Identifying CEA guidelines for developing countries**

Coding was very straightforward as content that was explicitly identified by the author(s) as being relevant to developing countries was sought. To guide coding, the following questions were applied:
  - If not targeted directly at developing countries, are the guidelines globally applicable?
• Is the topic area generally relevant to most types of health care systems?

**Objective 3 – Identifying donor funding impacts for CEA estimation**

This group was the most diverse in nature, from editorials to research articles to large-scale reports. A large portion of these data items was grey literature. Because donor funding is not an issue currently discussed within the cost-effectiveness literature, these data items were coded more for latent meaning than in the other sub-groups. Some of the questions used to decide on inclusion of data extracts were:

• Are the donors globally important? (i.e. not local groups or private individuals)
• Is the donor funding for vaccine and immunization interventions?
• What factors affect the financial sustainability of supported intervention?
• What is the funding impact on costing of vaccines and vaccine-related items?
• Is the vaccine under consideration a current, underutilized vaccine in developing countries? Is it a new vaccine targeted at developing countries?
• What is the disease burden of the vaccine target?
• What types of uncertainty are mentioned? How are they measured? How is the uncertainty treated to make it less uncertain?

3.1.5 **Step III – Development of candidate themes**

The *a priori* codes generated from a preliminary literature review established a basis upon which to start extracting information from the finalized Data Set. As the search for themes progressed through coding and review, the initial list was expanded and sub-divided to capture unanticipated themes and finer detail, and some individual codes were eliminated as they became irrelevant or were combined with others. They remained broadly defined by the first three research objectives, but several codes bridged the three categories, capturing ideas that cut across two or more objectives.
Codes for Objective 1 (Identifying Limitations of CEA for developing countries) initially represented the standard methodological elements of cost-effectiveness analysis. In the course of the analysis, and especially iterative review resulting from reading in other categories of the dataset and conducting the key informant interviews, it was apparent that reporting, generalizability and the use of CEA were also very important to developing countries, so codes were added to reflect these ideas. In the methodological elements it was felt that saturation was reached fairly quickly, that is, a smaller data set of papers may have sufficed in producing the same concepts. The main result of the initial coding was a sifting of the methodological issues mentioned in the Data Set to find the ones most relevant to the application of CEA to new vaccine introduction in developing countries, particularly rotavirus vaccines.

While codes for Objective 1 attempted to organize, capture and represent ideas, the codes for Objective 2 (Identifying CEA guidelines for developing countries) were used mainly to categorize the types of guidelines in the dataset and to locate specific elements that were considered most important to developing countries in the context of introducing new vaccines. Some of these elements were previously identified by the coding done for Objective 1, such as the methodological issues of herd immunity and the valuation of productivity. The main result of this analysis was to identify some perceived gaps in guidelines that were relevant to developing countries.

The development of codes in Objective 3 (Identifying donor funding impacts on CEA estimation) was influenced by the preceding development of codes in the other two objectives. One of the main results of this analysis was thus the prioritizing of themes. For example, time elements of donor funding became very important given the corresponding importance of temporal attribution of costs and benefits in the project life of immunization interventions.

It should be re-stated that the development of the final codes was iterative. The initially coded data extracts were organized into meaningful groups to check for patterns of ideas and to see how combinations of ideas might yield themes. Although the first pass of coding proceeded in order through the three objectives above, review, refining and reorganization of the coding, and the information they represented, occurred as new ideas occurred, linkages became apparent,
and the information from the key informant interviews became available. Recording codes through EndNote allowed the retrieval of research notes and also the re-grouping of concepts at the data item level. The Subject Bibliography function was used to regroup by items and to organize research notes.

Coding was adjusted in this period. Some data items were referred to multiple times to re-check the text surrounding the extract for semantic confirmation, especially for methodological limitations dependent on theoretical frameworks and on funding issues that were also related to larger issues of foreign aid. A start to gauge the importance of some of the data items was made at this point, using prevalence of themes as the main measure along with weight of theme. That is, a data item was more important if it contained a multiplicity of data extracts that contributed to developing patterns of ideas or if it discussed ideas in detail. Data items that were considered important were grouped as key papers.

Pattern codes to identify groupings of ideas were developed. These pattern codes were recorded in a term list in the “label” field and attached to the bibliographic reference of the data item containing the codes giving rise to the pattern code. This allowed for identification of data items by pattern code to check for fit. It should be noted that rechecking was done by hand, and proved to be time-consuming as no software (e.g. NVivo) was used. Summarization of data extracts (in point form) was done and recorded in the “research notes” field to allow easier retrieval.

When satisfied with the fit of the pattern codes to the content, the summarized data extracts were assembled in Excel spreadsheets by pattern code.

3.1.6 Step IV – Synthesis and review of themes

In Step IV the candidate themes and sub-themes were reviewed in order to refine them and ensure their validity, guided by Patton’s (1990) concepts (as reported in Braun and Clarke, p. 91) of internal homogeneity and external heterogeneity as criteria. That is, it was confirmed that
the data within the themes formed coherent patterns and that the individual themes were distinct. This review entailed a re-reading of the data items that were considered key papers and revision or renaming of pattern codes. Reflections on the themes identified by the pattern codes and their relationships were aided by the writing of more memos (and consultation of initial memos). All memos were stored in a binder that allowed easy retrieval and reorganization for re-writing.

**3.1.7 Step V – Relating themes to Washington Panel Reference Case (Objective 4)**

This step was the culmination of the thematic analysis. It was comprised of summarizing the large themes, re-examining the WPRC, and identifying which elements might be enhanced for developing countries. A considerable amount of time was spent in reflecting and reviewing of notes and rewriting. It was found that lack of a more sophisticated retrieval system (i.e. an electronic system) of codes, research notes and reorganization of materials hampered efficient progress.

**3.2 Key informant interviews (Objective 5)**

The purpose of the key informant interviews was to provide insights into the immunization decision- and policy- making environment in selected developing countries, particularly in regards to the use of evidence. The interviews supplement the thematic analysis in understanding the actual, potential and appropriate role for cost-effectiveness analysis and, therefore, also in understanding the applicability of an enhanced reference case. The interviews also helped to inform the development of the enhanced reference case as they occurred concurrently with the thematic analysis of the document Data Set. There was no assumption that economic evidence was used for decision-making, and in order not to bias the discussion, interviewees were not directly asked about economic evaluation nor were they expected to discuss it despite its active use by some of the key informants.
A pilot interview had been conducted face-to-face with a peer researcher to refine the questions and interview techniques, especially to gain experience in formulating and asking probe questions. The pilot interviewee had previously worked in a developing country, but had not taken part in decision or policy-making there. Most valuably, she drew on personal experience in conducting interviews and provided useful feedback and advice.

Thirteen candidates were invited to participate in the key informant interviews. One candidate declined, citing unsuitability, although she recommended a colleague who assented. Two candidates agreed to being interviewed, but scheduling conflicts proved impossible to overcome and they eventually did not participate. Eleven interviews were completed, nine by telephone and two in person.

The recruitment and interviewing of the key informants took place over the course of 18 months, mostly concentrated over 13 months. Nine of the interviews were conducted by Internet-based phone from Shanghai, China and Toronto, Canada to Ottawa, Boston, Cambridge, Chandigargh (India), Hanoi, Bangkok, Shanghai, Beijing, and Seoul. The two face-to-face interviews were conducted in Beijing and Toronto.

The transcripts were read together with the recordings to ensure accuracy and completeness. There were a significant but acceptable number of errors resulting from misunderstanding of non-standard vocabulary (e.g. non-English proper nouns, acronyms, technical terms) and of misunderstanding arising from accents. There was also a significant amount of missing data due to narrow bandwidth and sometimes-intermittent transmission of data over the Internet in China. In most cases the gaps were easily filled in by context and from memory or supplementary notes, but in particularly poor recordings where the key informant was also in a country with poorer Internet service or were using their cellular phone, there remain small unintelligible segments. The meaning can nevertheless be inferred from context.

The key informants were global health experts who may not be familiar with CEA, but who, in offering their opinions and experiences in regards pediatric immunization decision-making
evidences, could give insights into the potential role of economic evidence. As suggested by Marshall (1996), considerations for 1) role in community 2) knowledge 3) willingness 4) communicability and 5) impartiality guided sampling of key informants. A purposeful 2-stage sampling approach was used to select the participants. In Stage 1 potential candidates according to the criteria set out below were predominantly identified by two methods: authorship of articles pertaining to the research topic of this thesis and discussion with peer researchers in the same discipline. The potential candidates were approached by telephone, email and in person to participate. They were also asked to recommend further contacts and referrals (a “snowball” approach). In Stage 2 the secondary contacts were approached. The target number of interviewees was twelve.

The criteria for including the key informants were:

- They should have worked in the health sector
- They should have knowledge based on professional experience in regards to decision-making for immunization/and or vaccines.
- They should be English-speaking.
- They should have professional experience in one or more developing countries.

The key informants were sought from the following professions/roles:

- Developing country health services researcher
- Health financing researcher
- Multilateral funder, technical agency (health financing and immunization focus)
- Bilateral funder, technical agency
- Private funder, technical agency
- Developing country health ministry/authority
- International immunization initiatives
- Pharmaceutical/Pharmacoeconomist in developing country
- Health ministry personnel in developing country

Questions for a semi-structured interview were tested in a pilot interview with a peer researcher. Adjustments were made to shorten the number of questions from twelve to ten and question
themes and wording were refined. Possible probe questions were also developed. The questions followed the themes below:

- Respondent background and expertise
- Process aspects of pediatric immunization decision-making in developing countries
- Factors that influence pediatric immunization decision-making
- Informational inputs into the pediatric immunization decision-making process
- Actors in pediatric immunization decision-making and their relationship to one another
- Uncertainties of pediatric immunization decision-making in developing countries
- Trends in pediatric immunization decision-making in developing countries
- Own recommendations for improving pediatric immunization decision-making

First stage candidate key informants were invited by telephone to participate, except in the two cases where the contact information obtained was an email address. In these two cases a brief email was sent to ask if they might be contacted by phone to discuss possible participation. Both agreed. A participant, who was a referral herself, made two further referrals at a conference attended by the participant and author. They were invited in person to participate, and they also agreed. Another referral was contacted first by email, followed by an explanatory phone call. After agreement for participation was obtained, participants were sent a package including a cover letter, research study and audio-recording consent forms, as well as an interview guide. The cover letter is included in Appendix 8, the research consent form in Appendix 9, the audio consent form in Appendix 10, and the interview guide in Appendix 11. All interviews were conducted in English. Those conducted by telephone were recorded directly into the computer via Skype Call Recorder, and the two interviews conducted in person were recorded by a portable digital recorder.

Contact sheets were maintained to record the respondents’ address/phone/email information, the date of invitation, the date the information package was sent, the date of interview, the date of follow-up and any further relevant comments. The interviews were audio-taped and sparse note-taking of important points were made by hand during the interviews to capture emphasis or direct a subsequent part of the interview. However, note-taking was not relied upon for data-collection. Notes were appended to each respondent’s transcript records. A professional
transcriptionist transcribed all recorded interviews, verbatim, except one. The exception was transcribed by this author, as the sound quality and accent of the speaker made for a poor recording, and the required additional, extensive work by a contracted transcriber would have been beyond the transcription budget for this study.

To ensure accuracy each transcript was checked twice against the relevant recording, and errors and omissions were corrected. Hesitations, laughs, tonal quality, and speech overlaps between interviewer and key informant were noted in the margins in case they affected interpretation. During accuracy-checking reflections and questions on the interview and the key informant’s meanings were also recorded as margin notes. These margin notes were later incorporated into analysis memos, mentioned below.

A summary-aided approach to analysis was used. Miles and Huberman (1994) described this in the context of case analysis where field notes are summarized, coded, and drawn upon to write up results. In this thesis the summaries were not coded. Three passes of summarization were made, each time reducing the information further. Each corrected transcript was paraphrased into narrative summaries, removing non-relevant data (e.g. personal communication between interviewer and interviewee, off-topic discussion), collating similar thoughts and ideas (e.g. expressed when key informants thought of additional points further on in the interview), and reorganizing the information to highlight relevant information. The interviews were then listened to again, and immediately after each recording was finished, the paraphrased summaries were checked for faithful representation of the key informant’s meaning. Memos were made for each interview of the themes discussed and interesting insights presented. The memos, incorporating margin notes from the transcripts, were drawn upon when preparing a second round of shorter summaries. The short summaries highlighted the information that was the most salient to the research question and research objectives of this thesis. Short summaries were rechecked against the corrected full transcripts to see if there were overlooked points and to maintain accuracy of meaning. Finally, a third level of summarization was made to isolate the most pertinent points and most illuminating quotations for each key informant, by question. This most distilled level of data from the key informants was organized in an Excel spreadsheet. The spreadsheet was also used as a memory aid in retrieving the relevant transcript as writing
proceeded since constant referrals were also made to the transcripts and memos to refine the analysis and to satisfy the fit of the themes to the data.
4 CHAPTER FOUR: RESULTS

In this chapter Section 4.1 presents the framing elements that motivated and informed the results: the Data Set, the final codes used for the data extraction and the assumptions that underlay the analysis. In Sections 4.2 – 4.4 the results of the thematic analysis that fulfills Objectives 1-3 (Respectively, Identification of Methodological Limitations, Guidelines and Donor Funding Impacts, all for CEAs in LMICs) are presented. The culminating proposed enhancements of the Washington Panel Reference Case that fulfills Objective 4 (Section 4.5) follow, and the findings of the Key Informant Interviews (Objective 5 – Section 4.6) finish this chapter.

4.1 Framing elements of the analysis

4.1.1 Description of Data Set

The Data Set search and the initial coding process were described in Chapter 3.1. Below, Table 6 describes the characteristics of the Data Set.

Table 6: Description of Data Set

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of documents</th>
<th>Types of documents</th>
<th>Span of publication dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>85</td>
<td>Methods/study result reviews; methodology papers; CEA studies; journal editorials;</td>
<td>1982-2008 (2000-2008, n=77, 91%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>conference papers</td>
<td></td>
</tr>
<tr>
<td>Guidelines</td>
<td>28</td>
<td>Formal guidelines; manuals; expert consensuses; CEA studies</td>
<td>1982-2008 (2000-2008, n=24, 92%)</td>
</tr>
<tr>
<td>Funding</td>
<td>64</td>
<td>Peer-reviewed articles; working papers; OECD, UN and development banks publications;</td>
<td>1994-2008 (2000-2008, n=63, 95%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>policy briefs; conference papers</td>
<td></td>
</tr>
<tr>
<td>Total Data Set</td>
<td>157 (not total of)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Many of the documents fell in more than one group, although none fell into all three groups. Figure 3 below shows the overlap between the documents.

Figure 3: Overlap of Document Categories in Data Set
4.1.2 Assumptions guiding the synthesis of themes

The final list of distinct codes is presented in Appendix 9. In total, they numbered 85; by category they numbered 58 in “Limitations”, 10 in “Guidelines” and 17 in “Funding”.

To help clarify the process by which the resulting themes were organized, examined and synthesized through coding, the underlying assumptions held while reading the documents are outlined below.

Although CEA is often used to yield a solution for technical efficiency (as when the outcome measure is a natural unit), its broad goal is to inform decision-making for allocative efficiency (Gold et al., 1996). In this thesis this broader view was taken, so the elements of the Washington Panel Reference Case that address the use of CEA for policy-making and priority setting were emphasized. That is, summary outcome measures rather than natural units were emphasized.

In formulating the reference case, the Washington Panel was guided by the principles of welfare economics to make specific methodological recommendations. In this thesis, while the Washington Panel Reference Case is the starting point, this does not imply adherence to the underlying normative stance. Similarly, there is no adherence to a non-welfarist viewpoint, a more pragmatic application of cost-effectiveness analysis that relaxes some of the definitions and assumptions commonly held by a welfarist viewpoint (Brouwer, Culyer, van Exel, & Rutten, 2008).

CEA is assumed to be a desirable and but imperfect tool for decision-making in developing countries. The merits of CEA against other decision-making tools, whether economics-based or not, are not discussed. Particularly, cost-effectiveness analysis (and by definition in this thesis, cost-utility analysis) is not compared to cost-benefit analysis (CBA), which is considered a more appropriate technique for making decisions concerning allocative efficiency in part because opportunity cost is better captured by CBA (Donaldson, Currie, & Mitton, 2002).
The quality of the individual data items is equal. This means that there was no review of the documents for quality or validity, and therefore no explicit weighting of the individual items for importance. All items were read, summarized and coded with as equal attention as possible without prejudice.

There are no latent meanings in the text of the individual data items due to the technical nature of the research topic. That is, authors were taken at face value, and interpretations of results in those documents that were cost-effectiveness studies were not challenged. This thesis is not a critical review but rather, more of a survey to discern the questions that face researchers and practitioners in conducting and using CEA and in pondering the effects of donor funding in developing nations.

4.2 Results of thematic analysis for limitations of cost-effectiveness analysis for developing countries

The thematic analysis revealed three main observations in regards to the general application of CEA to developing countries as well as specific methodological items. In Sections 4.2.1 to 4.2.3 inclusive, the general observations are discussed separately, being, respectively: methodological limitations are not differentiated between industrialized and developing countries, but differences exist in emphasis of specific aspects of the limitations; methodological limitations regarding immunization are particularly relevant to developing countries; and, a disparity exists within developing countries and between developing countries and industrialized countries in the application of CEA. In Section 4.2.4 specific items of methodology are discussed: perspective; costing and costs; effectiveness measurement; and, discounting and the discount rate.
4.2.1 Methodological limitations are not differentiated between industrialized and developing countries

There is no explicit discussion of differences in methodological limitations between developing and industrialized countries, but the analysis of the Data Set reveals that, on the whole, the same problems that trouble analysts in developing countries also plague those in industrialized countries. The questions of generalizability, cost/benefit valuation, effectiveness and outcome measures, the treatment of future costs/benefits, discounting, and the treatment of uncertainty were identified to be issues of global concern (Hauck, Smith, & Goddard, 2004; Sculpher & Drummond, 2006). However, when discussed in the context of developing countries, different aspects of these topics come to the fore. Individual methodological limitations will be discussed in more detail below in Section 4.2.4.

The differing emphases placed on these limitations reflect underlying systematic epidemiological and health care system differences associated with national income level (Hsiao & Heller, 2007). For instance, in low-income (Stage I) and lower middle-income countries (Stage II), early stages of health system development according to Hsiao and Heller, citizens rely on self-care, seeking services from indigenous health care practitioners and pay-out-of-pocket. Communicable and infectious diseases are prevalent and are the major cause of death. Infant mortality and low life expectancy are also common characteristics. The epidemiological transition to more chronic diseases starts in the urban population, and low-resource governments must then deal with a double burden of communicable and non-communicable diseases. Two thirds or more of the health budget is spent on hospital services, mainly located in urban centres. Hsiao and Heller also state that Stage I countries typically give health issues low priority, and public health services are inefficient, estimated to be one-third to one-half of spending.

Because historically the burden of infectious diseases was relatively higher in lower income countries, CEAs for public health interventions predominated in the past (D. Walker & Fox-Rushby, 2000). As a consequence, CEAs located in lower income countries tended to be

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8 Below $826 Gross National Income (GNI) per capita and $826-3225 GNI per capita respectively, 2004 dollars.
conducted at the population or health system level, with associated issues such as population modeling, longer study horizons and the social opportunity cost of inputs coming to the forefront of discussion. Conversely, CEAs located in higher income countries are more diverse in focus, encompassing acute care interventions and new drugs and technology, and are often conducted at the patient level and increasingly, in a hospital setting. Discounting is then less contentious in these situations of shorter study duration, but elicitation of patient preferences to compose outcome measurements becomes more important.

The difference in emphases is also due to different disease profiles of the same disease in developing compared to industrialized countries. For example, hepatitis B is a disease of low endemicity in most industrialized countries and infection usually occurs in adulthood. In developing countries, however, hepatitis B is highly endemic and infects mainly infants and children. This has implications both for measurement of effectiveness and for discounting.

Even between developing countries there are differences in emphases, reflecting the wide diversity of disease burden and health systems between the countries of the developing world themselves and the transitional health profiles as income rises. For example, because a larger share of the population of middle-income countries are employed in wage-based economic activities (Hsiao & Heller, 2007), the estimation of parental productivity costs, important for pediatric interventions, becomes easier since valuation by wage rate is possible. A study set in South Africa (Griffiths, Botham, & Schoub, 2006), for instance includes productivity costs of paralysis due to polio infection, but that for infant vaccination against HIV in sub-Saharan Africa (Bos & Postma, 2001) does not. However, because the latter study did not explain why productivity costs were not estimated despite being declaring a societal perspective, it is unknown whether data limitations or imprecision in describing the study is at issue.

The difference in emphasis between methodological limitations set in industrialized versus those set in developing countries is not trivial because it indicates the issues that receive the most attention for resolution. Because most CEA researchers and analysts work in industrialized nations, the methodological issues pertaining to developing nations are relatively unexplored. Unresolved, these problems can have much more serious implications for the most economically
disadvantaged national populations and sub-populations. The inefficient use of resources and un-realized achievement of health gains resulting from methodological limitations can be overcome or mitigated in health systems that have some resilience and mobility and reserve of resources. However, most LMICs health systems are fragile, fragmented, and extremely resource-strained; inappropriate allocations therefore cannot be cushioned.

4.2.2 Methodological limitations regarding pediatric immunization are particularly relevant to developing countries

Another important finding is that conventionally, CEA methods do not fully address the special case of immunization and vaccines, that is, they do not fully capture the characteristics of the diseases prevented and the economic aspects of costs. As a result the economic value of vaccines is likely systematically underestimated (Beutels, Scuffham, & MacIntyre, 2008; Drummond, Chevat, & Lothgren, 2007). The presence of externalities, particularly herd immunity, the long time interval between treatment and (averted) onset of disease, the traditional target population of children and the complex implications of prevention, present methodological issues unique to immunization (Beutels et al., 2003; Hinman, 1999) The omission of these considerations biases resource allocations toward curative interventions rather than preventative and toward adult-oriented rather than child-oriented interventions.

These issues are disproportionately significant for the developing world because immunization is the single most important public health programme there, and it is much more important there relative to industrialized countries. Developing countries with per capita GNP under $3000 in 1998 allocated 0.13% of GNP to immunization services compared to the 0.035% of GNP that was allocated by the United States (Mahoney, Ramachandran, & Xu, 2000). Addressing efficiency for immunization programmes could address a significant part of health sector resources efficiency. Furthermore, children in LMICs carry a proportionately larger share of the disease burden than do children in high-income countries. Measured in DALYs lost, children in LMICs 0 to 4 years old carry 31% of the disease burden, while 5 to 14 year olds carry 8% of the disease burden. In high-income countries, those same age groups carry 5% and 4% of the
disease burden respectively (World Health Organization, 2008a). DALYs lost from measles numbered 6.5 million in South Asia alone compared to 23,000 lost in all high income countries in 2001 (Brenzel et al., 2006).

Immunization programmes have traditionally attracted much attention from donors, in part because of their relative cost-effectiveness. Renewed attention to cost-effectiveness, and an attendant focus on methodology, has been due to recent developments in the global health arena as listed below.

1. The international community had pledged support to decrease child mortality, much of which is attributable to vaccine-preventable diseases, through its support of the Millennium Development Goal Number 4 (Reduce by two-thirds, between 1990 and 2015, the under-5 mortality rate) (United Nations, 2010a). Consequently there was increased attention on the economic costs of scaling up immunization efforts, including introducing new vaccines, but there was a danger of not reaching the Goal, particularly in sub-Saharan African and Southern Asia. In September 2010, a MDG summit focused on maternal and child health garnered pledges of $40 billion from donors to accelerate progress on MDG Number 4 and Number 5 (Improve Maternal Health) (United Nations, 2010b).

2. One of the largest global health funds focuses on immunization. The private-public governance of GAVI (formerly Global Alliance for Vaccines and Immunization) emphasizes economic concerns and accountability.

3. There is a coordinated effort from private (e.g. donor foundations, non-governmental organizations) and public bodies (e.g the International Vaccine Institute) to make underutilized and new vaccines available to developing countries. Economic evidence is being included in their decision-making. GAVI, for example, funded a study of the cost-effectiveness of introducing a pneumococcal vaccine to 72 countries eligible for its funding (Sinha et al., 2007). CEAs also form a component of a package of diverse evidence developed for the introduction of new and underutilized vaccines into the Americas (Andrus et al., 2004; International Vaccine Institute, 2009).
Kim, Salomon, and Goldie (2007) in a literature review of CEAs for immunization noted that CEAs for vaccines increased disproportionately to other CEAs, in part reflecting the approval of many more new vaccines since the 1990’s. However, reported the authors, only 43 of 275 studies published between 1976-2007 were located in LMICs, “despite the fact that populations in these settings may benefit the most from vaccines.” Nevertheless, immunization studies set in developing countries are indeed increasing and it should be noted that there are current attempts to address many of the methodological concerns mentioned in earlier studies, particularly to capture transmission paths and externalities, by advances in modeling (Brinsmead, Hill, & Walker, 2004).

4.2.3 The application of CEA is divided within developing countries and between industrialized and developing countries

A third broad finding is that CEA takes two different forms in developing countries. One is the conventional form based on incremental analysis from a single, next best or existing, comparator and the other is the WHO-CHOICE Generalized CEA form, discussed in Section 1.3, based on a null-comparator, or a health sector-wide, analysis. The first form prevails. The second form is still not widely practiced, but since the year 2000 its methodology has been increasingly used or referred to in publications emanating from organizations concerned with global health (WHO, UNICEF, think tanks, bilateral donor governments) and their agents (i.e. consultants, co-operating centres). Additionally, the DALY is increasingly used as an outcome measure for immunization studies set in developing countries, although not those set in industrialized countries. 15 of the 18 studies from the Data Set published after 2000 reported CEA results in DALYs averted.

The existence of these divisions is emblematic of the growing variations in the health systems of the developing countries as demographic and epidemiological profiles change in tandem with economic change. Some middle-income developing countries that have the analytical resources and policy-making support for CEA (e.g. Thailand and Turkey), and who are early adopters of the technique, seem to be proceeding with conventional CEA contextualized for their own countries. Here, CEA is applied increasingly to drugs and health technology, mimicking the
emphasis on and innovation in incremental analysis shown in industrialized countries. International organizations or donors and international specialists, who perform the bulk of CEAs for the lowest-income countries that do not have the analytical resources, increasingly use the WHO-CHOICE technique. This health system view reflects the strong influence of the WHO to consider health and health care in a holistic manner as well as the urgent need to improve public health in many of the lowest income countries. However, this variation in practice, reflecting differing priorities, data availability, and skill base, results in fundamental variations in evidence, diminishing its usefulness for policy-makers who want to make international comparisons.

4.2.4 Specific methodological limitations

In this section, the aspects of the following methodological items that have special relevance for developing countries are discussed: perspective, costing and costs, effectiveness measurement, and discounting and the discount rate.

PERSPECTIVE

In Section 1.1 the definition of the analytical perspective and its importance to a CEA study was highlighted. The methodological decision made when choosing the perspective sets the limits of the study in regards to the costs and benefits to be valued and thus profoundly affects the cost-effectiveness ratio and its relevance to the decision-maker. Although studies may be performed from the perspective most relevant to the objective of the study question and to the decision-maker, the recommended perspective by the WPRC and most guidelines is the societal perspective to ensure that all resource costs and health effects are captured, regardless of to whom they accrue (Gold et al., 1996). The societal perspective is particularly recommended for public interventions like immunization and broad objectives like resource allocation efficiency.

In practice, however, a health system approach is often used. In the seven rotavirus immunization studies in the Data Set, dating from 2005 to 2008, all were conducted from the
health system perspective, with two of the studies reporting an additional societal perspective. However, the basis for the declared societal perspective was limited in scope. Isakbaeva et al. (2007) included only patient travel time and transportation costs in their study of rotavirus vaccine in Uzbekistan, and Rheingans, Constela, Antil, Innis and Breuer (2007) relied on lost caregiver productivity for a study in Latin America. In studying hepatitis B immunization in India, Prakash (2003) described his analysis as being conducted from a societal perspective yet did not include costs associated with patient treatment time, travel or lost productivity.

Typically, because medical costs are better documented and, because of reporting requirements for the EPI programmes, immunization programme costs are also more readily available, these costs predominate in many immunization studies regardless of the declared (Vimolket & Poovorawan, 2005). With the advent of the WHO-CHOICE project, databases for regional unit costs for hospital-based activities have been established and are readily available to analysts, reinforcing a health system focus. Data availability in developing countries may thus determine the choice of a perspective, rather than relevance to the study question.

Data limitations may also shape the perspective. Externalities and effects on other parties other than the patient and the resource use outside the health care system are difficult to trace in any jurisdiction, but more so in developing countries where there is weakness in the data gathering infrastructure, such as under-developed medical record keeping, disease surveillance systems and statistical agencies. Data gathering might be further complicated by large segments of the population living in rural or isolated areas. Costing based on facilities use may underestimate rotavirus burden as children suffering from rotavirus-induced gastroenteritis may be treated at home or in the community. Data gathering for treatment costs in the informal sector (traditional healers, pharmacists/herbalists, friends/household members) is difficult but ignoring costs incurred in this sector underestimates avoided societal costs (World Health Organization, 2005).

Furthermore, in some countries two or three tiers of health care provision may exist, with social insurance providing the most basic health care services to the lowest income citizens, to private/public mixes of better and more comprehensive health care for higher income citizens, to an elite system of private hospitals and services for the wealthiest citizens (Hsiao & Heller, 2007). In these cases, the pattern of resource use may be different for each tier and the resource
use may also shift between the different tiers depending on the intervention and the subpopulation addressed. For example, high-income families may have their children immunized through the public health system, but may choose private hospitals for curative treatment, where data may be proprietary. In a societal perspective, all facilities, including for-profit private inpatient and outpatient care, should be included. In the rotavirus studies of the Data Set, only one study discussed the exclusion of private facilities, justifying it on the basis of the small number of children (10%) normally treated there (Ho, Nelson, & Walker, 2008).

The guidelines for estimating economic burdens included in the Data Set implicitly and explicitly recognize data paucity in developing countries and provide useful information for finding secondary sources and for primary data gathering (World Health Organization, 2005a, 2005b, 2006a). However, by specifying only caregiver productivity costs in the category of societal costs, the healthcare system view is given predominance. Other guidelines for economic evaluations, not specifically aimed at developing countries, also focus on health care costs (Beutels et al., 2008), further reinforcing this outlook.

It might even be argued that because most immunization studies evaluate the addition of new vaccines to the EPI programme, and much more information is available for the EPI programme than for the general health system in many countries, an EPI programme perspective delimits CEA immunization evaluations in developing countries. In hypothetical studies, a malaria vaccine is delivered through the EPI system of Tanzania (Hutton & Tediosi, 2006) and an infant HIV vaccine through the EPI programmes of sub-Saharan Africa (Bos & Postma, 2001). In the latter study, the authors justified this setting, even though infants are not at high risk for HIV infection, by explaining that they wished to give an indication of the market for an HIV vaccine. Insofar as the EPI programme is the de facto public health delivery system for the population’s immunization programme, this perspective would coincide with the societal perspective. For middle-income and transitioning countries where the UNICEF-WHO supported EPI programme may be becoming less central (and less well supported by other donors) as their own social and economic circumstances improve, this would provide an unnecessarily constrained delimitation of analysis.
Therefore, although much of the focus of CEA in developing countries in recent years has been on aiding priority-setting (e.g. Disease Control Priorities Project, development of GCEA), which indicate wide population-based analysis, the government-plus (public system plus some patient productivity costs) perspective of immunization studies may be at odds with this objective. Because wider avoided costs and gained benefits are not captured, immunization cost-effectiveness is likely routinely underestimated. For example, in anticipation of a new vaccine, a broadly-based estimate of societal losses from malaria could provide better decision-making information. The WHO Commission on Macroeconomics and Health estimated that health loss due to malaria totaled 36 million DALYs in 1999 in the sub-Saharan population of 616 million, and if valued at the per capita income of the region, would amount to 5.8% of the gross national income of the area (Sachs & Commission on Macroeconomics and Health, 2001). A detailed and standardized definition of “perspective” and relevant associated costs and benefits is especially important in developing countries, thus, to discern the true social value of immunization programmes.

**COSTING AND COSTS**

Costing of immunization programmes is well established in developing countries as part of the planning, monitoring and evaluation of the EPI programmes (Kou, 2002; Kou & Nelson, 2001). A typical cost profile from the WHO/UNICEF guide for multi-year costing and financing of immunization programmes (World Health Organization, 2006a, p. 18) shows that vaccines are the largest single cost item:

- Vaccines – 29%
- Injection Supplies – 10%
- Personnel – 16%
- Transport – 7%
- Other recurrent costs – 19%
- Vehicles – 5%
- Cold Chain – 14%

The main costing approaches, which can be combined, include: 1) Ingredients approach that values inputs on the basis of quantity, unit price and percentage use for immunization. 2) rule-of-thumb approach based on published guidelines (e.g. enumerating vaccine supplies based on a
single dose of administering a specific antigen) and 3) budgeting approach based on past expenditures (e.g. smaller cost components, social mobilization, surveillance). In CEAs for immunization interventions, an ingredient approach is usually recommended (that is, a specification of required inputs along with their required quantities, multiplied together for total costs) to provide transparency and to improve transferability of results by allowing analysts from disparate countries use the same framework, adjusting for their local costs (Hutton & Baltussen, 2005).

Because of the emphasis on CEA for practical, planning purposes in developing countries a strong distinction is often drawn between capital costs and recurrent costs. Capital costs pertain to those input items lasting more than one year. These include vehicles and cold chain equipment (e.g. refrigerators). Recurrent costs pertain to items consumed within one year, including vaccines, vaccine supplies and training activities, and personnel (Kou, 2002). Listing and grouping these items together as either capital or recurrent allows budgeting information to be extracted from economic evaluations more easily by the programme manager or other decision-makers who are concerned with planning.

However, these clearly specified costing conventions (especially when spelled out in costing guidelines) might create a lowest-common-denominator standard that analysts overly rely on to determine resource utilization, and they may also be too prescriptive and limiting. Nevertheless, methodological quality is usually improved through standardization, and analysts may draw upon easily available literature to guide more in-depth and sophisticated analysis.

For example, a careful distinction is made between average costing and marginal costing, which is sometimes called incremental costing in a further refinement of terms when the analysis does not examine an expansion of current services, say increasing immunization coverage levels, but a comparison to alternative services (Hutton & Tediosi, 2006). Marginal costing pertains to the use of new resources, so, for example, if there is spare capacity to draw upon for the new intervention (e.g. underemployed personnel), it would not be counted as a cost. Average costing includes all costs pertaining to the delivery of a health intervention, including whether they are

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9 Personal communication of key informant who conducts CEAs in developing countries.
used for a new intervention, whether resources are drawn from other services and whether spare capacity is used. According to Hutton and Tediosi (2006, pp. 121-122), “The usefulness of presenting full economic cost through this analysis is that it enables comparison of intervention efficiency in the long-term, where all resources can (hypothetically) be redeployed in alternative uses. Therefore, average costs are useful for cost-effectiveness analyses for long-term planning decisions.”

Given the market distortions that characterize developing countries, financial/accounting prices should not be used, as they are routinely in industrialized countries. However, there is a long tradition in the World Bank of using shadow prices to reflect true societal costs in cost-benefit analysis, and Hutton and Baltussen make specific suggestions for valuing healthcare costs under conditions typically found in developing countries (Hutton & Baltussen, 2002, 2005). For instance, because developing countries often rely on imported goods for inputs into interventions, the opportunity cost for imports can be considered the foreign exchange used to pay for them. The international market price of imported goods should therefore be used to value imports. In the special case of price discrimination between countries for the same goods, Hutton and Baltussen (2005) recommended using the price available to the country in question. This would be directly relevant to developing countries in which the traditional EPI prices are much lower than they are in industrialized countries due to the practice of tiered-pricing.

Productivity costs are often valued by the appropriate industry wage rate, gross of taxes and deductions and including benefits, in the human capital approach (Drummond et al., 2005). This rests on the assumption that full-employment prevails. However, in countries with severe underemployment, as typifies many developing countries, the opportunity cost would be near or at zero at times, i.e. there is little or no other use for that labour. Furthermore, large segments of the population may be engaged in an informal sector where the exchange of goods and services that are not represented by a wage. In 2008, for example, vulnerably employed citizens (unpaid family workers and own-account workers) as a percentage of total workers were 23.6% and in 46.4% in Chile and Columbia respectively (World Bank, 2010b).\(^{10}\) The narrowness of this definition of productivity thus makes undervaluing the net health output especially acute in

\(^{10}\) Unfortunately, data were not available for lower-income countries.
developing countries. Unpaid productivity could be valued by the activities that are displaced, for example, lost agricultural production, or in urban areas, by assessing the annual income of citizens in the informal sector (Hutton & Baltussen, 2002).

In industrialized countries caregivers are assumed to be parents of the children and so basing an estimate of productivity costs on parents’ lost wages is fairly straightforward, especially as wage rates are typically easy to obtain through statistical bureaus and government agencies. However, aside from data availability problems, in developing countries many more household members are involved in caregiving, including older siblings and grandparents, especially if the patient is very young. Furthermore, children are often themselves economically active at a far younger age in developing countries than in industrialized countries. The World Bank reports that in 2006 48.9%, 18.2%, and 2.6% of children were economically active in Ghana, Guatemala and Turkey respectively (World Bank, 2010b). 11 Estimating a household opportunity cost might then be more indicative of the productivity costs of patients. Posnett and Jan (1996) noted that private or household opportunity cost can be higher than social opportunity cost, and if the size of the difference is large, it may determine the ease of implementing a proposed intervention. In the context of developing countries, then, parents who are subsistence farmers may not take time off during harvest season to take children to a remote healthcare facility for routine immunization, especially since by definition it treats a healthy child.

Future costs (and benefits) of health in years added by a healthcare intervention are particularly relevant to immunization programmes, but these are inconclusively or not at all treated in the Data Set. In other economics literature productivity benefits in the future are often portrayed in pure economic terms as an increase in wage level, and if healthcare is considered as an investment, future productivity could also be valued in terms of cognitive gains that result in labour productivity and higher wages (Belli, Bustreo, & Preker, 2005; Bloom, Canning, & Weston, 2005). Intergenerational costs/benefits could also be considered if current health losses/gains impact future generations, as in the case of children orphaned by AIDS patients. However, because of unresolved differences in the health economics field (Drummond et al.,

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11 Economically active children were defined to be children economically involved in economic activities at least one hour a week in the reference week of the World Bank survey.
2005; Gold et al., 1996) and the practical difficulties of obtaining data in developing countries, the Disease Control Priorities Project advised against including future costs and benefits (Jamison et al., 2006).

Similarly, averted treatment costs are often omitted because of the difficulty of extracting this information from resource utilization data. In evaluating the vaccination of women of childbearing age with tetanus toxoid to prevent neonatal tetanus, Griffiths, Wolfson, Quddus, Younus and Hafiz (2004) explained that this omission in their study lead to an underestimation of the cost-effectiveness.

**EFFECTIVENESS MEASUREMENT**

In Section 1.1 the QALY was described and in Section 1.2, the DALY. Despite ongoing concerns regarding its theoretical basis and usefulness (Birch & Gafni, 2006) the QALY is currently the most accepted metric for cost-effectiveness studies. (As noted earlier those using a QALY outcome are often termed “cost-utility studies”.) It is recommended for use not only by the WPRC, but also by many national agencies concerned with health technology assessments such as CADTH and NICE. Both QALYs and DALYs are criticized on ethical grounds: that the most sick and most poor are not prioritized; that patients who are the less treatable are discriminated against; and that there is no differentiation between life-saving and health improving outcomes (Gold et al., 2002). DALYs are also still strongly challenged for the ethical implications of age-weighting, which assigns lower disability weights to very early and very late years, and so can be interpreted as valuing the health of children and the elderly less. Economic evidence denominated by the DALY has become wide-spread since the late 1990’s, due mostly to large-scale attempts by the World Bank and WHO to provide global cost-effectiveness comparisons. As noted above in Section 4.2.3, the DALY is used almost exclusively in developing countries or international settings and the QALY in industrialized-countries settings. This may, however, simply reflect the fact that studies in these settings tend to be population-based and clinically-based respectively, and so the outcome measure used was chosen (appropriately) for its respective original motivation.
Because the two outcome measures are not interchangeable, care is needed to understand the underlying formulations and the potential impact on health outcomes and, ultimately, the policy implications. However, there are few head-to-head comparisons, and none of the items in the Data Set discuss the differential impact in a developing country context. There may be some insights relevant to this thesis provided in a comparison made by Sassi (2006), though. He calculated QALYs gained and DALYs saved (averted), using the standard 3% discount rate, for a non-fatal disease (tuberculosis when diagnosed and treated early) and a chronic and potentially fatal disease (bipolar disorder). Sassi found that the age of onset of disease was the most important factor for differences in the results of the two measures. When disease started in the early years of life and is of short duration, QALYs gained exceeded DALYs saved. When disease started in years of life up to early adulthood DALYs saved exceeded QALYs gained. However, when disease started in later adulthood and older, QALYs gained again exceeded DALYs saved (Sassi, 2006). Varying the discount rate did not affect the calculations, but varying the quality-of-life weights for QALYs and the disability weights for DALYs did affect the results to some extent. Sassi also pointed out that in using the DALY standard life expectancy (i.e. the life expectancy of Japanese citizens, which was not done in his study) for interventions preventing premature mortality would lead to consistently larger numbers of DALYs saved, and that the difference would be larger in countries where the actual life expectancy is lower.

To draw conclusions for pediatric immunization in developing countries from this one study would be dangerous, but it does highlight the fact that using one measure over the other could introduce possible systematic biases against certain sub-populations. Currently there is no single recommended outcome measure for immunization studies in developing countries, and in general, immunization studies have been heterogeneous in the use of outcome measures, with cases prevented, deaths averted, hospitalization averted, and persons immunized included among common measures. Kim and Goldie (2008) found that globally, there has been an evolution in use of outcome measures. ‘Cases-prevented’ was the most common outcome used in immunization studies from 1976 to 2007 (29% of all studies), and that measure was predominant 1976-1990 (69%). Between 2002 and 2007, though, only 14% of studies were denominated in ‘cases-prevented’, while QALYs, the second most commonly used measure in
the entire period (26%), was the most commonly used worldwide in this last period. They also found that from 2002 to 2007 the DALY was the most common measure used in LMICs, while the QALY was the most common in industrialized countries.

Given that the use of the DALY is predominantly used in developing countries, it is useful to see how age-weighting may affect decision-making there. Unfortunately, in the Data Set only one CEA discussed age-weighting in regards to decision rules. In a modeled study of prospective rotavirus immunization in Hong Kong, Ho, Nelson and Walker (2008) found that the ICER was particularly sensitive to age-weighting compared with the other variables tested in sensitivity analysis. At a vaccine cost of US$50/per child and with medical costs at the low-end of the estimated range, the ICER was US$94,000/DALY averted with age-weighting, as opposed to US$24,000/DALY averted without age-weighting. The authors pointed out that the comparison showed the ICER to lie on opposite sides of the World Bank/WHO-based cost-effectiveness threshold given Hong Kong’s per capita GDP of US$24,010 in 2002 (Ho et al., 2008). Other authors, perhaps acknowledging the controversial use of age-weighting, have also made it explicit that the DALY used was age-weighted (Fischer et al., 2005; Rheingans et al., 2007b; Sinha et al., 2007).

As an illustration of the distribution of age-weighting impacts over a life span, Arnesen and Kapiriri (2004) found that DALY loss would be the same for 185 new-borns, 17 6-month-olds, five 2-year-olds, one 25-year-old (as weighting peaks at age 25), two 67-year-olds, or three 83-year-olds suffered the same disability for one month. Thus, age-weighting has a significant impact on the results of pediatric interventions where benefits accrue predominantly in the first decade of life, such as for rotavirus immunization. Although the averted mortality and disability of preventing childhood diseases also extend into adulthood where weighting is heavier, the effect of discounting counters this additional benefit (Arnesen & Kapiriri, 2004).

**DISCOUNTING AND THE DISCOUNT RATE**

Discounting is the reduction of costs and effects in the future to the present day, the time period in which a decision must be made for the introduction of a health intervention. For the present
day decision-maker it enables comparison between programmes that accrue costs and effects at different points in time. To arrive at the present value, future costs and effects are weighted with the discount factor \((1+r)^{-t}\), where \(r\) is the discount rate and \(t\) is the year in which the costs or effects accrue, and then aggregated. The higher the discount rate, the more reduced are the values in the future. For interventions of short duration the discount rate is less important, and in acute care interventions discounting is sometimes not necessary if all costs and effects fall within a year. However, the choice of the discount rate becomes important for interventions of long duration, such as preventative interventions, because their benefits overwhelmingly accrue in the future, and are thus more reduced in value than costs, which typically fall closer to the present day.

While discounting costs is not controversial, the discounting of health effects is still contentious, especially in regards to interventions where effects accrue farther into the future and rise after costs (Drummond et al., 2005; Gold et al., 1996). Whether to discount effects and whether to apply a differential rate (lower or declining) to effects compared to costs is debated theoretically, and Drummond (2005) noted that a review summarizing 25 years of the arguments concludes that beliefs motivate the divide between support for non-differential rates (those who believe health can be exchanged for money at a constant rate over time) and for differential rates (those who do not believe this) (Lazaro, 2002). In practice, given the wide acceptance of influential recommendations by the Washington Panel Reference Case, NICE, and WHO, the use of constant and non-differential rates for cost-effectiveness analysis is global.

The accepted practice may, however, establish a systematic bias against interventions with effects arising in the more distant future, such as immunization (Cairns, 2006; Claxton et al., 2006; Drummond, 2008). This has especially important implications for pediatric interventions because of the longer life span of children compared to adults and because many pediatric interventions are preventative. For example, much of the benefits of measles immunization (e.g. preventing mortality) accrue within the first decade of the life of a child while benefits for hepatitis B immunization accrue later, in adulthood (e.g. preventing liver disease). To prevent penalizing future benefits Brouwer, Niessen, Postma, and Rutten (2005) advocate using
differential discounting (lower rate for effects) while Beutels et al. (2008) have suggested a slowly declining discount rate.

Other alternative discounting models for immunization are also proposed. Bos, Beutels, Annemans, and Postma (2004) suggest counting effects from the time risk is reduced (i.e. at immunization) rather than when the effect (e.g. mortality for hepatitis) occurs. Indirect risk reduction would also occur at the time of immunization in the population not immunized, and could be counted together with the direct risk reduction for a more favourable cost-effectiveness ratio.

Discounting reflects a preference for the present, or a positive time preference (Drummond et al., 2005). In CEA the social time preference is supposedly a reflection of individual time preferences, although the mechanism of how individual preferences could be directly translated into a social preference is unclear. Nevertheless, the choice of a social discount rate can be informed by individual time preferences.

For developing countries, very little information exists for the elicitation of patient time preferences. In one household survey study of six developing countries of varying income levels Poulos and Whittingdon (2000) found that although in each country the revealed preferences for saving lives resulted in discount rates higher than those from studies of the United States and Western Europe, there was not an expected relationship between income level, life expectancy and discount rates. Estimates for Mozambique, which had the lowest-income and second lowest life expectancy of the group, revealed the lowest median discount rate. The median discount rates estimated by the authors for Ethiopia, Bulgaria and Indonesia were 39%, 38% and 45% (for a 5 year horizon) respectively, compared to 17% in the United States. These high individual discount rates suggest that the upper bounds of rates used for sensitivity analysis (usually 10%) may be too low, according to Poulos and Whittingdon.
In a study from the Data Set, Robberstad and Cairns (2007) found that hyperbolic variations\textsuperscript{12} of the standard discounting formula best fit the data of Tanzanian households surveyed for their time preferences of non-fatal health outcomes. Furthermore, the authors found that the participants discounted future health far more than assumed under conventional discounting practices. The model best fitting the responses suggested a discount rate of 7\%, while lesser-fitting models suggested rates of 10-12\%. However, discounting with a hyperbolic model using an initial 7\% very far into the future (50 years) yielded similar results to the conventional model using a constant 3\% rate.

In regards to economic evaluations of pediatric interventions, Cairns (2006) raises further questions: should children’s time preference be taken into account? Do they have the cognitive ability to answer questions on preference elicitation instruments? What is the impact of an age-weighted discount rate? These issues remain to be resolved, but the last question is particularly pertinent to the topic of this thesis as discounting will become more important given that new and underutilized vaccines target diseases that have longer-term effects (e.g. hepatitis) or wider age groups (e.g. meningitis, typhoid fever) compared to the traditional vaccines in the current EPI programme that target childhood diseases (e.g. measles).

4.3 Guidelines for CEAs in developing countries

In most industrialized countries in which CEA is performed and used, formalized guidelines exist either explicitly for policy-making or regulation or implicitly through the conventions of practice and publication (CADTH, 2006; Craig et al., 2003; Dutch Health Care Insurance Board, 2006; French Health Economists Association, 2004; NICE, 2008; US Academy of Managed Care Pharmacy, 2009). Some of these guidelines have been established by national agencies or health care organizations specifically for the conduct of health technology and pharmacoeconomic studies (i.e. specific applications of CEA), reflecting the importance and growing share of medical devices and pharmaceuticals in health care expenditures. In OECD

\textsuperscript{12} In a hyperbolic discount model, values decline very rapidly in the years immediately in the future, but then very slowly in farther into the future.
member countries the number of magnetic resonance imaging units per capita doubled on average from 2000 to 2008 (OECD, 2010a). Spending for pharmaceuticals in Italy accounted for 20.3%, 22% and 18.4% of its national health expenditures in 1990, 2000 and 2008 respectively, while in Canada they grew from 11.5% to 15.9% to 17.2% of health expenditures the same years (OECD, 2010b). Despite the cumulative importance of these individual national guidelines, they were not included in the Data Set of this thesis, as their more limited focus, particularly on guiding formulary submissions, has less relevance to most developing countries. Instead, the following guidelines were sought: guidelines that make specific reference to methodological application or pertinence for developing countries; and guidelines that have wider application to other health care interventions or guidelines that purport to have global relevance, such as publication guidelines for high-impact journals. Some national guidelines are indirectly included in the reviews of guidelines, which is discussed below. Additionally, as the few guidelines from developing countries (e.g. Brazil, Mexico, China, Thailand) were not available in English during the literature search period, a proxy was used. This last is the ISPOR website tool allowing world-wide comparison of pharmacoeconomic guidelines (ISPOR, 2010). The table below summarizes the guidelines used in the thematic analysis and their general characteristics.

Table 7: Description of Guidelines

<table>
<thead>
<tr>
<th>Types</th>
<th>n</th>
<th>Purpose</th>
<th>Description</th>
<th>Audience</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Formal guidelines</td>
<td>2</td>
<td>Increase quality and comparability of CEA studies</td>
<td>Comprehensive recommendations for all aspects of CEA studies; issued by government agencies</td>
<td>Analysts, researchers familiar with CEA</td>
</tr>
<tr>
<td>2. Manuals</td>
<td>7</td>
<td>Provide theoretical and practical instructions</td>
<td>Focused on cost elements and local context for specific interventions; directly applicable to LMICs</td>
<td>Analysts, programme managers, government planners of LMICs</td>
</tr>
<tr>
<td>3. Consensus Statements</td>
<td>3</td>
<td>Provide expert opinion on specific issues</td>
<td>Vaccination CEAs, Modeling</td>
<td>Analysts familiar with CEA</td>
</tr>
<tr>
<td>Types</td>
<td>n</td>
<td>Purpose</td>
<td>Description</td>
<td>Audience</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---</td>
<td>---------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>4. Embedded recommendations</td>
<td>9</td>
<td>Clarify, provide methodology; reveal gaps</td>
<td>Specific, individual recommendations made in CEA studies or methodology papers</td>
<td>Analysts familiar with CEA</td>
</tr>
<tr>
<td>5. Checklists</td>
<td>3</td>
<td>Guide assessment of studies; summarize expected standards of quality, clarity</td>
<td>Broad recommendations, often in question form. Includes journal submission guidelines</td>
<td>Producers, users, appraisers of CEA evidence</td>
</tr>
<tr>
<td>6. Review of guidelines</td>
<td>3</td>
<td>Clarify objectives of guidelines. Identify use of appropriate guidelines</td>
<td>Broad classification of guidelines; Compare and contrast elements of guidelines; One specific comparison of those for LMICs.</td>
<td>Producers and users of HTA/CEA interested in global settings</td>
</tr>
<tr>
<td>7. Comparative guidelines</td>
<td>1</td>
<td>Comparison of main elements of current pharmacoeconomic guidelines</td>
<td>ISPOR website tool, based on formatted submissions by national HTA agencies (no analysis)</td>
<td>Members and other interested parties, not necessarily trained in HTA/CEA</td>
</tr>
</tbody>
</table>

The types of guidelines are described in more detail below.

1. Formal guidelines
The two included in this thematic analysis are the Washington Panel Reference Case (WPRC) as a comparator (and representing conventional CEA) and those emanating from the WHO-CHOICE project for Generalized Cost-Effectiveness Analysis (GCEA) (Tan-Torres Edejer et al., 2003). GCEA allows assessment of the efficiency of current in-place interventions, and so the conventional focus on marginal, incremental analysis is shifted to average (cost) analysis. The CGEA concurrent analysis of multiple interventions allows better achievement of allocative efficiency compared to the conventional analysis, according to the WHO-CHOICE authors. It also better emphasizes consistency and comparability across interventions.
The GCEA methodology, discussed in Section 1.3, was conceived for but not limited to developing-country analysis. Because the WHO-CHOICE project also includes establishment of regional databases covering all regions of the world to enable sharing of more local, contextual data, and because WHO provides access to the databases as well as to the analytical tools to perform a CEA within this framework, it can be surmised that analysts from both industrializing and developing countries can take advantage of these data and tools. It is unknown whether analysts in industrialized countries do so, however. For recent studies set in developing countries, though, the costing methodology and the data by themselves have been increasingly cited (Akumu, English, Scott, & Griffiths, 2007; Hogan et al., 2005; Isakbaeva et al., 2007; Rheingans et al., 2007; Sinha et al., 2007). Isakbaeva et al. (2007) noted that WHO-CHOICE regional costs for their setting (Uzbekistan) were higher than those they sourced themselves locally.

The GCEA framework itself was used to evaluate nine child health interventions13 for two regions in sub-Saharan Africa and South East Asia to suggest strategies for reducing under-5 childhood mortality and improving child health (Tan-Torres Edejer et al., 2005). Average cost-effectiveness ratios (ACERs) were first calculated to establish and rank the cost-effectiveness of the selected interventions as if none of them were already implemented. This helped to clarify which interventions were the most efficient for the region. The most efficient (lowest ACER) intervention then was used as the starting point for a strategy to add interventions (in order of their cost-effectiveness) as resources permit or became available. Decision-making is aided by the estimation of incremental cost-effectiveness ratios (ICERs) following conventional CEA methods was used to reveal the respective technical efficiency of the increasingly larger packages. Table 8 shows these results from this study.

13 Oral rehydration therapy; case management of pneumonia; supplementation and fortification with vitamin A or zinc; provision of supplementary food during weaning, with counseling on nutrition (with and without growth monitoring and targeting); and measles immunization.
Table 8: Cost-effectiveness Ratios for Child Health Interventions in WHO Region Afr-E

<table>
<thead>
<tr>
<th>Intervention package</th>
<th>Description (coverage) of package</th>
<th>Additional Interventions*</th>
<th>ACER ($Int per DALY averted)</th>
<th>ICER ($Int per DALY averted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Vitamin A and zinc fortification (95%)</td>
<td>Vitamin A and zinc fortification of food staple</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>A2</td>
<td>A2 + measles immunization (80%)</td>
<td>Measles Immunization</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>A3</td>
<td>A2 + measles immunization (95%)</td>
<td>Measles Immunization</td>
<td>28</td>
<td>58</td>
</tr>
<tr>
<td>A4</td>
<td>A3 + case management of pneumonia (80%)</td>
<td>Case management of pneumonia</td>
<td>47</td>
<td>73</td>
</tr>
<tr>
<td>A5</td>
<td>Vitamin A and zinc supplementation + case management of pneumonia (80%) + measles immunization (95%)</td>
<td>Fortification replaced by supplementation</td>
<td>55</td>
<td>85</td>
</tr>
<tr>
<td>A6</td>
<td>A5 + oral rehydration therapy (80%)</td>
<td>Oral rehydration therapy for diarrhea</td>
<td>72</td>
<td>106</td>
</tr>
<tr>
<td>A7</td>
<td>A6 (95%)</td>
<td>Coverage expanded to 95%</td>
<td>95</td>
<td>243</td>
</tr>
<tr>
<td>A8</td>
<td>A7 + provision of supplementary food and nutrition counseling and growth monitoring and promotion (95%)</td>
<td>Provision of supplementary food and nutrition counseling and growth monitoring and promotion</td>
<td>225</td>
<td>12 791</td>
</tr>
</tbody>
</table>

*In order of cost-effectiveness.

Extracted from Tan-Torres Edejer (2005), Table 4.

It would be reasonable to assume that the intense data and analytical requirements of a simultaneous evaluation of multiple interventions implied by the study above would be a significant barrier for adopting GCEA guidelines on a large scale. Even with WHO-CHOICE provided tools and data, they would be impractical to implement. None of the recent immunization studies (2000-2008) included in the Data Set for this thesis was prepared using the GCEA methods, although some of them made use of WHO-CHOICE databases. For example, Akumu et al. (2007), used cost per day-bed and per outpatient visit from the database in their assessment of Hib vaccine cost-effectiveness in Kenya.
2. Manuals
Most of these were prepared by international organizations such as the WHO or UNICEF. They are specific to an intervention, usually for a communicable disease (HIV/AIDS, childhood diseases, rotavirus), reflecting the disease priority and the programmatic emphasis of the particular agency. They range from comprehensive guides for planning and evaluating whole immunization programmes on a multi-year basis (World Health Organization, 2006a) to specific topical guides for aspects of immunization programmes, such as costing studies to identify, quantify and price programme inputs (Kou, 2002; Kou & Nelson, 2001). These latter are aimed at the local manager of immunization programmes, and provide templates for resource capture (e.g. listing and volume specification of resource consumption), calculation formulae, and contextualization suggestions (e.g. substitutions for inputs or other resources based on local availability). There is no expectation that the final users are trained in health economics or technology assessment. Overwhelmingly, the focus of the manual-type guidelines is on costing, either as input into economic evaluations or for health financing assessments. For example, in anticipation of introducing rotavirus vaccines, the WHO published prescriptive guidelines for estimating the economic burden of rotavirus diarrhea (World Health Organization, 2005). Kaddar, Makinen and Khan (2000) provided checklists and template tables for information gathering and estimation of costs and financing needs.

Recently, manuals have been produced for national governments to guide the evaluation of immunization programmes for expansion. Kou (2002) and the Rotavirus Vaccine Program (2007), for example, specifically addresses the programmatic and financial needs of new vaccines in the EPI. This is in concert with the increased resources made available for new vaccines and programmatic strengthening. The focus is on costing, using many of the same guidelines as for CEAs, targeting expenditure efficiency and financial sustainability.

3. Consensus statements
One of the consensus statements dealt with the broad methodological issues especially pertinent to economic evaluation of immunization programmes, such as the discounting of distant future benefits (Beutels et al., 2002). Although not specific to developing countries, it nevertheless is
highly relevant given the preponderance of CEAs for immunization programmes. The other two consensus statements made recommendations for modeling practices. Model-based CEAs are now common, particularly to analyze complex diseases or complex intervention settings, such as for infectious diseases, to overcome data deficiencies, such as in developing countries, and also for prospective economic analysis.

4. Embedded recommendations
These recommendations are mostly found in discussion sections of CEA studies or reviews as solutions for encountered methodological problems. Many of them pertain to the lack of standardization of analytical practices in developing countries, such as the definition or estimation of productivity losses when productivity cannot be measured by wage labour, as in agricultural or non-wage based economic activities (e.g. exchanging goods and services through bartering). Mills (1992) strongly emphasizes the collection of data at the household level to comprehensively understand and estimate lost days of work. She points out that productivity losses might be minimized if other under-employed household members take on the work for the patient, or they could be more significant if these extra duties took place at crucial periods of time, say, harvest season. Deficiencies in methodology are partly related to a lack of good quality data in developing countries, which often resulted in the forced improvisation or substitution of estimation techniques or of values by analysts. Hinman, Irons, Lewis, and Kandola (2002) stressed the use of standard methods and use of local data while Johns, Baltussen, and Hutubessy (2003) recommended and demonstrated an “ingredients” (explicit identification of inputs) approach for the valuation of administrative costs removed from the point of delivery. Recognizing the punitive effects of discounting on preventative interventions, Griffiths et al. (2005) recommended differential discounting of costs and effects and presented a hepatitis vaccine study with non-discounted as well as discounted effects. As the introduction of newly developed vaccines became more possible, attention was also turned toward costing of the expansion of current EPI programmes. For example, Hutton and Tediosi (2006) gave methodological advice for introducing the malaria vaccine into the Tanzanian EPI programme, including the delineation of cost items, as well as practical advice, such as the calculation of distribution costs from health districts to individual health facilities.
5. Checklists

Three checklists were examined, two publication guidelines and one for assessing generalizability of studies. They are tools for streamlined study conceptualization as well as for appraisal of finished studies. The manuscript submission guidelines of the British Medical Journal are especially authoritative as they were developed in conjunction with NICE, and they set the implicit standard for other journals (Drummond & Jefferson, 1996). For research authors from developing countries who wish to publish in top-tier journal, these guidelines would need to be met as well. It could be inferred that these authors, if successfully published, would then disseminate these guidelines by example to their compatriots. To address the lack of generalizability of economic evaluations Boulenger et al. (2005) developed a checklist of methodological standards when assessing studies from other settings.

6. Review of guidelines

Only one review of guidelines included those targeted at developing countries, and it made specific comparisons between those for developing and industrialized nation settings (D. Walker, 2001). Some of the differences, including a narrow focus on process indicators or intermediate outcome indicators (e.g. immunization coverage rates) and recommendations for one-way rather than more sophisticated sensitivity analysis (e.g. probabilistic), are due to the constraints of time, money and technical capacity. Walker (2001) points out that one of the most significant differences is that guidelines for developing countries explicitly point their users to consider affordability. He noted that common to guidelines for both industrialized and developing countries, cost-benefit analyses (where both costs and effects are valued in monetary terms) are not recommended.

The other reviews of guidelines in this Data Set provided useful global observations, and were a contrast in their respective breadth and depth. Hjelmgren, Berggren, and Andersson (2001) comprehensively compared 25 guidelines from North America, Europe and Australia in several methodological categories and judged them to be fairly homogenous. He pointed to the need, nevertheless, to harmonize outcomes and effectiveness for study comparability, and suggested that guidelines provide recommendations for appropriate choice of outcomes. Jacobs, Ohinmaa, and Brady (2005) examined the costing recommendations of pharmacoeconomic guidelines and
recommended guidance for the translation of resource utilization under experimental care to that under normal care, important as economic data is now increasingly being collected alongside random control trials in both industrialized and developing countries.

7. Comparative guidelines
This set of comparative guidelines is a web-based database of standardized guideline elements collected from the pharmacoeconomics/HTA guidelines of member nations of ISPOR (ISPOR, 2010). Users of the comparison tool may view fields of elements across two or more nations. It is useful for a “first-cut” view of the differences and similarities of application and wide range of variation of stated guidelines. For example, in the “perspective” category, it can be seen that a societal perspective to frame a study is not universally held and most recommendations are pragmatically stated (e.g. whichever perspective fits the study question). This, however, may be a reflection of the fact that pharmacoeconomics/HTA studies are centered on questions of technical rather than allocative efficiency at a specified level of decision-making. There is no discussion of the individual methodological elements or the work of the individual agencies.

Conclusions
In identifying the appropriate CEA guidelines for developing countries the main conclusions are noted:

1. The one comprehensive set of guidelines specifically targeting developing countries, GCEA is used almost exclusively by international organizations and offers a competing vision of CEA to that used in industrialized countries. The validity of the technique and results has not yet been established, although it has been used as support for decision-making in pursuing large-scale, sectoral objectives such as those identified by the Millennium Development Goals. This may cause an “evidence divide” between industrialized and developing nations, where there are different foundations for economic evidence.

2. Guidelines aimed at developing countries tend to be disease specific and take a “cook book” or “ingredients-based” approach. Local analysts and decision-makers are the target audience.
3. Guidelines aimed at developing nations are more heterogeneous in their objectives, audience and level of technical sophistication. In contrast, those aimed or used in industrialized countries are more homogenous and are predominantly intended for pharmacoeconomic evaluations.

4. Most of the developing nations guidelines are focused on the costing aspects, whether for economic or financial costs. Costing techniques are detailed and prescriptive. The costing focus was intensified in the climate of health financing scrutiny and the push to scale up the intensity of efforts to meet the health care targets of the Millennium Development Goals (Adam et al., 2005; Gottret & Schieber, 2006b).

5. Various middle-income countries with developing HTA capacity are preparing their own CEA guidelines, some formalized within national agencies. They are often focused on pharmaceutical applications, and are specific to local needs and priorities.

6. The following gaps are noted:
   - There are no guidelines on how to appraise and interpret CEAs from industrialized world or other regions for transfer to developing nations.
   - Effectiveness guidelines are focused on preferences-based measures not derived from nor validated in developing countries.
   - There are no guidelines for statistical meta-analysis of economic evaluations from multiple sources or for qualitatively integrating economic evidence, which is needed for developing countries that must import their evidence.
   - There is no formal guidance on the choice of decision rules for developing countries, although many researchers have adopted the World Bank/WHO rule-of-thumb categorization of cost-effectiveness based on national income that was described in Section 1.2. In this regard, there is no guidance on how to relate historical cost-effectiveness to current situations as income levels change in individual countries.

4.4 **Donor funding impacts on cost-effectiveness estimation**

In considering donor funding in this thesis the view of CEA is broadened. Conventionally, in industrialized countries especially, it is considered that CEA’s role is to inform decisions of
technical efficiency within the circumscribed boundaries of a clinical setting. In CEAs for developing countries, addressing the wider questions of allocative efficiency is also important, as the development of Generalized Cost-Effectiveness Analysis demonstrates. This thesis takes that view, and follows Chisholm and Evans (2007) in examining CEA’s role in achieving efficiency within a health financing framework, which introduces considerations of health, and to a limited extent, budgetary, policy objectives. Within this framework, CEA’s main function lies in the efficient purchase of health goods and services, which could free up financial resources for additional health goods and services. Efficiency in health financing contributes to final health systems goals of maximizing health gains. When viewed in this framework, the links to other economic cost and effects outside the immediate health care intervention become more transparent.

Donor funding as an explicit and integral component of financing of a healthcare intervention, both as an expansion of the budget constraint and also as inputs into supported interventions, is highlighted. In Section 1.7, the extraordinary role of donor funding in the health care sector of some of the lowest-income countries was pointed out; some healthcare sectors rely almost exclusively on external funding for their immunization programmes. (See also Appendix 1: Selected Health and Development Indicators.) In this section, to understand the impacts of donor funding on CEA estimation, some problems of donor funding in the healthcare sector in general are identified in Section 4.4.1, GAVI’s contribution to aid effectiveness in Section 4.4.2, and the implications for the assessment of cost-effectiveness are considered in Section 4.4.3.

4.4.1 Problems of donor funding

Questions of the impact of donor funding have mainly been discussed in terms of aid effectiveness, that is, whether funding was successful in affecting final outcomes. The Paris Declaration on Aid Effectiveness (2005) explicitly recognized that aid was often ineffective and stated donors’ commitment to address insufficient funding, lack of alignment with recipient country priorities, short-term funding horizons, unpredictable and volatile disbursements and fragmented aid delivery (OECD, 2005). Signatories to the Declaration included donor and recipient governments, international organizations and funding agencies.
Hsiao and Heller (2007) pointed out that often public health and disease prevention programmes supported by donors were especially effective relative to other non-supported programmes. However, they also recognized that although many gains and benefits resulted from donor funding at the project or programme level, aid could have unrealized, unintended, or even deleterious effects on recipients’ health systems. Countries sometimes create vertical programmes to deliver donor-specified services, creating a separate bureaucracy, set of facilities and supply system for them (Birdsall, 2005; Hsiao & Heller, 2007). If health is not a high priority, countries neglect to make budgetary allocations to other healthcare programmes and funded programmes tend to draw resources, like scarce trained personnel, away from unfunded programmes (Oomman, Wendt, & Droghitis, 2010). Some of the impacts on health systems result from macro-economic impacts such as increases in the general price level, shifts in sectoral allocations of public expenditure, or disequilibrium between labour demand and supply (Khaleghian, 2001; Lane & Glassman, 2007; Levin, Ram, & Kaddar, 2002; Levine & Blumer, 2007; Murray, Lu, & Michaud, 2007; Nossal, 2003; Radelet & Siddiqi, 2007).

Unpredictability, or unreliability, and volatility, the difference between committed amount and the actual disbursed amount, of donor funding have been particularly criticized as they make financing and planning difficult and prevent local governments from fully integrating stated objectives of the supported programme with their own local objectives (Schieber, Baeza, Kress, & Maier, 2006). Birdsall (2005, p. 18) described the experience of Malawi, which received highly varying amounts of total aid ranging from 8 to 20 percent of GDP in the 1990’s, as “equivalent in the U.S. of quintupling the deficit in one year, and then a year later absorbing a huge recession-like effect on jobs and incomes.” Unpredictability and volatility might even cause decision-makers to forego needed and proven cost-effective programmes (Birdsall, 2005), thereby having an indirect impact on the efficient allocation of resources. A World Bank study concluded that from 1997 to 2001, donor funding had limited positive impacts on under-5 child mortality in several African nations, gains being offset by funding volatility and sustainability that caused disruptions and discontinuity in health care programmes (Gottret & Schieber, 2006b). Brugha et al. (2004) found that when expected disbursements from the GFATM did not arrive in time, the governments and NGOs charged with administering the supported
programmes had to seek alternative funds. This would have increased administrative costs, if not also negatively affected health outcome due to delayed treatment.

The fungibility of donated funds can also have unintended consequences. Fungibility refers to the diversion of donor funds from their intended use or, secondarily, the diversion of local funds freed up by donor funding to other public expenditures. The consequences may be positive, say if local funds were diverted to support secondary health facilities that would otherwise not be funded by either local governments or donors. Gottret and Schieber (2006b) in their study of off-budget donor funds (i.e. funds not going directly into health ministries but managed outside the budget) found that reduced maternal mortality was positively associated with increased donor funding but only indirectly so. The authors concluded that the positive impact was due to the fungibility of funds, which caused government expenditures to flow to hospitals and clinics. However, fungibility may also be negative if non-optimal reallocation of health funds (donor or local government) resulted, toward debt repayment, for instance (Birdsall, 2005; Cavagnero, Evans, & Carrin, 2007; Gottret & Schieber, 2006; Michaud, 2005; OECD, 2005; Schieber, Baeza, Kress, & Maier, 2006; World Bank, 2007).

The large health funds, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) and the GAVI Alliance, have been successful in increasing service provision, raising national and international participation in the disease areas, and have over time been better able to integrate into national health systems. However, they have also been criticized, and HIV/AIDS funding is often held up as an example due to its sheer size. An International Monetary Fund (IMF) working paper showed estimates of combined potential funds (disbursed plus undisbursed) for 2005 from the GFATM, PEPFAR and the Multi-Country HIV/AIDS Program for Africa (MAP) forming substantial proportions of national healthcare budgets and GDP. For example, in Ethiopia, Haiti, Rwanda and Uganda, the share of potential donor funds of the healthcare budget (and of GDP) were 43.8% (1.1%), 26.2% (0.8%), 80.6% (2.5%), and 150.2% (3.1%) respectively (Heller, 2005). Such large presences suggest that HIV/AIDS, and the management of the related interventional activities, is a major focus of healthcare and budgetary policy in these countries, and may be crowding out other priorities in the health systems, including preventative interventions. Huge infusions of funds aside, health priorities of recipient countries might not be
aligned with priorities of donors. Michaud (2005) found that in Indonesia, Cambodia, and Sri Lanka there was common agreement between the national governments and donors to aim for broad goals to improve infant mortality and maternal-child health, but the actual allocation of funds to specific programmes required compromise.

One effect of these disease-focused funds is reduced spending on other preventative and curative programmes, as the fund-supported programmes require extraordinary commitments of local resources in support of their activities (Drechsler & Zimmerman, 2006; Garrett, 2007; Hsiao & Heller, 2007). Additionally, because of the underdevelopment, fragility or instability of the health systems that are targeted by the three large health funds, substantial inflow of funds can have disproportionately large and disruptive impacts, particularly on financial, budgetary and human resource management. Volatility, unpredictability and fungibility impacts may also offset some of the health gains that could be realized by the large health funds (Gottret & Shieber, 2006).

Lane and Glassman (2007) recast the issues surrounding aid effectiveness as aid efficiency. funding referred to in Section 1.7, questioning the efficiency of fund allocation for maximizing global health gains. They reasoned that certain characteristics of funding, particularly its duration, predictability and the tying of funding to specific uses, affected the purchase of healthcare goods and services in recipient countries, and so affected allocation efficiency within those countries. The way that donor funding was implemented (i.e. the financing structure and administrative requirements) affected technical efficiency. Using 2005 donor-reported data to OECD to examine the relationship between global funding allocation and recipient country characteristics, Lane and Glassman found that health aid in total, from large health funds, donor countries and international organizations, was aligned with disease burden (defined as total DALYs lost per 100,000 population); a one percent increase in disease burden was associated with a one percent increase in aid per capita. Funding was also positively associated with country capacity as measured by the Economic Freedom Index (a measure of governance and accountability) and commitment to health (measured by the share of health in government spending). They found that as national income rose, health aid quickly dropped off. They also found that health aid was negatively associated with population size, implying inefficiencies in
allocation, and concluded that aid efficiency could be improved by reallocating aid from smaller
to larger countries to minimize the high cost of aid in the former and the lower amount of aid
per capita in the latter. In addition to inefficiencies introduced by fragmentation and
proliferation of aid, which resulted in duplication of activities, increased administrative burden
and excessive funds, Lane and Glassman noted that donors often did not employ CEA results to
help decide their funding choices. This last finding is contrasted to that of Schiffman (2006),
who showed that donors were attracted to interventions that have demonstrated cost-
effectiveness. Among interventions he grouped as “highly cost-effective” (less than $25/DALY
saved according to a World Bank classification of cost-effectiveness), he found that donor
dollars per DALY was high. These interventions included the immunization programmes using
the traditional EPI vaccines. However, for these cases Schiffman does not explore whether
donors were guided by CEA results or other sources of information and their own priorities.

4.4.2 GAVI and aid effectiveness

GAVI’s pre-eminent role in the funding of immunization interventions globally was discussed
in Section 1.7. In this section evaluations of its successes and deficiencies in effectiveness, as
measured by aid efficiency and health impact, are highlighted.

In the study above by Lane and Glassman (2007), GAVI was mentioned for practices which
would contribute to allocation efficiencies in its recipient countries. The authors singled out
GAVI for not tying their aid to specific geographic areas, a general donor practice that the
authors cite from the OECD as resulting in inefficiencies of US$110-$300 million in 2005.
GAVI’s multi-year support would also reduce unpredictability and allow the development of
local capacity and institutions for delivering immunization programmes. GAVI’s funding was
made less volatile and longer-termed by it being able to draw on an ensured flow of funds from
the IFFIm for ten years. GAVI also gave clear indications of its terminal date for funding,
allowing recipient countries to plan ahead to help avoid disruptions to programming. Financial
sustainability plans required by GAVI committed recipient governments to develop local
financing and budgeting to sustain the programmes after GAVI’s withdrawal. On the other
hand, Lane and Glassman found that GAVI practices also potentially contributed to allocation inefficiencies in recipient countries. These included its support for high-cost vaccines like the hepatitis B and rotavirus vaccines without prior cost-effectiveness study and adding to the proliferation of funding organizations.

In examining the progress of infant immunization in Africa, Arevshatian et al. (2007) concluded that increases in donor spending, especially that of GAVI, had led to increases in spending on immunization and related improvements in programme performances, resulting in dramatic increases in coverage in Africa. However, its influence on immunization sustainability was less successful; despite developing financial sustainability plans, most of the 19 GAVI-supported countries did not use them as expected. Arevshatian et al. reported that GAVI would instead be requiring multi-year costing plans that would be incorporated in national budgets.\(^\text{14}\)

Furthermore, the potential health gains of introducing the GAVI-supported hepatitis B vaccine were delayed several years due to the vaccine’s high cost, weak local infrastructure, and low interest from other donors.

Lu, Michaud, Gakidou, Khan and Murray (2006) assessed GAVI’s health impact by examining the effect of its Immunization Services Support (ISS) on DPT3 coverage rates. ISS is one of GAVI’s streams of support, providing cash and in-kind support for the introduction of new vaccines and injection safety (but not for vaccines themselves). At the time, ISS support was contingent on per planned (as stated in country application targets) additional child immunized and an external audit of the reported immunization coverage rates. ISS awarded successful countries US$20 per additional surviving child immunized. Lu et al. (2006) found that GAVI’s ISS funding successfully contributed to the increase of DPT3 coverage for countries that had coverage rates of 65% or lower at the time of their application. The cost per child to GAVI was $8.40 to $20, about the same as the award to ISS recipients, which suggested an efficient use of GAVI resources. However, the authors found that there was no impact on countries with higher rates of coverage, where about 40% of the ISS funds had been disbursed, so they suggested it would be more efficient to move GAVI resources to countries of low coverage rates.

\(^{14}\) For the interested reader the individual country plans (cMYPs) are made available on GAVI’S website www.gaviassociation.org.
At the request of GAVI an assessment was made of the ISS by Chee, Hsi, Carlson, Chankova and Taylor (2007). The authors found that the ISS practice may have displaced government expenditures for immunizations in GAVI’s first phase (2001-2005). Excluding GAVI vaccine and ISS expenditures, government expenditures decreased 4% from the pre-GAVI period, a result that implies a threat to future sustainability of programmes when GAVI funding ends. On the other hand, contrary to Lu et al., the authors found that at all coverage levels the ISS had had a positive health impact, with US$1 of ISS accounting for a 10% increase in the odds of DPT3 immunization in the year funding was received and another 10% in the year after. The authors noted that they had used one more year of data than Lu et al., and that they had based their estimates on expenditures rather than disbursements. The same regression model had been used in both cases. Overall, the ISS was judged to be successful, and Chee et al. recommended continuation of the programme for GAVI’s second phase. (It should be noted that the performance awarding system has since changed, but any subsequent review is not captured in the Data Set.)

Based on rotavirus cost-effectiveness in the literature, burden of disease and financing scenarios from an investment case (PATH, 2006) GAVI has committed to investing in the subsidization of rotavirus vaccines and in activities related to the accelerated introduction of an immunization programme (e.g. enhanced disease surveillance, post-marketing surveillance, demonstrations projects, clinical trials, effectiveness studies, vaccine demand/supply monitoring). In a phased programme, eligible countries in the European and Latin American regions were permitted to apply for support in the 2007 to 2010 period, while Asian and African countries will be permitted to apply after 2010. To the end of December 2009, Bolivia, Honduras and Nicaragua have added rotavirus to their routine immunization schedule (World Health Organization, 2010g).

GAVI has actively tried to address the issue of sustainability, that is, the ability for recipient countries to maintain donor-funded programmes after donor support is withdrawn (Lydon et al., 2008). In addition to new vaccine purchase it supports health system strengthening to enable the elimination of structural barriers to immunization and to shore up public health infrastructure. It
has also required recipients to be directly responsible for finding internal resources and co-sharing costs. For applicants of the different aspects of vaccine programmes that it supports, GAVI has created templates for gathering information, estimating financial costs and developing budgets in conjunction with other health care priorities and expenditures (i.e. the multi-year plans). These forms are submitted as part of the application for GAVI support, to ensure that applicants have taken a detailed assessment of their needs (GAVI Alliance, 2008, 2010d).

### 4.4.3 Implications for cost-effectiveness analysis

In this section some of the implications that large donor funding have for the estimation of CEA values are explored. From analysis of the Data Set, the impacts are centered on costs and costing. In the context of pediatric immunization these impacts will likely be most pertinent to low-income developing countries, as middle- and high-income developing countries (those having a GNI per capita of more than US$1000 in 2003) are not eligible for GAVI funding, although they do receive donor funding from other organizations.

At the macro-economic level the general price level, and therefore prices of the individual inputs into immunization programmes, may be affected by large inflows of donor funding either in cash or in their import of programmatic inputs (Cavagnero, Evans, & Carrin, 2007). It is difficult to determine whether donor funding will cause the general price level to rise (i.e. cause inflation) or not, as domestic economic policies also affect inflation. Nevertheless special attention needs to be paid to applying deflators or inflators (as appropriate depending on a retrospective or prospective study respectively) in countries where large inflows of external funding is suspected of contributing to inflation to obtain economic costs. Furthermore, persistent and high inflation also impacts the real interest rate, which is defined as the nominal, i.e. bank lending, rate minus inflation. As the real interest rate is the opportunity cost of money, valuing of capital goods is affected. While in the current EPI schedule capital costs are not the most significant component, they may become more significant with the addition of new
vaccines. Rotavirus vaccines, for example, require two to three times more refrigeration volume in its current packaging than all the traditional antigens combined (PATH, 2006).

Donor funding has the most impact on the cost of vaccines, especially significant as vaccines are the largest cost component of immunization programmes. At the international level, UNICEF and PAHO dominate the buying of vaccines and are able to command relatively low prices due partly to its ability to buy in volume and to assure a market for vaccine manufacturers. UNICEF supplies vaccines for all low-income countries, whether or not supported by GAVI, negotiating a single price with vaccine producers. Middle-income countries not eligible for UNICEF/GAVI immunization support may also request UNICEF to negotiate on their behalf. PAHO negotiates vaccine prices on behalf of its member countries, but vaccines are not donated. Rather, vaccines are paid for by PAHO members themselves through pooled resources in the Revolving Fund. The practice of differential, or tiered, pricing of vaccines by manufacturers has allowed them to charge higher prices to buyers in industrialized countries for the same or similar vaccine. In industrialized countries, prices are again differentiated between public and private sector. Table 9 below illustrates the differential pricing for vaccines relevant to developing country immunization programmes, contrasting prices in the United States with those available for lowest-income countries. Prices for the Centers for Disease Control (CDC) reflect contracts for vaccines to be used in state health departments and federally supported immunization programmes, while private prices are those reported to the CDC by manufacturers (Centers for Disease Control, 2010). Unicef and PAHO prices are those negotiated by the respective organizations for their member countries and, in the former organization, for GAVI, too (PAHO, 2010; UNICEF, 2010a, 2010b).
Table 9: Comparison of Public and Private Sector Prices for Pediatric Vaccines

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<tbody>
<tr>
<td>DTP-HepB-Hib</td>
<td>Liquid, 10 dose pack</td>
<td></td>
<td>$2.10</td>
<td></td>
<td></td>
<td>$3.20</td>
</tr>
<tr>
<td>DTP-Hib</td>
<td>Liquid, 1 dose pack</td>
<td></td>
<td>$3.40</td>
<td></td>
<td></td>
<td>$3.30</td>
</tr>
<tr>
<td>DTaP (Infanrix®)</td>
<td>10 pack vials</td>
<td>$14.25</td>
<td>$20.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>1 dose + diluent UNICEF/PAHO</td>
<td>ActHib® 5 pack</td>
<td>ActHib® 5 pack</td>
<td>$3.40</td>
<td>$3.10</td>
<td>$3.10</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Lyophilized, 10 dose pack+ diluent</td>
<td></td>
<td>$0.89</td>
<td></td>
<td></td>
<td>$0.70</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>RotaTeq® $59.176</td>
<td>RotaTeq® $69.59</td>
<td>RotaTeq® $102.50</td>
<td>3-dose scheme $5.15</td>
<td></td>
<td>$7.50</td>
</tr>
<tr>
<td></td>
<td>Rotarix® $83.75</td>
<td>Rotarix® $23.606</td>
<td>Rotarix® $48.31</td>
<td>2-dose scheme $7.50</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>BCG</td>
<td>10 vial pack</td>
<td></td>
<td>$0.10</td>
<td></td>
<td></td>
<td>$0.10</td>
</tr>
<tr>
<td>Polio, oral</td>
<td>e-IPV (inactivated virus)</td>
<td>e-IPV (inactivated virus)</td>
<td>(plastic squeeze pack)</td>
<td>(plastic squeeze pack)</td>
<td></td>
<td>(plastic squeeze pack) $0.18</td>
</tr>
<tr>
<td></td>
<td>$111.74</td>
<td>$24.709</td>
<td>$0.178</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>MMRII® 10 pack</td>
<td>MMRII® 10 pack</td>
<td>(Urabe Mumps strain)$1.60</td>
<td>(Urabe Mumps strain)$2.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$18.634</td>
<td>$48.31</td>
<td>10 dose pack</td>
<td>1 dose pack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTP</td>
<td>10 pack</td>
<td></td>
<td>$0.178</td>
<td></td>
<td></td>
<td>$0.145</td>
</tr>
</tbody>
</table>

Sources: CDC, UNICEF, PAHO.

The very low prices of the traditional EPI vaccines (bottom most in the table) reflect not only the buying power of UNICEF and PAHO, but also the willingness for manufacturers to sell them at marginal production cost. For these particular products there are also multiple
manufacturers, some of which are located in developing countries that have lower costs of production and can therefore exert some competitive pressure on prices. Of the 29 makers of vaccines prequalified by WHO (i.e. authorized to sell to U.N. agencies) as of February 2010, 13 were from developing countries, and their products are predominantly focused on EPI programmes (World Health Organization, 2010e).

In an example of intra-country price differentiation, Yadav (2010) cited GAVI sources in noting that the manufacturer GlaxoSmithKline (GSK) offered the hepatitis B vaccine to the Indian government and NGOs at about US$1 per dose and to the private sector at US$2 a dose. In Brazil the vaccine was offered at US$0.58 a dose to the public sector and US$5 to the private, with multiple prices in between (Yadav, 2010). Thus, it is important to recognize that like many industrialized countries, developing countries may also have multiple markets for vaccines. For a societal perspective, CEA estimation would require that all these associated vaccine costs are captured and aggregated.

Differential pricing helps to inform the economic, or opportunity, costs due to the insights provided for vaccine marginal cost. It may be more difficult to assess the economic prices of new vaccines that are supported by GAVI or recommended by the WHO (e.g. rotavirus, pneumococcal vaccines) if manufacturers do not find it attractive to offer them to markets in lower income countries. Because these vaccines are more sophisticated than the old antigens, like those using recombinant DNA or conjugant technology, and are earlier in the product pricing cycle (i.e. before research and development costs have been recovered), they are more expensive and may not find markets in developing countries for several years. They thus require a larger role and effort by donors to help lower the price to make their introduction affordable to developing countries. The significant impact of the donors in the pricing, and therefore CEA costs, of vaccines is illustrated by the fact that PAHO has been able to negotiate a significantly lower price for the rotavirus vaccines despite the recentness of their licensing. In Table 9, PAHO per dose price of US$5.15 and US$7.50 for RotaTeq® and Rotarix® respectively can be compared to those of the CDC, at US$59.176 and US$83.75. Although it is still unknown what the UNICEF negotiated price on behalf of GAVI will be, it will likely be similar to PAHO’s, as historically the same vaccines procured by the two agencies are very close in price.
To create the market conditions for vaccine development as found in high-income countries, donors, spearheaded by GAVI, have initiated a programme of advance market commitments (AMCs) to the pharmaceutical industry for as yet undeveloped (Berndt et al., 2007) Sponsors (donors) can make commitments to buy vaccines at a price that would give financial incentives to produce or accelerate the production of a vaccine that would not have been profitable to sell in LMICs. Interest by donor governments was expressed for malaria, HIV, and pneumococcal vaccines, and an AMC pilot project for the last was launched in 2009. One aim of these commitments is to create shadow or opportunity pricing for new vaccines (Berndt & Hurvitz, 2005). The long-term price (based on the marginal cost) to producer is to be arrived at eventually and dynamically, affected by the particular development costs of the vaccine, the entry of other manufacturers (and other market conditions), and the uptake of the vaccine. Berndt et al. (2007), modeling various contracts and assumptions for malaria, tuberculosis and HIV/AIDS, suggested that a hypothetical vaccine under an advance market commitment would be cost-effective, as defined by WHO benchmarks of cost-effectiveness for low-income countries.  

In the donor efforts to use economic evidence to inform the accelerated introduction of new vaccines, the impact on CEA estimation is to introduce more complexity and uncertainty for the vaccine cost parameters and related parameters. Estimation becomes assumption-driven and more analytically- and data-intensive. The CEA case for a malaria vaccine delivered through the AMC mechanism rested on the basis of an initial US$15 per person immunized falling to US$1 per person (the hypothetical cost) (Berndt et al., 2007). There have been no studies to examine results under alternative assumptions.

Besides adding to the complexity of assessing vaccine costs for CEA, the presence of donor funding add to the complexity of assessing personnel costs. The creation of large programmes demand extra personnel, and in countries that are heavily dependent on health aid, drive up demand for skilled labour and strain (already strained) governments by competing for its own

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15 Berndt et al. report that for a $15 commitment for the first 200,000 persons covered there would be a $15 per year of life saved for malaria, $31 for tuberculosis, and $17 for HIV/AIDS.
workers (Birdsall, 2005). However, Musgrove in Waddington (2004) also pointed out that the draw of labour to donor-funded projects may not be a distortion, but could also be a correction of a labour market that was already distorted. Nevertheless, in countries where very large amounts of donor funding have flowed in, and over a very short time, there could be severe disruptions to the labour market in the short term and the costing of personnel based on market rates would compromise CEA results. This would be exacerbated in a societal perspective, where productivity costs are based on wage rates.

This can be illuminated in considering the case of the extraordinary escalation of HIV/AIDS funding. In assessing the impact of the GFATM, PEPFAR and MAP on the health workforce of Africa, Oomman et al. (2010) found that there were indeed severe and negative problems. They discovered that the programmes supported by these funds relied on “task-shifting”, a redistribution of tasks from more specialized to less specialized workers in order to improve access to services, instead of training new workers. Furthermore, the shifts occur without adequate support or resources; nurses are particularly overburdened. Time taken away from regular duties to train for the delivery of the funded programmes strain both the workforce and the healthcare system. One key informant from Zambia was quoted, “Up to 70% of the doctors in the districts are just not at work because they are always on training,” (Oomman et al., 2010, p. 31). Pay and incentive practices (e.g. paying “volunteer” community workers more than regular staff in order to attract service providers) have resulted in drawing health workers away from other services in Uganda and demoralized workers who don’t receive similar compensation. Shifting of the workforce also results when facilities run by different funds offer varying pay and incentives.

The escalation in donor funding, and of the number of donors, have also increased the transactions costs of dealing with donors. In CEA estimation transaction costs are not typically included so there is an underestimation of costs in the evaluation of donor-supported programmes. Transaction costs are incurred in the reporting, evaluating and auditing required by the programmes. For example, GAVI requires from their recipient countries substantial and stringent documentation for application (e.g. burden of disease evidence, cMYPs), maintenance (regular coverage and financial reports) and evaluation processes (GAVI Alliance, 2010a).
Costs are also incurred for field trips, meetings and social activities when donors visit programme sites. The burden imposed on the Mozambique government is described by a key informant in a study of coordination mechanisms among the key funders thus: “We spent 7 months last year on the Global Fund\(^{16}\), 8 months on the Clinton Foundation\(^{17}\), and 3 months on MAP…” (Brugha et al., 2004, pp. 98-99). Lane and Glassman (2007) reported that Cambodia received funding from 14 bilateral donors, five multilateral donors, and had 100 NGOs working in the country, all resulting in more than 400 visiting donor missions a year.

Changes in coverage rates are often used to measure effectiveness of immunization programmes, and in the past was not uncommon as a process measure for cost-effectiveness (Khaleghian, 2001). However, the validity of officially reported rates has been questioned. Murray et al. (2003) compared official reports made to UNICEF/WHO to immunization data obtained from World Bank Demographic and Health Surveys (DHS), which are household-based, in 45 countries. They found that DPT3 coverage rates in official reports consistently exceeded those in DHS estimates over the 10 years examined. Murray et al. attributed the differences to four reasons: differences in collection of data, different underlying sources of data, weak information systems, and deliberate inflation in response to financial or non-monetary incentives. In an assessment of its first five years of operation (2000-2004), GAVI was shown to have dramatically increased coverage of all traditional vaccines in its target countries, especially measles (Lu et al., 2006). However, more recently critics have leveled that coverage rates are exaggerated by national governments, perhaps in response to performance-based incentives offered by GAVI for ISS funding. In comparing DPT3 rates reported by country officials with their own examination of administrative data and a variety of other surveys, Lim, Stein, Charrow and Murray (2008) found that the survey-based coverage rates, while showing improvement, did not improve as much as officially reported rates or WHO/UNICEF’s own estimates in the 51 countries that received GAVI funding for immunization services support. Analysts should be cautious in using official reports as baseline estimates to assess immunization programmes, then, as they may bias the cost-effectiveness results downward.

\(^{16}\) An abbreviation for the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM).
\(^{17}\) The William J. Clinton Foundation, a private foundation concerned with economic development.
Increasing immunization coverage rates nonetheless has been and continues to be a major objective of GAVI and national governments. The change in coverage rates has, however, implications for the costing of immunization programmes. The CEA assumptions of constant returns to scale and perfect divisibility means that the average cost of a unit of health for any given intervention is the same no matter how much health is produced. In data-constrained environments such as in developing countries these assumptions are not only useful but makes analysis feasible, and so in practice a straight-line extrapolation of costs is usually applied as coverage is expanded. This is especially useful in comparing a number of interventions with different cost structures, as was the case in using CEA for priority-setting in Zimbabwe, where even using these simplifying assumptions required intensive, time-consuming data collection at a fairly aggregated level (Hansen & Chapman, 2008). In reality, though, marginal costs may rise as coverage is extended, particularly as programmes are extended out of urban areas into rural and more remote areas. Fixed costs are higher at the margin if new fixed facilities (e.g. clinics) need to be constructed and new infrastructures (e.g. cold-chain and distribution points for vaccine and supplies, purchasing and hiring of vehicles) need to be established. In a study of the geographical impacts on expanding a nutrition intervention, Johns and Baltussen (2004) also point out the extra supervisory and management costs for more complicated administration and delivery of a more remote programme. Furthermore, the population is thinner, may be hard-to-reach or is resistant to seeking immunization, so that the average cost of immunizing a rural child is higher than for an urban child. On the other hand, effectiveness might be higher at the margin if the un-vaccinated population has a higher incidence of the disease or has a higher mortality rate, which is often the case in rural areas of developing countries.

Bishai, McQuestion, Chaudry and Wigton (2006) highlighted the complexity of assessing immunization expansion and the need for systematic and thorough examination of corresponding changing costs. The authors plotted DPT3 coverage against DPT3 costs both with and without vaccine costs (the latter to correct for the variability in vaccines included in national programs) for a large number of low income countries (11-33 depending on the year) over five years. They found that average costs per child decreased with an increase of coverage, and countries that immunized more children had lower average costs than those that immunized
fewer. However, in a sub-analysis of 14 countries where data permitted a comparison of change of costs, it was found that average costs rose over time and in nine cases, DPT3 coverage fell while costs rose. Grouping these countries as a whole, the authors estimated that a 10% increase in coverage would increase costs by 8.4%, implying declining marginal costs, and concluded that technical efficiencies could still be gained using the same strategy of routine immunization, but on a regional rather than national basis.

To explore the use of alternative strategies to increase coverage Pegurri, Fox-Rushby and Walker (2005) reviewed studies that included improving staff training, employment of mobile teams, changing immunization schedules, increasing parent education, improving clinical services (e.g. reduce waiting times) and using mass campaigns. They found that the cost profiles varied considerably depending on the strategy; personnel costs, for example, ranged from 20% to 70%. Using the available cost-effectiveness results (although the studies were not directly comparable due to study design and differing assumptions), the authors found that mobile health units operated by community health workers dominated the other strategies. All strategies were found to be effective in improving coverage except that of mass campaigns run for over a year. Their high concentrated and intense resource use and their required elevated attention from the political and medical system that diverted attention and resources from routine immunization were thought to be reasons for their relative lack of success in improving coverage. However, the authors emphasized the uncertainty surrounding all these estimates and the lack of generalizability of the individual studies, and warn that the policy question of increasing coverage for existing programmes versus adding new vaccines (which is a current focus of donors) is only partially answered and no firm conclusions could be reached. More transparency in presenting cost estimates in studies and more studies in costing were the authors’ recommendations.

It must also be added that striving for coverage rates that are based on targets such as the WHO’s 80% rate for DPT3 (a proxy indicator for full immunization coverage) requires more careful consideration of local cost profiles and effectiveness constraints. While these targets are serviceable as tangible, and sometimes political, goals, they may be unrealistic in many countries, evidenced by the relatively rapid slippage in coverage rates in sub-Saharan Africa due
in part by the decline in donor support in the 1990’s and the deleterious health system and resource impacts of the AIDS epidemic. In estimating the cost of adding a malaria vaccine to the EPI system of Tanzania, Hutton and Tediosi (2006) found that the operational aspects of the EPI programme (e.g. management and organization at four levels of facilities, vaccine handling and wasteage) were critical to coverage and eventual costs and effectiveness. Johns and Baltussen (2004) estimated that diseconomies to scale for nutrition programmes started at coverage rates as low as 30%. Equivalent comparisons for immunization programmes were not found in the Data Set.

4.5 Possible enhancements to the Washington Panel Reference Case

In this section a synthesis of the foregoing sections in Chapter Four is used to identify some areas of possible enhancements to the WPRC. Findings of the Key Informant Interviews, presented in the Section 4.6, were also integrated, having the most influence in the suggestions for Reporting. Below, a table of recommendations is presented, with further discussion presented in Sections 4.5.1 to 4.5.7.
<table>
<thead>
<tr>
<th>TOPIC AREA</th>
<th>SPECIFIC ENHANCEMENTS</th>
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<tbody>
<tr>
<td>Nature and limits of a cost-</td>
<td>• De-emphasize using a societal perspective and choose a perspective appropriate to the relevant decision-makers and their objectives.</td>
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<tr>
<td>effectiveness analysis</td>
<td>• Define perspectives recognizing the heterogeneity of healthcare systems in developing countries and the possible existence of multiple systems within one country.</td>
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<td>• Multiple perspectives may be presented, with implications for affected sub-populations as well as for national populations.</td>
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<td></td>
<td>• A new extra-societal perspective to address healthcare resources that flow from sources outside national boundaries.</td>
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<tr>
<td>Costs and effects</td>
<td>• A resource utilization study should be conducted to the fullest extent given data constraints. Detailed costing can be a preliminary step to a full CEA.</td>
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<td></td>
<td>• The ingredients approach developed by the WHO can be employed to make resource use transparent.</td>
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<td></td>
<td>• Include the source of the resources, whether externally or domestically supplied.</td>
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<td></td>
<td>• Add country co-pay amounts to the prices of vaccines supplied or supported by GAVI.</td>
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<td></td>
<td>• Productivity costs/savings should be calculated for the entire household, not only for patient and caregivers.</td>
</tr>
<tr>
<td>Outcome measure</td>
<td>• Analysts should understand the difference between the DALY and the QALY and the respective local implications of their respective use.</td>
</tr>
<tr>
<td></td>
<td>• Consider the use of the DALY for use in international settings where global allocations of health benefits and effects are important.</td>
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<tr>
<td>Discounting and the discount rate</td>
<td>• Sensitivity analysis should be conducted using a higher than conventional rate for costs to reflect financial markets and time preferences in developing countries</td>
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<td>• Sensitivity analysis should be conducted using differential rates for costs and effects, with lower and/or declining rates for effects.</td>
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<td>Reporting</td>
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<td>costs and benefits, both discounted and undiscounted, should supplement CEA results.</td>
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<td>Breakpoint analysis should accompany an ICER, varying key variables such as vaccine price or immunization coverage level.</td>
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<td>Resource utilization studies and or cost studies should complement CEAs, with recurrent costs not supported by donors isolated and valued in both financial and economic prices.</td>
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<td>Off-budget interventions should report costs that are shared with on-budget interventions and when and where inputs are required from the government or community.</td>
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<td>A sustainability analysis should complement a CEA study.</td>
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4.5.1 Nature and limits of a cost-effectiveness analysis

The foremost task of a CEA analyst is to choose an appropriate perspective. A societal perspective is recommended by the WPRC to ideally implement the broadest distribution of the most beneficial health interventions, as decided by those who are constrained by budgetary resources, but who seek to maximize welfare. However, the Washington Panel, in its discussion of this recommendation, also recognizes that it is appropriate to take into consideration not only the gainers of health but also the payers of health when choosing an analytical perspective. Other considerations for choosing an appropriate perspective might be defined by the information that is relevant to the decision-maker. For example, the decision to purchase a single vehicle to bring immunization teams to a few isolated villages might confine the perspective to the district hospital and the patients that are served by it. In contrast a national strategy to increase coverage to the least-served populations, typically those far from the capitals and cities of developing countries, requires a societal perspective. The broadness of an intervention thus also helps decide the appropriate perspective.
Routine immunization is one of the broadest of public health interventions, yet many of the studies in the Data Set use a healthcare system or healthcare provider perspective (Akumu et al., 2007; Hansen & Chapman, 2008; Ho, Nelson, & Walker, 2008; Podewils et al., 2005; Vimolket & Poovorawan, 2005) This choice reflects in part the difficulty of obtaining patient-related data such as travel time or estimates of productivity for rural-based or non-wage earning patients. Even facilities-based data might be difficult to obtain. For example, Akumu, English, Scott and Griffiths (2007) based their Hib vaccine study on a convenience sample of health facilities in one rural area of Kenya that already had a good surveillance and immunization programme. Other study authors do not justify their choices, but given the accompanying discussions of affordability or the search for a break-even vaccine price in these cases, it is reasonable to conclude that the objectives of the studies are payer-driven, hence a healthcare provider perspective results. Even with the stated objective of determining allocative efficiency for healthcare in Zimbabwe, Hansen and Chapman (2008) used a health provider perspective. However, their study scope might have been constrained by the overwhelming data requirements for examining 65 interventions simultaneously. For studies set in developing countries, then, data limitations and a relatively heightened concerned for affordability means that the societal perspective is not necessarily the appropriate choice, although it is the ideal.

If analysis took the perspective of the healthcare sector, then a more precise definition and delineation of the “sector” is needed. The healthcare sector of developing countries can be composed of multiple healthcare and healthcare financing systems (Gottret & Schieber, 2006a; Hsiao & Heller, 2007), and in some cases, the public or government system delivered a limited portion of the total service. Appendix 1: Selected Health and Development Indicators, illustrates this further. In 2007 public expenditures accounted for 33.6 percent of total health expenditures in Bangladesh, for 20% in Cambodia and 26.2% in India. Not including the healthcare delivered by private providers would severely underestimate the health resource utilization in these countries. Khan et al. (2004) showed this very clearly in their examination of EPI delivery in healthcare facilities located in Dhaka. In contrast to rural Bangladesh, immunization services were delivered predominantly by NGOs in Dhaka. NGOs managed 77% of EPI sites and gave 62% of all vaccinations. The authors estimated that on top of resources used that originated from
donors, the NGO-provided services used about US$1.4 million (1999 dollars) worth of resources. The NGOs also used about US$15,000 in community-provided resources in their outreach sites (e.g. local schools, community halls). Because of the significance of healthcare delivery from non-government providers in developing countries, distinguishing a “government” perspective from a “health sector” perspective is especially important. Identifying the composition of the health sector and valuing the resource utilization of each system or segment becomes critical in analysis from the societal perspective, as all systems should be aggregated for an efficient allocation of resources, through the comprehensive summation of the QALYs for the individual health sector, as is the general practice for aggregation in a non-subdivided health sector ¹⁸.

Likewise, the patient perspective needs to be accorded proper scrutiny and adequate weight given patients’ role as highly significant payers in lowest-income countries, as measured by out-of-pocket expenditures for healthcare. For example, in Bangladesh in 2007, out-of-pocket payments made up 97% of private expenditures, which in turn accounted for 66.4% of total health expenditures (see Appendix 1). Thus, the patient view needs to be expanded to cover not only the person directly benefiting from an intervention, but also his family members and household, as health payments originate from household budgets. Utilization of health resources is accordingly made from a household perspective. For example, a family may choose to seek treatment for a wage-earning member of the household but delay for a non-wage earning member for financial reasons. Again, insofar as patient perspectives are added to health sector perspectives to form a societal perspective, the proper valuation of resources at the sub-societal level would improve the assessment of efficient allocation of resources at the societal level.

Thus guidelines for CEAs set in developing countries may explicitly recognize the practicalities of data gathering and the heterogeneity of healthcare provision by suggesting the adoption of the perspective (or even multiple perspectives) most pragmatically realized or policy and decision-relevant. A societal perspective might be de-emphasized or held up as an ultimate goal, instead.

¹⁸ The summation of QALYs, while conventionally practiced, is controversial as it implies that all QALYs are the same, whether they pertain to different segments of the population or to different diseases.
Furthermore, a societal perspective is bounded by national borders, but in this thesis the focus on donor funding in developing countries highlighted the fact that some important actors and stakeholders involved in maximizing healthcare gains of a particular country are not part of the society there. This international level of actors, bilateral and multilateral donors and public-private foundations are important payers in most of the lowest-income countries, as evidenced by their contribution to domestic healthcare expenditures. They are also constrained by budget, as determined by their sponsors and members, ultimately, and predominantly, the citizens of industrialized countries. Determining whether the global allocation of donor funding is efficient in broadly distributing beneficial health interventions is of importance to these citizens, too, as well as to the donor community. This theme was discussed in Section 4.4.2 in regards to GAVI effectiveness, most explicitly by Lane and Glassman (2007), who found that GAVI’s support of high-cost HepB vaccine was globally inefficient and also pointed out that allocation efficiency was important to ensure national sustainability of funding and funded programmes. Capturing the resources that are used in healthcare programmes in a developing country that receives substantial donor funding thus requires breaking through the national boundary set by the conventional societal perspective for an extra-societal perspective.

However, as mentioned above, the Data Set reflected the pragmatism necessitated by the constraints of data and analytical capacity, forcing most analysis through sub-societal and limited societal perspectives. Only the resources of the large international organizations (World Bank, WHO, GAVI) have allowed analysis at the international, societal and inter-sectoral level. To extend the analysis to the global level would thus be infeasible for developing nation analysts. A limited extra-societal perspective from the payer point of view might nevertheless give some idea of the efficiency of donor funding. For example, the global distribution of donor funding might be compared to the global distribution of disease to see if there is a correlation. This would be a first-cut indication of whether health outcomes are globally maximized to originators of donated funds as they become more concerned with aid effectiveness and efficiency. The United Kingdom, for instance, will be reviewing all donor agencies to which it contribute funds, providing cash top-ups to those deemed to demonstrate value for money and success in fighting poverty and withdrawing funding to those that are not (DFID, 2010). Examining the opportunity costs to individual nations as well as to donors of re-distributing the
allocation of global funds among disease burdens would be an objective for which an extra-
societal perspective would be appropriate.

As a final comment on the nature and limits of a CEA study, the WPRC recommends that
comparison be made with existing practice and (if necessary) a viable low-cost alternative. The
WHO-CHOICE generalized CEA (discussed in Section 1.3) uses a “zero intervention” scenario
so that resource utilization of all relevant interventions can be assessed simultaneously. While
the WHO-CHOICE approach may be especially relevant to developing nations with poorly
functioning health systems it is extremely data and analysis intensive, and it is not known if
policy-makers find this approach more meaningful than conventional CEA. Even trying to
define the disparate healthcare provision modes and quantify the related resource utilization as
described above, would require much more intensive data collection and analysis at the facility
and household level than conventionally done.

Analysts should be cognizant of these constraints, but also recognize that national and global
health information systems are improving and evolving (e.g. GAVI’s financial support for
health system strengthening, the creation of the Institute for Health Metrics and Evaluation) so
that increasingly, more rigorous application of a broad-based framework will be possible.

4.5.2 Costs and effects

The WPRC made only general recommendations to capture “all” costs and effects relevant to
the intervention, leaving it to the analyst to determine them himself. In Section Error!
Reference source not found. costing and costs of CEAs set in developing countries were
discussed, and it was noted that standard costing of intervention inputs were well established
due to guidelines developed for planning and evaluating immunization programmes. The
ingredients approach was especially recommended for its completeness and transparency in
capturing and reporting resource utilization. For decision-makers concerned with affordability
and sustainability, the approach also pinpointed resource distribution among inputs and over
time. This approach also allows personnel who are not trained in economics or accounting to collect, collate and aggregate data. A similar approach for general resource utilization could be followed, for example, breaking down an intervention into its components by units, determining the required resources, identifying the source of the resource and specifying when it would be used. A resource utilization study, or a costing study, is laborious and time-consuming, but would yield valuable information for not only economic evaluations, but also those for facilities performance, budget impact and personnel deployment. Following the discussion of the impact of donor funding in Section 4.4.1, identification of the source of the resource, that is, whether donor provided or not and which donor, may also help illuminate the sustainability of supported interventions. In valuing vaccines provided by GAVI, the amount of the co-payment per dose required of recipient governments should be added to the procurement price to better reflect local social opportunity cost. While a co-payment might engender a sense of national ownership, and thus encourage sustainability, the alternative use of that co-payment portion must be examined.

Other categories of costs are less well standardized and are often not included in economic evaluations, similar to the practice in CEAs set in industrialized countries. Non-health costs continue to be uncounted, but have relatively large significance in developing countries. For example, the loss of education due to ill health in childhood could lead to unfulfilled cognitive development, which may result in lower earning ability, and eventually lessen contribution to national economic development (Bloom, Canning, & Weston, 2005). How and whether to include future costs and benefits, and which are related or un-related, remain unresolved. For developing countries the resolution is important, particularly in regards to childhood interventions, as the long-term efficient improvement of health is tied to long term economic development (Belli, Bustreo, & Preker, 2005).

Externalities (spill over costs and effects from the directly treated population to the untreated) from interventions, especially in public health interventions, are also not commonly included. However, the under-estimation of benefits resulting from disregarding the externality of herd immunity in evaluations of immunization is well-recognized (Szucs, 2005). Recent standardization in modeling methodology to capture the complexity of disease transmission
paths, force of infection and age shifts in infection caused by immunization promise that herd immunity will become more commonly included (Kim & Goldie, 2008; M. C. Weinstein, 2006).

Productivity costs and effects, discussed in more detail in Section 4.2.4.2, is a methodologically challenging item for developing countries, as the concept is based on the human capital approach. This is especially inappropriate for developing countries in which much economic activity is non-wage based or takes place in the informal sector and the household. Basing productivity on wages biases interventions towards people who earn a wage and people who have higher incomes. Friction costs, presenting an alternative concept of productivity (Koopmanschap, Rutten, van Ineveld, & van Roijen, 1995), are not normally included in CEAs, but explicit inclusion could better illuminate labour resource flows in characteristically under-employed developing countries. For example, a caregiver’s lost productivity in having to give up a job based on unskilled labour can be very quickly offset by the productivity gain of another worker who might otherwise have been queuing at a job site, say in construction. This method also requires intensive data, however, and may be difficult to implement. In accord with a household perspective discussed above, it might be reasonable to consider basing productivity on household income. The World Bank household estimation of income based on Demographic and Health Surveys (DHS), which estimates income based also on household possessions (e.g. number of bicycles, ownership of a stove) could be a source of data (World Bank, 2010a).

Again, it is important to recognize that developing countries have data limitations and relatively low analytical capacity. In order to implement the costing studies suggested above would take considerable investment in information infrastructure and personnel. One should also consider whether the cost of that additional costing information for a new intervention is worthwhile, especially if the investment can be otherwise spent in that potential intervention. Value of information analysis might indicate whether carrying out a data- and analytically-intense CEA is warranted. That is, the decision-maker’s willingness-to-pay (or expected payoff) for the additional costing information that could be used in a potential CEA using these enhanced recommendations could be explored systematically.
4.5.3 **Outcome measure**

The WPRC recommends the use of the QALY, but it must be noted that at the time the DALY was still newly developed. Above in the thesis, the use and characteristics of the DALY was discussed in Section 1.2, and in Section Error! Reference source not found. the QALY was compared to the DALY. Both measures have advocates and opponents, and there is statement of the superiority of one over the other. As observed, the DALY is used almost exclusively for CEAs set in developing countries, which decreases the comparability of those studies to the large body of evidence already generated using the QALY, located both in industrialized and, to a lesser degree, in developing countries. As the DALY is also used to measure burden of disease globally, it may be appropriate for analysis of an international nature, say, with the extra-societal perspective suggested above. Having two widely used outcome measures would not be in conflict if their use could be consistently compartmentalized, say, but clear consensus would be needed from analysts as to the appropriate application of the two measures. This would entail direct comparisons of the two for a variety of interventions in a variety of settings; so far there are no comprehensive comparisons, however.

Analysts then must take care in fully understanding the underlying construction of each of the measures to determine which is the most appropriate for the disease or condition being studied. For example, the DALY has a more limited range of disability classes and the weight assignments that are discrete rather than continuous compared to the QALY. For complex conditions and multiple sequelae, e.g. AIDS, the analyst may find this constraining. On the other hand, the DALY has been standardized for application in most parts of the world, allowing wide-ranging comparison of results under the Global Burden of Disease Project. However, it should be pointed out that the two global applications of the DALY use different formulations. The DALY used by the current Global Burden of Disease Project (2004 version) is discounted at 3% and age-weighted, whereas the DALY used to estimate cost-effectiveness in the Disease Control Priority Project is discounted, also at 3%, but is not age-weighted (World Health Organization, 2008a).
Complicating a definite recommendation for using the one measure over the other is the fact that at the time of writing of this thesis, the Global Burden of Disease Project was recalibrating the disability weights for the DALY. Revisions include expanding disability classifications and eliciting preferences from the general public through online surveys (World Health Organization, 2010a). Nevertheless, that the DALY is being increasingly used and is well accepted by international organizations requires inclusion in a reference case.

4.5.4 Discounting

The WPRC recommends that a constant discount rate of 3% be applied to both costs and benefits. The implications for pediatric immunization studies, specifically, the undervaluing of benefits caused by constant discounting, were discussed in more detail in Section Error! Reference source not found.

In this section it is reiterated that the 3% real rate of capital is based on more stable financial markets of industrialized countries and do not necessarily reflect the more risky markets of developing countries. Unfortunately, the Data Set did not yield any methodological discussion on risk-adjusting the discount rate for developing nations. The second component of the discount rate, time preference, also reflects underlying economic and social conditions of industrialized countries. The growing research on personal time preferences in developing countries yield derived individual discount rates that are higher than in industrialized countries, suggesting that social discount rates may also be higher. For these reasons, it is quite plausible that higher discount rates are appropriate in developing countries. For illustrative purposes, one could consider that in high-income or high middle-income countries settings, as found by Beutels (2001) in a review of economic evaluations for hepatitis B, base case discount rates were also higher, up to 8% for costs and 7% for effects. Authors in this review also presented results undiscounted. Along with the range of discount rates, the zero-discounting reflect the unresolved treatment of discount rates for immunization studies. Section 5.3.1 outlines further various considerations for selecting higher discount rate values, including capital market rates,
government social project rates, and guidelines other than the WPRC either for base case (or reference case) analysis or for sensitivity analysis.

However, without more substantial research evidence directly conducted in the context of developing countries, this author feels that enhancements to the WPRC might only suggest a consideration of higher discount rates be used only in sensitivity analysis, past the usual limit of 10%. Given the ongoing methodological debates over the use of differential interest rates, discussed in Section 4.2, it is also most prudent to explore the potential impact on health gains by sensitivity analysis. In order to assess the impact on immunization and other preventative programmes, it might be useful to conduct sensitivity analysis with both a differential and a declining rate for effects. For example, one scenario could be examined with a 15% discount rate for costs, and a declining rate from 3% for effects.

The use of probabilistic sensitivity analysis (PSA) could be applied to calculate joint probabilities of varying the discount rates differentially. PSA is being increasingly used to address uncertainty in sophisticated and complex CEAs (Drummond et al., 2005), and can be particularly useful for testing the robustness of immunization studies based on modeling (decision-analytic or dynamic disease), because the typically large number of variables in these models make multi-variate sensitivity analysis extremely cumbersome and introduces decision uncertainty. With new research on non-linear discount rate (e.g. hyperbolic models), PSA may also be a suitable approach. However, a remaining challenge is that the analyst must still characterize the probability distributions of discount rates in the context of developing countries.

4.5.5 Reporting

The thematic analysis and the key informant interviews revealed that policy-makers and decision-makers in developing countries are concerned with issues of affordability and sustainability. The key informants thought that these two issues took precedence over cost-effectiveness. Researchers have made efforts to address affordability with statistical solutions
based on cost-effectiveness acceptability curves\(^{19}\) (Kim et al., 2007; Sendi & Briggs, 2001)

However, these cost-effectiveness affordability curves are complicated, and it is unknown whether they have been applied in policy-making. Similarly, methods and practices have been developed for budget impact analysis, which specifically addresses the affordability of new drugs to official formularies. Budget impact analysis, is a full and detailed analysis on its own, and may be too onerous and overly data-intensive for supplementing a CEA to assist policy-making.

Although they may not be formally integrated into the CEA estimation, affordability and sustainability could be addressed by including information supplemental to the ICER that could be selectively pursued by the policy-maker depending on his needs.

To assist decision-makers concerned with affordability, analysts could present contrasting streams of benefits and costs over time, both undiscounted and discounted, to give a better idea of recurrent costs and corresponding budgetary needs. This is especially important for vaccines against diseases like hepatitis B and human papillomavirus (HPV) where benefits fall in adulthood, some as far as fifty or sixty years from the time of vaccination. It is also useful for programme managers to know what costs and when costs occur in short-term and to plan for cost events in the long term.

In the Data Set several studies calculated a breakpoint vaccine price at which an intervention introducing that vaccine would become cost-effective based on pre-specified thresholds. This was particularly true for studies anticipating the introduction of new vaccines (Akumu et al., 2007; Bos & Postma, 2001; Fischer et al., 2005). Although prices were hypothetical, policy-makers could have a sense of the magnitude of resources required. Other breakpoints could be explored (such as capacity utilization levels, immunization coverage levels) to give an idea of the strain on current resources.

\(^{19}\) Cost-effectiveness acceptability curves are summaries of the uncertainty surrounding an ICER at specified threshold levels. That is, they encapsulate the probability that an intervention will be accepted (or rejected) by a policy-maker having in mind an ICER ceiling.
The extensive resource utilization or cost analysis suggested above could be presented with recurrent costs that are not supported by donors separated out and valued in both financial and economic prices with short- and long-term horizons. Results should be presented in both undiscounted and discounted terms.

Off-budget interventions (i.e. those receiving funds not passing or documented through national treasuries, but delivered directly from donor to programme site) should indicate which resources are shared with in-budget interventions and whether additional resources are required from the government or community and when they would be required. Otherwise the social opportunity cost as defined by the use of resources for alternative government programmes may be underestimated.

A sustainability analysis is especially important for expensive chronic interventions where health gains depend on long term, uninterrupted treatment such as for tuberculosis and HIV. This could include the proportion of donor resources in a project, the proportion of imports in an intervention, the proportion of external funding in the health sector, or the rate of change of personnel.

### 4.5.6 Other factors affecting decision-making

Cost-effectiveness information is but one piece of information used for decision-making and as will be emphasized in the next section below, the Key Informants findings, it can be relatively unimportant or even not useful. Brinsmead et al. (2004) concluded that CEA results without accompanying information about budget constraints did not provide much guidance to decision-makers considering the introduction of Hib vaccine in both industrialized and developing nations. In considering the introduction of new vaccines against typhoid, cholera and shigellosis, DeRoeck, Clemens, Nyamete and Mahoney (2005) found that policy-makers from several Asian and South East Asian countries thought that the burdens of disease, the extent and seriousness of these diseases, in their countries were unknown and official estimates of incidence unreliable. The economic impact (treatment costs, loss of work time) was important to them, and cost-
effectiveness was important to a lesser degree among a few country representatives. Vaccine price and affordability was one of the most important factors for policy-makers, along with vaccine efficacy and safety. Whether the vaccines would be able to be produced locally was important to the policy-makers of countries that had local manufacturing capabilities. Tellingly, the authors report that some of the policy-makers felt that better water and sanitation was a better use of national resources than new vaccines, despite not having formal cost-effectiveness information to make this judgment. In a similar study of policy-maker views, this on the introduction of a dengue fever vaccine, the information that dengue fever was predominantly urban-based was deemed important as well as potential information from disease surveillance studies and local vaccine trials and pilot programmes (DeRoek, Deen, & Clemens, 2003). Information provided by international consensus organizations on recommendations for vaccine use is also valuable, and most importantly for vaccine adoption, contact with international organizations and the broad international immunization policies (e.g. the global push for implementing EPI programmes) (Gauri & Khaleghian, 2002).

The practical constraints facing decision-makers were explored by Hauck, Smith and Goddard (2004), who pointed to the influence of interest groups, particularly those whom decision-makers could ill afford to alienate, say urban-dwellers as opposed to rural-dwellers or powerful media or medical providers. Interest groups could include pharmaceutical groups and supranational groups, including donors. Implementing new policies could also impose transaction costs to decision-makers, another practical constraint. Gauri and Khaleghian (2002) had also found that the political organization and climate of the country affected vaccine adoption and coverage: democracies had higher coverage rates but not at low-income levels. The quality of political and social institutions, coupled with national income level, were more important to high adoption and coverage rates, however.

4.5.7 The context of differential levels of economic development

In this section, the recommendations outlined above are discussed in the context of the difference of income levels in developing countries themselves. Because the level of national
income not only affects political, social and economic organizations but also the epidemiological and health profiles of countries, general recommendations for enhancements of the WPRC need to be tempered with acknowledgement that healthcare systems of developing countries are not homogenous but are highly heterogeneous. Furthermore, health and healthcare characteristics do not necessarily always correspond directly to income level. For example, even when it was counted among low-income countries, China had a level of immunization coverage as high as some industrialized countries.

Nevertheless a general description of healthcares systems by income level is possible, and the characterization developed by Hsiao and Heller (2007) was used in Section 4.2.1 to distinguish developing countries (Stage I and II health systems) from industrialized countries in explaining the differing emphases on methodological limitations between them. In this section the differences in healthcare between low-income and middle-income countries are considered in more detail.

There are four major differences between low-income and middle-income countries (as defined by the World Bank) that are relevant to the application of the recommendations outlined in the above sections: the burden of disease, the size of the affluent population; the extent and capacity of government services and financing; and the proportion of the work force in the informal sector (Hsiao & Heller, 2007). When the DALY is broken down into its components of years of life lost (YLL) and years of life lived with disability (YLD), 90% of global YLD is borne by LMICs together, with 44% accrued in low-income countries (World Health Organization, 2008a). The diseases that contribute to that similar disability burden are, however, quite dissimilar. The top ten diseases for low-income countries are, in descending DALY burden: lower respiratory infections; diarrhoeal diseases; HIV/AIDS; malaria; prematurity and low birth weight; neonatal infections and other; birth asphyxia and birth trauma; unipolar depressive disorders; and ischaemic heart disease. For middle income countries the leading ten diseases are: unipolar depressive disorders; ischaemic heart disease; cerebrovascular disease; road traffic accidents; lower respiratory infections; chronic obstructive pulmonary disease; HIV/AIDS; alcohol use disorders; refractive errors; and diarrhoeal diseases (World Health Organization,
Communicable diseases, mostly requiring public health interventions, dominate the burden of low-income countries compared to that of middle-income countries. The size of the relatively affluent population grows as economic development proceeds, driving shifts in government services and health financing modes. At the low-income end, government services are limited, and the population pays out-of-pocket for private sector services, which is often of poor quality. Because the private sector is popular (i.e. cheap and accessible) and treats diseases of public health importance, such as malaria and tuberculosis, its poor performance is a concern (Mills, Brugha, Hanson, & McPake, 2002). However, public sector provision, is also often poor (underpaid, poorly trained staff, poor facilities, over capacity), and being concentrated in tertiary care, is inaccessible to poorer patients. In Tanzania in 2000, 60% of the government health budget was spent in hospitals, although that amount was deliberately decreased to 48% by 2002 in favour of expenditure on primary care facilities (Gottret & Schieber, 2006b). Donor support is more heavily concentrated in low-income countries, augmenting government health budgets and care. As the affluent population grows, however, it demands better quality and more accessible healthcare, and government financing expands, with increased tax revenues, to provide more services and risk-pooling mechanisms like insurance schemes. Private provision expands, too, however, and the better quality provision now increasingly serves the richest segments of population. In middle-income countries, the affluent often influence the government to provide high-tech, advanced treatments (e.g. cardiac, oncology, transplant interventions) for themselves, thus affecting the allocative efficiency and equity of public healthcare (Hsiao & Heller, 2007). A wide disparity of healthcare, and consequently, health status, results. The work force in the informal sector is difficult to estimate as it is not regulated, paid wages nor accountable for taxation, and it is variously defined, but it is generally agreed that it is larger in low-income than in middle-income countries (Pratap & Quintin, 2006). The growth of the formal work force as economic development proceeds also affects health financing. Revenues are gathered from increasing wages and wage-earners, and insurance schemes are often funded and first offered to workers, especially public sector workers.
From the foregoing description it could be concluded that recommending a societal perspective in low-income countries would be appropriate, given their large communicable disease burden. Yet a patient perspective may be warranted, too, as patients are the main payers of healthcare, and productivity losses and gains are difficult to derive from a largely informal workforce. Choosing a societal perspective would not necessarily capture more costs and effects given the lack of relevant data, and in effect there may not be much difference in the respective ICERs of either perspective until the size of the workforce in the formal sector becomes significant.

Because government provision is limited in low-income countries, choosing a healthcare perspective would capture only the narrowest distribution of health gain. The exception in which a healthcare perspective would adequately capture a broader distribution of health gain would be in the case of a donor-supported communicable disease intervention that is delivered through the formal healthcare sector and has a wide population target. The appropriate perspective, thus, rests on the objectives of the decision-maker who ultimately uses the CEA results, but as demonstrated, providing multiple perspectives gives a more complete picture of the impact of a proposed intervention.

The implementation of a resource utilization study preceding a CEA would have the most benefit in low-income countries as much (sometimes the majority) of healthcare is delivered outside the government sector and would otherwise be more difficult to capture. The unregulated private health sector, especially individuals providing informal (e.g. untrained or traditional) treatment, is a case in point. Mills, Brugha, Hanson and McPake (2006) noted that very little is information is known about consumption patterns in low-income countries for either informal or formal (nurses, doctors, pharmacists) private care, and whether the poor rely on poorer quality care than do the more well-off. Low-income countries are the preferred recipients for donor funds, too, which may be delivered by a multitude of NGOs. As mentioned in Section 4.5, donor funds, whether delivered through public or private health sectors, are often off-budget and therefore not subject to government oversight. Resource utilization studies would also better reveal the healthcare seeking behaviour of patients and their caregivers, specifically time used in travel or taken from productive activities. This would reinforce the recommendation for estimating productivity at the extended household level to counter low valuation of patient productivity gains that would result from simple wage proxies, having an
especially large impact on CEs set in low-income countries. In middle-income countries, detailed resource utilization studies would nevertheless also be valuable, providing information that would not otherwise be available through official sources. This might include, for example, resource flows between the tiers of healthcare as patients combine private and public care or resource flows to the respective extremes of socio-economic groups.

The discount rate chosen may have a different impact on low- and middle-income countries, related to the types of interventions most likely to be studied in the respective grouping. The recommendations for using differential rates, higher for costs and lower and/or declining for effects, would better capture the value of communicable disease interventions that are needed to address the disease burden in low-income countries, but would bias against the acute care interventions that are more needed in middle-income countries. On the other hand, because both the QALY and DALY are indicated for use with conditions having long-term disability (Drummond et al., 2005), and YLD burden is similar in both grouping, there may be no bias created in using either in each setting. However, the lack of direct comparison between the two measures does not permit any conclusions to be drawn in regards to individual interventions, especially as their delivery may be very different according to the individual country.

While it is tempting to attempt to draw conclusions about the impact of certain recommendations according to the level of national income, it is apparent from the foregoing discussion that the analyst must assess each recommendation in light of the local context and the intervention in question. The terms “low-income” and “middle-income” are but artificial boundaries for a continuum of healthcare status, organization and delivery. However, it may be worthwhile considering that, from the viewpoint of CEA’s role in improving efficiency in a health-financing framework, middle-income countries can concentrate on methodological items that stress technical efficiency (e.g. more precise and detailed marginal costing) in purchasing healthcare so that allocative decisions can be made with the freed fiscal space. Lower-income countries may focus on methodological items of allocative efficiency, such as the WHO-CHOICE average costing, to help in priority-setting of multiple, needed interventions.
It must be acknowledged that the recommendations made by this author have more data requirements than those conventionally used. Thus, for low-income countries where data limitations are most severe, they may be infeasible or impractical and thus have no impact on improving CEAs to better capture the most relevant costs and benefits in this setting. A final observation is made here, thus. The establishment of sub-regional HTA networks would be helpful in addressing the needs of countries having little data and technical capacity. Already formed national HTA agencies like those in the middle-income countries of Thailand and Turkey could provide context-appropriate consulting services and technical assistance, as well as help to establish similar agencies.

4.6 Key informant interviews

Section 4.6.1 below describes the key informants and the interview process. Section 4.6.2 discusses the findings that emerged from the interviews, while the next Section 4.6.3 lists some additional points brought up by a few of the key informants. Conclusions reached about the key informant interviews are presented in Section 4.6.4.

4.6.1 Key informant and interview characteristics

The 11 interviewees were all experienced researchers, middle to senior members of their respective organizations, most of them in leadership positions. One directed a multidisciplinary academic institute concerned with global health equity issues. One was an official from a quasi-government donor agency, directing a unit responsible for global health research funding and technical assistance to developing nation health ministries. All had direct experience in primary data collection in at least one developing country and six had experience in more than three developing countries. All had participated in generating evidence for primary health care policy-making. None was a policy-maker or decision-maker him or herself, that is, an elected/appointed member of the government, or belonged to an official body directly charged
with immunization policy decisions. All of them, however, were close to the decision/policy-making process and worked with policy-makers in some capacity, usually in providing research support or technical assistance. Only one key informant was a government employee, the director of a health ministry research unit.

Five of the key informants were very familiar with cost-effectiveness analysis, having conducted it. Two others were not practitioners but had a good understanding of the principles and applications, one being a professional economist and the other extensively involved in promoting health technology assessment. The remaining four key informants were cognizant of the concepts of economic evidence and its role in health care decision-making and evidence-based medicine, but did not mention that they had ever been directly involved in any type of economic evaluation.

The key informants were engaged in wide-ranging activities pertaining to evidence generation, although not all of them had a focus on immunization. Of the five key informants engaged in producing evidence for a decision currently under consideration by public health authorities, two were conducting costing studies (for Vietnamese and Thai health ministries and collaborative international projects), one was performing cost-effectiveness analysis alongside vaccine clinical trials (for the International Vaccine Institute/WHO projects in various Asian countries), one provided expert opinion and clinical advice on immunization practices (for the national immunization authority and medical community), and one analyzed facilitators/barriers for new vaccine introduction (for various international agencies). Of the other six key informants, five were engaged in community or public health research that encompassed immunization (for their respective universities and governments). Only one key informant did not have any involvement with immunization decision-making per se, providing instead related but relevant input from the pharmaceutical/vaccine industry into Chinese drug reform decision-making.

Many of the key informants had worked or were currently working in multiple countries, enabling wide perspectives and inter-country or global comparisons, including direct comparisons between industrial and developing nations.
Importantly, the key informants had a clear perception of being closely and actively linked to policy-and decision-making, some at the highest national level, as evidenced by one key informant: “I still work, and worked in, at the Mexican Health Foundation as a health economist and provided a lot of evidence, I think, that was used in the reform.” The key informants, with the exception of the funding agency official, saw their contributions in concrete terms and as tangible service to national governments.

Table 11 below summarizes the main characteristics of the key informants and of the interviews.

Table 11: Characteristics of Key Informant Interviews

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of interviews</td>
<td>11</td>
</tr>
<tr>
<td>Length of interview</td>
<td>Ave. = 41 minutes; range = 27 – 60 minutes</td>
</tr>
<tr>
<td>Disciplinary backgrounds of key informants</td>
<td>Epidemiology (2), Economics (including health economics) (2), Medicine (5), Pharmacology/Pharmacy (1), Political/Social Science (1)</td>
</tr>
<tr>
<td>Professional capacities of key informants (total exceed number of informants as some served in multiple capacities)</td>
<td>Academic researcher (4), research scientist (2), economist (2), health economist (2), global health researcher (1); clinician researcher (2); donor agency official (1); technical consultant (1)</td>
</tr>
<tr>
<td>Places of employment of key informants</td>
<td>University, industry, public research institute, international technical assistance organization, donor agency</td>
</tr>
<tr>
<td>Gender</td>
<td>Males = 5; Females= 6</td>
</tr>
<tr>
<td>Industrialized-world nationals</td>
<td>4</td>
</tr>
<tr>
<td>Developing-world nationals</td>
<td>8 (one dual citizen)</td>
</tr>
<tr>
<td>Based in developing world</td>
<td>8 (these do not coincide exactly with above)</td>
</tr>
<tr>
<td>Work predominantly in developing world</td>
<td>11</td>
</tr>
<tr>
<td>Main countries covered by key informants’ work</td>
<td>China, India, Thailand, Vietnam, Mexico, Tanzania, general developing nations (1)</td>
</tr>
<tr>
<td>Field of work</td>
<td>Community health, public health, immunization/vaccine policy, pharmaceuticals</td>
</tr>
<tr>
<td>Principally engaged in providing evidence for immunization or vaccine decision-making</td>
<td>5</td>
</tr>
<tr>
<td>Mode of interview</td>
<td>By phone = 9; in person = 2</td>
</tr>
</tbody>
</table>
4.6.2 Findings from key informant interviews

As described in Section 3.2 the raw transcripts were paraphrased into summaries, and these summaries were in further summarized to distill the major points salient to the research question. The paraphrased summaries and the short summaries are included in Appendix 12.

In this section the derived understanding about the decision-making environment of selected developing countries, and the role of evidence within, are presented. The eight major themes are:

- Heterogeneous, non-formalized frameworks of decision-making
- Centrality of burden of disease evidence
- Evidence synthesis and use
- Influence of opinion-leaders
- Uncertainties
- Priority of addressing data uncertainties
- Heavy influence of international organizations in vaccine introduction
- Aids needed for new vaccine introduction decision-making

1. Heterogeneous, non-formalized frameworks of decision-making

Key informants did not identify a unique pathway or set of circumstances that would be critical or useful to decision-making but had opinions on what could be important aspects. Some of the answers reflected the individual’s own research framework, such as the importance of using integrated health-system wide evaluation or understanding what was actually feasible in the local context. Three of the answers reflected the low and middle-income status of the countries represented; budgetary impact and financial cost were the prime delimiters for decision-makers. Half of the key informants thought that opinion leaders (“famous professors”, “centers of
influence”, local politicians) and human relationships (“golfing buddy”, exchanges on trust) were the most important factors, even if unofficial, in shaping decision-making. A point was made that the capacity of the decision-makers themselves to understand and assess evidence, especially economic and technically sophisticated evidence, was the key to making systematically robust decisions for new intervention introduction. One declared decision-making was driven by special interest groups, secondarily by cost/budget, and was not evidence-based at all in China.

Although the centralized economy-wide planning that had in the past characterized some of the countries (China, Vietnam, somewhat India) was no longer a determining framework for healthcare decision-making, it was vestigially evident in the fact that local decisions must reflect nationally decreed policies. For example, decision-making in these countries was highly hierarchical, with fixed responsibilities at different levels. Many key informants alluded to cyclical planning processes that affected the timing of decision-making.

2. Centrality of burden of disease evidence

Burden of disease, measured by mortality and prevalence/incidence particularly, was the type of evidence most often mentioned as being the most important, followed by other types of epidemiological information (e.g. whether epidemic or endemic, population demographics).

Burden of disease measured by QALYs or DALYs was mentioned by only one key informant, but significantly, as being unimportant to local decision-makers. “DALY doesn't mean anything. That's more of a donor driven statistic.”

Vaccine efficacy and effectiveness, vaccine cost and general drug pricing were thought to be of high importance to decision-makers by only half the key informants. Although there is reliance on or acceptance of global surveillance data and externally generated evidence found in international vaccine/immunization literature, some of these interviewees pointed out that the desire for local and not extrapolated or generalized data, was gaining:

And the countries now… they more and more want local data, they want local data on the vaccine, its efficacy, its safety in local population, and of course its cost is very important, what the price is.
But there are a lot of countries now doing, even if a vaccine's been licensed internationally, even if it's, in some cases, offered by GAVI, they want a local efficacy and safety study done.

Information about and from the local and international vaccine markets was discussed extensively in three interviews, reflecting the key concerns of pricing of vaccines and drugs, and, related, of access to vaccines and drugs. Economic information emanating from the pharmaceutical industry, in terms of pricing and marketing, seem to be influential in India and China, probably due to the size and importance of the manufacturing centers located there. In regards to pharmacoeconomic studies, one researcher pointed out a distinct difference in emphasis:

In North America … we were mostly relate [sic] and kind of focused on more like a commercial sector oriented ideas. Whether or not that kind of production scheme can be cost effective enough to produce such a number of doses when we consider large amount of investment, capital investments for development of such a product for North American region. Versus now, we are working mostly on the economic part. So, more increasingly we have to work on…I mean of course cost effectiveness is important for everywhere but especially in Asia it is so much related to the decision making process of each government. Because of their concern about sustainability and affordability.

Economic evaluation and cost-effectiveness were considered useful by seven key informants, but that type of evidence figured low on their list of information inputs, and one doubted the transferability of vaccine cost-effectiveness analyses conducted elsewhere but being adopted as evidence in his country. Budgetary information – financial costs, sources of finances, budget allocation patterns and discretionary amounts – figured more highly, that is, was mentioned closer to the top of the list of inputs. One key informant thought that even when presented with both costs and benefits, policy-makers tend to ignore the benefits:

Actually, they don't want to see the benefit part, they want to see the cost part. Okay how much money we spend on the project, tell me. How much money we spend for one place, for one person, that's it. See they're more focused on the budgetary things, not for the input and the output.
Once sensitized, though, governments and researchers are receptive to economic evidence and a rapid awareness of cost-effectiveness analysis seems to be underway. “[From] let’s say about three to four years in [sic] recently, whenever I meet people we talk about, you know, what is the economic impact of the vaccine.”

Three key informants thought decision-makers also used information about health care systems (immunization coverage rate, incorporation details into current immunization programmes, available human health resources). Often, decision-makers invited “individual experts in the particular field to provide their inputs based on experience and data.” The type of assistance and inputs from international organizations, and significantly, whether or not GAVI funding was available, were thought to be important information by key informants who were involved in international research efforts. The simple conveyance of the information affects decision-making:

Another one is if it's an urban disease it gets more attention because that's where both the media live and the politicians…And of the three enterics, when we did the DOMI study of typhoid, cholera and shigellosis, by far typhoid had the most…there was the most interest in typhoid in most countries, and I think that had to do with the urban setting.

Two key informants made a very strong case for the importance of political information, centering on knowledge about both national and local political concerns and processes and the actors who facilitated decision-making. For example, vaccine approval at the national level may be based on population data, but implementation requires knowledge about individuals, as found by one of the informants who was trying to identify a local decision-maker in India:

So when we spoke to district collectors, they said oh yes, the policies are good and we try to do things. So they definitely have quite a bit of influence because they make allocation decisions. But in interviews with them, they said but you know, ultimately it rests on the Chief Medical Officer.

Interviewer’s note: DOMI - Diseases of the Most Impoverished.
3. Evidence synthesis and use

Formalized health care planning processes (e.g. multi-year plans) were mentioned in the cases of China, India, Vietnam and Mexico, but there was no detailed discussion how the above-mentioned information was integrated in that process. Rather, the more extra-ordinary processes of recent health care reform in these countries were used as the context for information integration for pediatric immunization, particularly in the expansion of basic public health or the extension of universal health insurance. In China, unsurprisingly, the government is the main consumer of the information and controls the information more tightly, being the initiator or collaborator of most data collection, including foreign-led studies. Recent health care reform here has included many consultative components, although the actual integration of the invited input was not discussed in detail with the key informants. One key informant commented that consolidating the information and coordinating consensus will be difficult and time-consuming as fourteen ministries form the health reform steering committee.

Vietnam’s health care is also centrally planned, but, as suggested by three key informants, it is more dependent on or open to information generated from outside the country or by outside investigators, especially from surrounding countries. This reflects at the same time gaps in local information and also a desire to have locally or regionally specific and appropriate data, a point strongly emphasized by most of the key informants. Similarly in India, many organizations and individuals are invited to offer technical advice or assessments, along with unsolicited opinions and advice, to supplement international data. According to a researcher there, however, this does not always yield a locally-focused solution:

So most committees together put all this data together and then plan also to seek being in line with the recommendations and guidelines of international bodies like the WHO. Sometimes they use, often the American Academy of Pediatrics recommendations and ACIP 21 guidelines. Put all these things together and produce a kind of guideline that is ultimately at the end of the day, kind of an extrapolation of what already exists in other countries.

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21 Interviewer’s note: ACIP - Advisory Committee on Immunization Practices, an American CDC body.
In all cases, key informants said that ministries of health collate and aggregate the information regardless of the point of entry into the health care system, a centralized approach to be expected for public health decision-making. One key informant gave a fuller view of this process. In Mexico decision-making is sophisticated and complex, with actors experienced in making six-yearly health care plans. In the reforms to extend health care coverage and insurance to the lowest income (and uninsured) population, an enormous effort was made to generate, collect and use evidence to define a guaranteed essential package of health services and interventions, which included immunization. Evidence came from a multitude of sources and channels, “from different parts of the government, several structures feed in like the National, like the INEGI\textsuperscript{22} informatics agency. And then outside of government in terms (of) feeding, I think it’s academics, advocacy groups, NGOs and clients, users, patients”. Macro-economic and cost-effectiveness data generated both internationally and locally were further used to win budgetary protection for this package from the Ministry of Finance. Instrumental to the decisive success of the reforms was a proactive “technocracy” in the Ministry of Health who counted among them “some of the best economists and epidemiologists in the world.”

One key informant, referring to lower-income countries in Africa, stated that governments often had difficulty in collecting data, integrating it into the central planning process, and then using it to target interventions appropriately:

Most of the information that you get at ministry level deals with facility-based information, people coming to health facilities and that’s encounter-level information. But they are not able to identify which are the households that haven’t been immunized. Where is there a pregnant woman that requires attention?

Sometimes health-related data must be amalgamated with data from other sectors if government allocations occur on a sector-wide basis. For example, district managers in two regions in Tanzania are responsible not only for health care, but also for other government services and must prioritize allocations based on information from multiple, competing sources. Even for the health sector alone, one key informant thought that more complex indicators capturing

\textsuperscript{22} Interviewer’s note: INEGI - Instituto Nacional de Estadística y Geografía, National Institute of Statistics, Geography and Informatics.
effectiveness was needed, beyond burden of disease and CEA indicators, “a third generation” of indicators she called them.

Identifying pertinent information and matching it to the decision-maker most able to use it was considered to be a practical route to putting evidence to use, although decision-makers themselves need to be available or agreeable. “So I don't know if decision makers want to be reachable in a mass way, probably not, right.” In trying to introduce unfamiliar economic evidence, one key informant thought that a personal relationship with the decision-maker was helpful:

If you give them scientific evidence and if your research was conducted in the rigorous methodology [sic] and if you can have the chance to talk with the policy maker face-to-face and say it kind of building up the relationship, is trusting relationship, and then they will trust your results, findings. Depend on the relationship.

Several key informants stressed striving for contextual precision of evidence, “rooted in the specifics of ground level needs”. However, political expediency can obviate carefully formulated evidence:

So one of the ideas is to try to put this on the political agenda and so in one of our discussions, it's interesting because one of our discussions with a member of the legislative assembly, you know Bangalore…. So he said, you know there's an election coming up, is this something that would be useful?

And he said, oh well you know health is not an election issue. You know that's nice but we would deal with that later. You know elections are about 10 rupees per kg rice and all that.

You know, it’s interesting. You know he just said that health and politics, you know it's just not an issue. We can deal with health in our free time, but in election time we deal with issues that people care about.

One key informant was adamant in stating that vaccine introduction, including the initiation of probe studies and clinical trials, is recently driven by international organizations and the promise
of donor funding, specifically by GAVI. Another key informant, involved in rotavirus vaccine field trials supported by several international organizations, bore this out:

I mean this is the, almost the first time that any Asian country has the whole package for at least the rotavirus vaccine. … So then the timing of collecting all the information and cost-effective analysis will be the time when Vietnam’s government has to make a decision for GAVI money for rotavirus vaccine support… So I’m going to, I’m encouraging the Vietnamese government actually to utilize this package information when they apply for this GAVI money.

4. Influence of opinion-leaders

In all countries, high-level officials in government ministries of health were the ultimate and chief decision-makers, but there was important involvement of related government agencies and non-health ministries. There was also a varying degree of non-government actors, reflecting the degree of openness of the government. Ministries of finance were thought to be the most important actor outside the health ministry by most of the key informants:

… very quickly, very quickly the government want[s] to know how much it costs, what's the implications for budget. So that's a question that comes from central government and most time you need to lobby not the health people, you need to lobby finance, Ministry of Finance.

Central planning bodies, supra-ministerial bodies responsible for multi-sectoral planning, were also very important according to two key informants. Besides line ministry departments, medical and technical advisory groups were the most influential in decision-making support. In some cases, such as rotavirus vaccine introduction in Asia, these groups are struck up ad hoc to study specific problems. Others are standing groups, like pediatric associations, that are invited to give specialized advice. Depending on the conventions of the country, unsolicited advice is also sometimes welcomed. Only recently, informs one interviewee, have specialized national vaccine and immunization advisory bodies been formed to study and formulate policy and practices, but that is a fast growing trend in Asia. In a departure from the past, the recent health system reform planning in China has included public consultation. “You know, in the old days,
you know, there’s not much open… there’s no channel for open discussion or consultation. But there has been change, significant change…”

Three key informants distinguished between the decision-makers at the central planning level and those at the implementation level. In both India and China, the decentralization of health care provision to the provinces and districts meant that some local decision-makers had a significant amount of latitude in using local data and in allocating resources. For example, in one province in China, a rabies vaccination programme was implemented based on local need, although it was not included in the central government’s plan for universal immunization. In India, district health action committees formed from local stakeholders have discretionary spending authority over unallocated funds, usually using them for interventions for which there is no formal budget. Yet, decentralization also hampered decision-makers at the implementation level if planning and budgeting were not synchronized. In China, for example, policies were decided centrally, but financing was raised provincially, leading to disjointed decision-making and unevenly (and inequitably) implemented health programmes, even those deemed of a universal nature like immunization. Local decision-makers are also subject to ad hoc, parochial requests, as explained by one key informant in describing the role of district collectors (financial officers) in India:

   This person you know, sits at a desk and is inundated by supplicants throughout the day, for all kinds of petty issues. … They're not petty, but, I mean some of them may be grave issues, but they're individual ones. And that's, like most of his day is spent doing that.

Key informants also discussed the actors who had unofficial but significant roles in decision-making. Individual academics play an extraordinarily influential part in supporting decision-making in Asia, perhaps reflecting a cultural emphasis on education. Academics or scientific academicians were not only invited to provide expertise, but also used to provide validity to government policies, maintained one key informant. Sometimes special interest groups also use academics to influence decision-makers, as a key informant in China stated: “And they use some famous professors to push the policy maker to issue the policies.”
The state-run vaccine industries in India and China were also thought to have strong voices in decision-making; government relies on them to provide scientific and pricing information. However, formal and structured pharmacoconomic studies, as known in North America and Europe, are still a negligible source of evidence, and are not policy-oriented. In both countries there are also private or quasi-private (joint-venture) sub-sectors that are increasingly important factors in decision-making as they accommodate growing private demand for vaccines and drugs. One key informant thought that the private availability of the expensive rotavirus vaccine to wealthier Indian citizens complicated the decision-making, creating demand that may be accelerating the consideration to provide the vaccine on a universal basis.

5. Uncertainties

Overwhelmingly, key informants thought lack of or poor quality data was the main uncertainty in decision-making for vaccine introduction. This concern pertained mostly to deficiencies in local disease prevalence and incidence rates, but extended to having to use data extrapolated from other countries. The unknown price of new vaccines was the single most cited type of deficient data, especially worrying those concerned with cost data. In the context of cost-effectiveness analysis, seven key informants mentioned non-local or unknown effectiveness data (including local rotavirus-induced diarrhea prevalence) as sources of uncertainty. Not being able to measure effectiveness over time could be costly in financial and health terms, according to an India-based key informant:

This is something we lack and therefore this is one of the important reasons why we have not included any new vaccines over the last 25 years and the fact that we continue to battle poliomyelitis with no definite end point in sight.

Some key informants also discussed more general issues of uncertainty for the adoption of new vaccines. In this case they cited constraints related to the status, organization and developmental stage of the health care system. Unknown decision-makers and rapid turn-over of decision-makers, unknown resources (human and financial), the identity and location of patients, lack of
control of data if international organizations were involved, and the lack of capacity to generate and understand evidence all contribute to uncertainty. Leadership at the implementation level can be a constraint. For example, a vaccine addition may be decided upon at the national level, but implementation at the local level requires a precise knowledge of the key facilitators.

So when we spoke to district collectors, they said oh yes, the policies are good and we try to do things. So they definitely have quite a bit of influence because they make allocation decisions. But in interviews with them, they said but you know, ultimately it rests on the Chief Medical Officer.

Micro- and macroeconomic conditions also figured in the concerns of four key informants. The entry of more vaccine manufacturers into local markets and looming regulation of the vaccine industry suggested pricing uncertainty to two key informants, while three of them discussed the uncertain impact of the recent economic downturn on drug markets, government budgets and planning for basic services like immunization.

6. Priority of addressing data uncertainties

Because of the dominating concern for data deficiencies, a corresponding concern was expressed to address the establishment or improvement of data generation and collection. Most often, key informants mentioned the need for formal disease surveillance systems, targeting either individual or grouped diseases (e.g. enteric diseases). Key informants also desired the ability to manage information, to circulate it, to use it at the appropriate time, and to integrate disparate types of information. Measuring impact and evaluating outcomes were desirable to two key informants for mitigating uncertainty.

By contrast, one key informant asserted that there was a general underestimation of the capacity of developing countries to produce and use evidence. “There’s been, you know, pretty impressive effort to be able to produce at least some of the basic evidence in terms of burden of disease, cost effectiveness of certain interventions.” Another mentioned a “second body of
literature [that] is locally generated data, which might be available in journals and publications that may not be indexed internationally.”

Making internationally available data locally relevant was a strategy that was employed to overcome data deficiencies in one case:

Now over the last few years, I would say three to four, we have been trying to change that by trying to be more evidence based in the sense of not just picking up evidence from literature and applying it, but trying to contextualize these pieces of evidence to see where and how they fit in the scenario of our own country rather than simply extrapolating the evidence from elsewhere and trying to recommend based on that.

7. **Heavy influence of international organizations in vaccine introduction**

All of the key informants had worked with international global health researchers or organizations and were highly aware their role in their national health care systems. Some thought they formed, whether explicitly or implicitly, part of the decision-making process: “Inputs are taken from these (organizations) and decisions are framed.” Nevertheless, most of them considered the involvement favourably:

In China, most of the new ideas, to be honest, most of the new ideas come from the foreign research professor. And most projects initiated by the international organizations, for example DFID, the World Bank…

The proliferation of CEAs for new vaccines conducive by international organizations was also considered positive, leading to local governments demanding the use of the technique (even if the capacity to understand it was not yet in great enough) and thereby strengthening the movement to evidence-based medicine in developing nations.

Key informants welcomed the general increase in donor funding and the presence of related donor activity in their countries, although also noted that the increase in funding was very narrowly applied to a few disease areas. The increase in international and foreign organizations
studying China’s health care system influenced decision-makers to include rural health finance protection in reforms, for instance. One key informant, who worked with international collaborators, thought that international organizations were becoming more sensitive to local needs and were helping to adapt important medical guidelines to local contexts. The key informant from Mexico, which by dint of its upper-middle-income status is unaffected by increased donor funding, thought that tremendous achievements in local vaccine and drug access (e.g. to antiretrovirals) have followed from the influence, if not funding, of international organizations, and that the new international public-private partnerships could be models for domestic health care provision.

Technical capacity was often brought up in connection with international organizations. Two cited the need for local training or other ways of decreasing reliance on technical assistance provided by international organizations. On the other hand, two key informants welcomed international assistance to increase capacity for economic evaluation, and assistance in measuring effectiveness and impact evaluation would be more valuable to two others.

Interestingly, the one key informant who worked for an international organization primarily concerned with vaccines was critical of the domination of donor organizations, particularly GAVI, in the prioritization of immunization objectives, of research orientation, and promotion of financially unsustainable programmes. “If it's a GAVI funded vaccine, all of a sudden it goes way up to the top of the list, even if the country can’t afford it, doesn't know they have the disease.”

GAVI’s role in introducing new vaccines to LMICs featured prominently in many of the key informants’ comments, and sustainability was a key issue:

GAVI has offered to make the pneumococcal conjugate vaccine available at very low cost for a period of about four to five years. What is not clear is why GAVI should be willing to finance and fund only this particular vaccine and only for a limited period of time. For example, I am given to understand, though I have no proof, that if the Indian government were to ask GAVI to fund another vaccine which we think is more important, we might not get as encouraging results as for this pneumococcal vaccine.
8. Aids needed for vaccine introduction decision-making

Since all the key informants were past or active researchers, most of the responses related to improved information and knowledge, whether it was represented by epidemiological/economic data and data systems, or understanding the socio-economic/political barriers and facilitators to immunization. A formal channel or structure to move information was very important to one respondent. Two key informants cited a need to integrate multi-disciplinary evidence (to “homogenize” data, as one key informant put it). Three key informants spoke of knowledge translation, too, and implied that the translation needed to go both ways between developed and developing nations. They emphasized a full and specific understanding of the local context to correctly identify needs, to find enabling decision-makers and opinion-leaders, to deliver appropriate health care messages, and to sensitively adapt tools for evidence generation and gathering. One suggested that perhaps a “best-buy” knowledge translation tool should be sought, meaning that the best-buy intervention was the one that would be most likely to be taken up by the local population.

One key informant thought a tool was needed to sort country-specific health priorities, and another thought the co-ordination of donor inputs and funding would clear up much uncertainty in recipient countries. Still another valued having more methodological/analytical guidelines in general. Only one key informant specifically named and discussed economic evaluation as an important tool to address uncertainties; while another recognized its potential, she thought her government was not considering specific tools yet. Four key informants thought improved technical capacity was more important than tools.

4.6.3 Additional points

Being semi-structured, the interviews allowed key informants freedom in expressing related opinions. Each of the following points was discussed by at least two key informants.
Better utilization of resources or reallocation of resources was considered to be more important than expanding resources. The key informants believed that many inefficiencies exist in the current systems of their countries and that attention should be paid more to eliminating these than to seek out new external resources. One of the key informants also pointed to the inequitable distribution of resources between different provinces in his country requiring priority attention, citing his belief that there is really no need for additional resources, but rather a redistribution of resources.

The cost of information gathering and the use of the information need to be carefully considered, thought the key informants directly involved in costing studies. CEA data requirements were deemed very high, and in two countries key informants were working on regional cost studies to extrapolate to national level studies. Although they were confident of the robustness of the data they were gathering, they were less confident about their generalizability. A barrier to using evidence in decision-making is the cited decision-maker view that creating information infrastructure is expensive and “not worth the trouble”. An investment approach to evidence (explicating the “payoff” of dedicating funds to generating evidence), and using language more familiar to business than healthcare, could be useful in convincing some decision-makers, thought a key informant.

Several key informants were adamant that personal relationships, trust and exchange are equally or more important than evidence. The importance of opinion-making individuals to decision-making was discussed above. This more subtle point refers to the two-way flow of information engendered by secure relationships that permit privileged information to influence both evidence-generation (e.g. what kind of information is wanted) and evidence use (e.g. what kind of information is put into action). Key informants themselves were conduits between high level ministry officials and community health workers in these situations.

The strength and efficiency of the public health system is the most important determinant of the effectiveness of vaccines, especially factors that give rise to, for example, the coverage rate, the immune response in individuals, and the spoilage rate of vaccines. A key informant who had worked in several lowest-income countries believed that priority should be given to bolstering
health system capacity before adding any new vaccines. Another pointed out that the troubling gap in rotavirus vaccine efficacy between high-income and low-income countries (80+% compared to 68%) was due to epidemiological differences that could be traced to health system inadequacies.

Appropriate decision-making tools are difficult to identify definitely, because, as one key informant said, “They are related to governance and governance is not an easy topic.” The issue of political systems and political will was also discussed, but although the key informants acknowledged this point, they had no suggestions for a solution.

Assessment of the feasibility of a particular decision should be the particular purview of the local decision-makers, not of international experts, according to a few informants domiciled in a developing countries. Key informants representing one country in particular were very sensitive to the perceived patronizing attitude of some donor organizations. For example, one of them blamed the lack of progress on polio eradication on an inadequate understanding by international experts of sub-national and local epidemiological context and healthcare seeking behaviours.

Funding for new, expensive vaccines by GAVI seem to be a mixed blessing to some key informants. While GAVI’s offsetting the cost of vaccines is welcomed, there is also concern that it is driving demand for vaccines for which the exact need based on local disease burden has not yet been proved and for which incremental pressures on the health care system are unknown. Additionally, there is concern that countries are tempted by the funding to implement programmes that will be unsustainable and costly in the long run.

One of the key informants helping to analyze new vaccine introduction thought that WHO economic evaluation guidelines are not locally useful or are inadequate. In regards to the guidelines for the evaluation of rotavirus, “…(academic economists) don’t regard the information coming from those, uhm, guideline based studies as very academic or very economic oriented information.” This quoted key informant, who had experience conducting CEAs in industrialized countries, thought that the guidelines were too simplistic, and that
studies generated from them should be considered non-rigourous. However, this was not discussed in detail, and whether decision-makers could or should use these results was not ascertained.

4.6.4 Conclusions

1. Decision-making for immunization is highly centralized in health ministries, tempered with budgetary constraints imposed by finance ministries. In support, research evidence and expert opinions are sought in varying degrees from medical professionals and technical experts, and in limited cases, other health care stakeholders. Significantly, in Asian countries local professors and academicians are highly sought not only for their expertise, but also to provide authority or validity to decision-makers.

2. Health care reforms, ongoing or planned, in all of the countries represented in the key informant interviews have been catalytic in stimulating substantial and dynamic analytical activity for decision-making. Immunization decisions are centered on the introduction of new vaccines, and are made predominantly with evidence from a diverse variety of internationally derived sources. Structural changes in the health care systems related to increasing research and technical capacity, such as the establishment of technical advisory bodies specialized in immunization practice and policy or health technology assessment, further stimulates the demand for more and better evidence.

3. Evidence-based decision-making is reportedly well regarded and well known to the research community as well as the policy/political community, although defined and applied variously. Personal, human relationships, that engender trust in evidence and political exchange, for example, are nevertheless highly influential in decision-making, especially at the local, implementation levels. For effective decision-making, providing the appropriate evidence to the decision-maker who has actual or de facto authority is critical.

4. Epidemiological evidence is most important to decision-making, but with varying degrees of emphasis. Economic evidence is also thought to be important to government,
although usually from the cost or budgetary point of view. There is a range of awareness and capacity for economic evaluation, from high middle-income countries like Mexico with well-developed data infrastructures and deep technical and analytical capacity among its decision-makers to low-income countries like Tanzania that rely on international organizations and foreign experts to assist in economic evaluation and capacity-building. Overwhelmingly, cost-effectiveness analysis is a nascent tool and plays a minimal role in decision-making in the countries represented by the key informants, there is a rapidly increasingly awareness and focus on it.

5. Significantly, field trials for the rotavirus vaccine in Vietnam are being accompanied by economic data collection and costing studies, intended for full-scale cost-effectiveness analysis.

6. The greatest uncertainty in decision-making for the introduction of new vaccines is their unknown cost. The main constraint for the adoption of these vaccines into universal immunization programmes, even for those countries economically classed as middle-income and regardless of vaccine effectiveness, is the certainty of their much higher cost compared to the current vaccines in these programmes. Thus the vaccine manufacturing industries in China and India are comparatively important partners in decision-making as they may provide a lower cost and more stable supply of alternatives to vaccines produced in industrialized countries.

7. International organizations have an unofficial but substantial role in decision-making. WHO/UNICEF and the International Vaccine Institute continue to provide expert scientific and technical assistance and programmatic/funding support for the traditional immunization functions as well as analytical support through formal and informal guidelines on the financing and costing of immunization activities, including the introduction of new vaccines. GAVI has become a key player of the decision-making process in some nations, being funder, capacity builder, motivator for research, and priority-setter of vaccines for introduction.

8. In the countries represented by the key informants, there is desire for the priorities and applications of evidence and analysis to better reflect national and internal rather than international and external decision-making concerns. The availability of locally
generated and locally relevant epidemiological and economic data was paramount to key informants, and in the absence of local data, appropriately contextualized regional data.

Significantly, the information of the key informant interviews expanded the focus of enhancing a reference case from methodological to include implementation issues. As researchers who themselves were front-line formulators and shapers of evidence, and who were close to national and local decision-makers, they could provide a real-world perspective on the requirements of guidelines for using economic evidence. Very importantly, they highlighted the need of targeting the appropriate evidence to the right decision-maker. This implies a large role for knowledge translation.
5 CHAPTER FIVE: DISCUSSION

In this final chapter Section 5.1 summarizes the background of this research question and the results pertaining to each objective, Section 5.2 provides a synthesis of the findings, and Section 5.3 includes further discussion on the discount rate and a conceptual extra-societal perspective. Limitations are described in Section 5.4. Conclusions follow in Section 5.5, and Section 5.6 details lessons and implications for four main stakeholders of CEAs in developing countries. To complete this thesis, directions for further research are given in Section 5.7.

5.1 Summary of research question, objectives and findings

Large donor funds for health care, unprecedented in their volume and delivery methods, started to flow in the early 2000’s especially to the lowest-income countries and notably for immunization programmes. Cost-effectiveness analysis is a logical analytical tool to assess new interventions in the context of expanded national health care resources, and it had become increasingly important in the analysis of health care interventions in developing countries following the explicit linking of economic development to health care improvement by international organizations in the mid-1990’s. Yet, CEA is not without its limitations and even in industrialized countries its direct impact and usefulness in helping to prioritize and decide resource allocation is unclear. In this thesis, the reference case concept was used to help answer the following research question, how can cost-effectiveness analysis for pediatric immunization be adapted for use in developing countries?

Applying thematic analysis to a selected Data Set of literature drawn from peer-reviewed and grey literature sources, three initial research objectives were reached to help answer this question:

1. To identify the methodological limitations of conventional CEA when used in developing countries, particularly for pediatric interventions
2. To identify guidelines and recommendations for CEA methodology and application specific to developing countries
3. To identify the impacts of donor funding on the selection and estimation of costs, outcomes and the measurement of uncertainty for cost-effectiveness analysis

The findings from the thematic analysis were used to reach a fourth objective:

4. To adapt the reference case approach for developing countries

Finally key informants with expertise in evidence generation and use in developing countries were interviewed to realize the last objective:

5. To understand how to use adapted reference case by understanding the decision-making environment in developing countries

FINDINGS

Identifying methodological limitations in regards to developing countries: Methodological limitations identified in the Data Set were not differentiated between those for industrialized countries and developing countries, but different aspects of the same problem (e.g. valuation of productivity costs) were highlighted depending on the setting. The difference in emphasis arises from the systematic differences in disease burden and health system characteristics according to income level as described by Hsiao and Heller (2007). Methodological issues result in the underestimation of the value of vaccines and immunization (Beutels et al., 2008). The societal perspective recommended by CEA guidelines is vaguely defined and allows considerable interpretation as to which costs and effects should be included. In practice then, poor data limits the capture of the wide costs and effects that accrue to the prevention of infectious diseases. Discounting further undervalues the effects of immunization, which accrue farther in the future than costs do. CEA typically does not include estimation of the positive effects of herd immunity or the inclusion of children’s preferences in effectiveness measures. The valuation of costs based on the opportunity cost concept poses particular difficulties for developing countries where market distortions requires extensive estimation of proxies or “shadow” prices (Hutton & Baltussen, 2005). Although methodological limitations for pediatric immunization is important in an industrialized setting, they are amplified in developing countries because immunization is a proportionately more important health care intervention there, accounting for a larger share of
government resources and having potentially larger health impacts due to the heavier burden of vaccine-preventable diseases. Undervaluing immunization in developing countries could thus result in unrealized health gains.

Thematic analysis of the Data Set also revealed that there is a divide between developing countries and industrialized countries in the way CEA is used and applied. Most notable is the development of the DALY metric by the World Bank and WHO which is used both for measuring burden of disease and effectiveness. It is used exclusively for CEAs set in developing countries. This divide in the use of outcome measure makes studies done in either setting incomparable, and exacerbates the lack of generalizability of CEA results. A second notable difference is the use of WHO-CHOICE generalized-CEA approach also exclusively in developing countries. This approach examines interventions on a sector-wide rather than single-intervention, incremental basis, so aims at achieving allocative efficiency. The generalized-CEA approach was developed for application in developing countries, but so far it has been seldom used, applied only to studies that examines multiple interventions together.

One notable gap identified through the thematic analysis are the development of methods and reporting (through improved generalizability or knowledge translation) that would specifically address the mobilization of the considerable bank of economic evidence from industrialized to developing countries.

**Identifying guidelines for CEA in developing countries:** The literature Data Set revealed that guidelines for CEAs take many forms, ranging from global guidelines with room for interpretation to highly prescriptive costing manuals for immunization programmes that are supported by calculation instruction and software. Seven types of guidelines were identified that have relevance for developing countries: formal guidelines supported by national governments, manuals from technical agencies, consensus statements by CEA experts, recommendations embedded in CEA studies, checklists of methodological and reporting quality, reviews of CEA guidelines, and comparisons of specific elements of formal guidelines. In the past those that were specifically developed for developing countries, mostly manuals, were disease-specific and were aimed not at economists and analysts, but rather immunization programme managers or
planners. More recently, however, the WHO has developed more guidelines of a more global nature to support analysts using its WHO-CHOICE technique (Tan-Torres Edejer et al., 2003). Most recently (in 2008), the WHO has published methodological guidelines for the economic evaluation of immunization programmes, reflecting its long cumulative experience in immunization implementation and evaluation and the current global need to evaluate new vaccines targeted for introduction in both industrialized and developing countries.

It was noted that many national governments, including some middle-income countries, now possess pharmacoeconomic guidelines that emanate from health technology assessment agencies and address the evaluation of medical equipment and drugs (Jacobs et al., 2005). This reflects the types of health care decisions predominantly being made in industrialized or industrializing countries as opposed to the types of decisions made in developing countries, that is, for wider population-based and public-health interventions. There are no explicit guidelines addressing the choice of economic evaluation options when the data and analytical intensity required for good quality CEAs are short.

**Identifying donor funding impacts on the estimation of CEA:** For this thesis a focus on donor funding introduced a health financing view. The characteristics distinguishing this flow of resources from domestic resources were identified from literature on general aid effectiveness as well as analysis from political economists and development specialists. Noted is the substantial increase in health care funding for a narrow range of interventions, immunization included, and in a shift to a private-public mix of donor funding (World Bank, 2007). The general problems of funds volatility, delayed disbursement and short-term duration stem from donor governments’ and organizations’ obligations to their tax-payers and stakeholders (and sometimes investors), but they make it difficult for recipient countries to plan and implement allocation of resources and to sustain programmes (Birdsall, 2005). Large and substantial inflows of funds and goods also affect the general price levels of small developing nations and draw scarce resources away from other programmes, both health and non-health, to that supported by donor funds. The diversion of donor funds to other uses than initially intended also creates uncertainty for programme planning and implementation.
Although increased donor funding for immunization has precipitated the increase of CEAs for immunization interventions, particularly for rotavirus-induced diarrhea prevention, there has been no explicit examination of the above effects on estimation of CEA variables, most notably on costs and costing. Transaction costs are not normally estimated in CEA studies, but in the case with proliferation of funds and funders, can be high and ignoring them would severely underestimate opportunity costs.

The leadership of GAVI, a consortium of WHO, UNICEF, the Bill and Melinda Gates Foundation, national governments and pharmaceutical industry representatives, in funding and promoting new or underutilized vaccines in developing countries has both been welcomed and criticized. Review of GAVI funding in its initial years show dramatic increases in coverage of the traditional EPI vaccinations, especially for measles. Added to its support for immunization infrastructure and services, this has raised the effectiveness of immunization programmes. However, recipient governments incur high transaction costs associated with administering GAVI’s demanding and stringent application, monitoring and evaluation and reporting requirements. The new rotavirus vaccine to be introduced with GAVI support will raise national EPI costs considerably due to the high cost of the vaccine itself and the additional demands for medical and administrative personnel and cold chain expansion. Not only is there uncertainty in regards to the final vaccine price and the final storage requirements, but there is also concern about financial sustainability of the new vaccine in the long term when GAVI support ends. GAVI has been credited with explicitly addressing the problems of sustainability and funds volatility and in mobilizing financial resources from innovative sources.

Findings from the examination of donor funding clarified the potential directions in which methodological changes may be made for more meaningful results for developing country decision-makers.

**Enhancement of the Washington Panel Reference Case:** The use of a reference case approach provided a foundational basis in identifying what emphases or development in CEA methodology and practice are important to developing countries when evaluating routine immunization programmes. The findings regarding methodological limitations and CEA
guidelines pointed to specific needs to elaborate and delineate perspectives to capture the resource provision and utilization originating outside national jurisdictions, and to define new variables of costs and effects through the policy- and decision-making process and environment, to incorporate herd immunity effects (Brisson & Edmunds, 2003), to elaborate the preferences of children (or their representatives) in effectiveness measures (Keren, Pati, & Feudtner, 2004), to more thoughtfully apply the discount rate (Cairns, 2006), to expand the usual variables considered uncertain to include aspects of resource flows in the healthcare sector as well as between that sector and other non-health sectors (Hsiao & Heller, 2007).

Additional insights from the key informant interviewees based or working in developing countries helped to highlight the lack of data and technical capacity in performing CEAs and corroborated the need to better understand the political, social and economic environments of the decision-making. Importantly, the key informant interviews pointed to a premature and unrealistic expectation that CEA was important to developing world decision-makers themselves. This finding de-emphasized the focus on methodology in favour of that on applicability and practicality.

When viewed through donor funding, and tempered by supplemental information from the key informants, the suggested enhancements to the Washington Panel Reference Case center on perspective, costing, discounting and the policy-related issues of affordability, sustainability and reporting. Recommendations include a deviation from the societal perspective to a decision-maker and payer perspective, more explicit guidance for a wider range of discount rates based on private sector interest rates and time preferences, on expanding definitions of costs and effectiveness to include elements of the wider economy, and the presentation of supplemental information to aid the decision-maker.

**Findings from key informant interviews:** The key informant interviewees, all involved in research support for decision-making, revealed that decision-making processes and structures in the countries of their work were all highly different and the use of evidence for decision-making ranged from highly integrated and formalized to ad hoc and non-systematic. In all cases, though, the decision-making process was evolving quickly, propelled by national health care reforms
and the emergence of new vaccines. One result is the establishment of technical agencies specialized in the assessment and regulation of vaccines and vaccination being established across Asia. Middle-income countries represented by the key informants had more analytical and technical capacity to create and use evidence, but all key informants said decision-makers in their countries recognized the role and value of economic evidence for decision-making. However, in most cases economic evidence important to decision-makers was limited to cost or financial data; they considered burden of disease more compelling evidence. Cost-effectiveness analysis was not considered an important decision-making tool, although decision-makers are cognizant of and receptive to it. Local opinion-makers, especially academics, are highly influential actors in decision-making, as are representatives of international organizations. Local vaccine manufacturers in India and China were also important actors. GAVI is the most important external actor in immunization decision-making.

In regards to decision-making about new vaccines, the unknown price of the rotavirus vaccine was the single most worrisome uncertainty among the general uncertainty caused by the lack or inadequacies of local data. The unknown local prevalence of rotavirus disease and the unknown local effectiveness of the rotavirus vaccine were also considered majority uncertainties. Sustainability and affordability are therefore key considerations in vaccine adoption. In general key informants desired locally-informed or generated evidence for decision-making, while acknowledging that international evidence, properly contextualized, would be acceptable, too.

5.2 Synthesis

Almost all vaccine-preventable deaths occur in the developing world. Developing countries are challenged to make the best use of very limited resources for their nascent or underdeveloped health care sectors to address this enormous burden and donors from industrialized countries are challenged to make the best use of their own resources to provide the global public good of broken infectious disease transmission. Although the recent emergence of non-traditional donors and funding mechanisms focused on vaccines and immunization programmes, the scale, focus and prominence of some of the funding have also raised questions of their effects on national
health priorities as well as on the opportunity costs of the interventions supported by this funding.

Because the population usually served by vaccines are children and because vaccines differ from other drugs through their complicated economics and difficult research and development process, special consideration is needed to assess both the costs and effectiveness of immunization programmes. Particularly, the perspective of the analysis must be broad enough to capture the widespread and indirect benefits that spread past the child to the health sector to the educational sector to the wider economic sphere. Similarly, resource identification and associated costing must be more finely attuned to the health sector heterogeneity of developing nations as well as to the payers of programmes who are not bound by the national boundaries of the destination of their resources. Health outcomes measurements for children and for preventative interventions are equally underserved by current methodology. Methodological guidelines are limited in instructing analysts and decision-makers in CEA of childhood public health interventions, being focused on patient-level, clinical models of health care provision. The few guidelines that have been developed to incorporate developing country CEA concerns are relatively unknown to the vast majority of CEA analysts and practitioners and risk being ghettoized. This analytical divide between industrialized and developed world is exacerbated by an evidence divide that cannot be bridged, as the accumulating economic evaluation knowledge from the former, even if appropriate, is difficult to transfer. Key informants corroborate that a divide exists and emphasize the need for CEA applications more relevant to the national health objectives of developing countries and supplemental information more meaningful to local decision-makers. Increasing the local capacity for health technology assessment and economic evaluations, including the supporting data infrastructure, appears then to be a logical investment of resources, both donor and local, to better achieve more efficient allocations of resources that can not be wasted. The usefulness of an enhanced Reference Case would lie in guiding the local contextualization of methods to the particular health burdens and individual level of economic and health system development of developing nations.
5.3 Further discussions

Section 5.3 presents a further discussion with information not obtained through the Data Set. The discount rate and an extra-societal perspective are discussed first, and then 5.3.3 suggests a potential role for GAVI as a de facto decision-maker in the healthcare systems of lowest-income countries and a global decision-maker for immunization interventions.

5.3.1 Discount rate

Despite widely established conventions for the use of the discount rate as suggested by agencies such as NICE and CADTH, debate around discounting in CEA continues in the theoretical literature (Beutels et al., 2008; Claxton et al., 2006). As discussed in Section 4.2.4, the cost-effectiveness of preventative interventions like immunization, where benefits accrue in the future, and sometimes very far in the future, is particularly sensitive to discounting. Bos et al. (2004) also assert that the commonly used effectiveness measures (e.g. QALY, life-years gained) do not fully represent the time and health preferences of patients and thus the choice(s) of a discount rate should be guided by a fuller examination of the effectiveness of a given intervention. In this section the potential differences in the preference for time, which underlies the discount rate, is discussed in connection with the stakeholders involved in immunization decision-making in developing countries.

Through the key informant interviews the following important actors were identified: national government, GAVI, the WHO, the local pharmaceutical industry, and individual opinion-leaders. It was noted in Section 4.6 that GAVI is composed of both the public and private sector, notably in the latter group, the Bill and Melinda Gates Foundation and representatives of multinational pharmaceutical companies. Additionally noted, the International Finance Facility for Immunization (IFF-Immunization) raises funds in international capital markets expressly for the use of developing countries in their immunization programmes. The funds are channeled through GAVI. Commonly the discount rate in CEA is defined as a social preference for time. Given the current importance of the private sector in the immunization programmes of
developing countries, it may be instructive to also consider a CEA discount rate that takes account of private sector opportunity cost of capital. (A private sector discount rate reduces a stream of future net cash flows from an investment project to present values.) This would reflect private sector time preferences influenced by risks not included in public sector project rates. In considering the time preferences of the above actors then, it may be informative to survey a variety of discount rates used in both the public and private sector. Table 12 below compares recommended CEA discount rates against prevailing rates used for capital projects (infrastructure, buildings), financial projects (capitalization for goods and services), and social projects (social development projects such as education, environment).
Table 12: Selected Discount Rates

<table>
<thead>
<tr>
<th>WHO Guide For Immunization</th>
<th>HTA/CEA (Sensitivity Analysis)</th>
<th>Capital projects</th>
<th>Financial projects</th>
<th>Social projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govt of Canada</td>
<td>Rate prevailing in country of analysis SA: 0%, near-zero, 5%, 10%</td>
<td>8% (3%, 10%)³</td>
<td>8% (3%, 10%)³</td>
<td>3%³</td>
</tr>
<tr>
<td>Govt of U.S.</td>
<td>2.1% (3-yr project) – 2.8% (30-yr project)⁴</td>
<td>8% (3%, 10%)³</td>
<td>8% (3%, 10%)³</td>
<td>3%³</td>
</tr>
<tr>
<td>NICE</td>
<td>3.5% (0-6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico (Pharmacoeconomic guidelines)</td>
<td>Costs: 5% (3-7% range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand (Pharmacoeconomic guidelines)</td>
<td>Outcomes: 5% (0-7%)⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO-CHOICE</td>
<td>3% (also rate prevailing in country of analysis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian Development Bank⁶</td>
<td>12% (justify if lower)</td>
<td>12% (justify if lower)</td>
<td>12% (justify if lower)</td>
<td></td>
</tr>
<tr>
<td>Advance Market Commitment</td>
<td></td>
<td>8% (applied against estimated revenue streams of neglected vaccines)⁷</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources:

2 CADTH, 2006.
In presenting the case for establishing an Advance Market Commitment to encourage research and development of new vaccines for developing countries, Berndt et al. (2007) had suggested that vaccine manufacturers use a discount rate of 8%, the real cost of capital, to obtain the net present value of the potential revenue streams of very early stage malaria, HIV and tuberculosis vaccines. This higher rate reflects adjustments for minimizing risks (e.g. through upfront payments from government sponsors, committed purchase amounts, avoided marketing costs) due to the AMC being sponsored by the international public sector (mainly donor governments). Berndt et al. (2007) reported that this rate is lower than the real cost of capital used in earlier estimates of returns to the vaccine industry, 11%, but the rate is still much higher than conventional CEA rates. However, insofar as the co-operation of the pharmaceutical companies is essential for providing access to new vaccines needed by developing countries, their reflected time preferences may be taken into account when deciding a rate for discounting costs, if not effects. In any case, the AMC rate can be used as a highly credible value in a range of discount rates to be used in sensitivity analysis.

Using a higher discount rate in developing countries is not without precedence. Beutels (2001) reported that in a cost-benefit-analysis of infant immunization against hepatitis B set in Romania, the authors used a discount rate of 7%, which reflected the cost of the World Bank loan contracted to buy the hepatitis B vaccine.

The funding of immunization by the International Financing Facility for Immunization through the sale of high quality bonds in capital markets shows the complexity introduced by private funding of immunization programmes. The 5% interest paid on the initial offering of US dollar denominated bonds is close to the conventional CEA rate, which itself is based on long-term

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6 Asian Development Bank, 2003. As in the World Bank, discount rates for economic evaluations were historically developed for cost-benefit analysis of capital, non-health projects. Analysts of health sector projects may apply other rates as justified.

7 Berndt et al. (2007).

8 International Financing Facility for Immunisation. Pricing Supplement Dated 9 November 2006, Offering Memorandum. (Note: From prospectus for issue of bonds on international financial markets for support of GAVI projects.)

government bonds. This offering was aimed at the US/European markets. Subsequent offerings have been made in the Japanese financial market, however, where to meet local demand, Rand denominated bonds bearing relatively higher interest rates were issued. The shortness of the terms, 2 years and 5 years respectively, also reflect the time preferences of the investors, who are now part of the collective private donors to immunization programmes. (It should also be pointed out that the Japanese government is one the largest bilateral donor of general health assistance, if not specifically for immunization.) As mentioned in Section 4.4, though, the short time horizon of donors contributes to the short-term flows of funding that compromises health programmes that have long-term recurrent costs.

The short time horizon of donors thus needs to be considered alongside the choice of a discount rate and a study horizon. In a donor-driven perspective, valid from their payer and decision-maker roles, a study horizon relevant to the capture of all costs and effects important to the donor might be quite short. It could correspond directly to the funding cycle, typically spanning ten years. The funding cycle in turn corresponds directly to planning cycles, for which 10 years are usually the maximum given the uncertainty associated with the farther future. The funding cycle of public donors (e.g. governments, UN organizations) is also influenced by political expediency, often expressed in election time lines. Private corporate donors (e.g. pharmaceutical companies) might be influenced by shareholders, who prefer to see the results of their investments sooner than later. The short time horizons of donors that result in short study horizons, however, cuts off the capture of longer-term benefits for preventative public health interventions like pediatric immunization. It would especially bias against vaccination targeting disease onset in adult years, such as hepatitis B vaccination against liver disease. In cases like these, the discount rate should be adjusted to offset the deleterious effect of a short study horizon on the ICER. Differential rates for costs and effects should definitely prevail, with lower rates for effects. For a study of very short horizon, one to five years, a non-discounted base case should be considered. In any event, sensitivity analysis should test rates in the low range only, 5% and lower.

The foregoing paragraph demonstrates the complexity in defining and choosing an “appropriate” discount rate when taking into consideration the underlying, and perhaps
conflicting, motivations for donor time preferences. If time preferences of all the decision-making actors in the current private/public mix of immunization funding are used to guide the selection of discount rates, then the implications are that CEA modeling variables and sensitivity analysis should also reflect their associated uncertainties. These would include the investment risks of the actors, e.g. liquidity risk of the funding from the IFF-Immunization, legal risks that prices negotiated with vaccine manufacturers are not enforceable, currency risk that exchange rate changes will alter the cost-effectiveness of the programme, operational risks of failure of a new vaccine programme. Complexities and nuances such as these factors, and those described elsewhere in this section, calls for sophisticated modeling of uncertainty, such as through probabilistic sensitivity analysis.

In this section an attempt was made to explore the impact of donor funding characterized by investment-oriented donors, whether from the private or public sector (such as the development banks) which may exert decision-making influence. Taking into consideration their time preferences, as expressed through the CEA discount rate, may thus further encourage allocation of donor resources to activities that yield short-term, tangible results, at odds with the view that immunization is an investment in the human capital and thus the social and economic development of a country (Bloom et al., 2005). In this case, it bears repeating that cost-effectiveness analysis should not be used in isolation of other decision-making information and that mindfulness of national health objectives and priorities is necessary. Better capture of patient preferences in developing countries, for both time and health, would also mitigate any conflicting or deleterious impacts from preferences of donors.

5.3.2 An extra-societal perspective

An extra-societal perspective extending the scope of analysis beyond the traditional national boundaries of the societal perspective is considered in this section. It is a concept giving a framework for capturing the international flows of resources that are associated with donor funding. In this view, these costs and effects accruing to the originators of the funding would
also be captured. Global and national linkages in healthcare resource utilization and outcomes would be clarified.

The choice of a perspective is the single most important aspect in the design of a CEA study, as who is asking the question determines the answer. Since many of the most influential decision-makers for immunization programmes are international organizations and governments who are accountable to taxpayers to distribute tax revenues through healthcare programmes, and whose opportunity costs of allocating those resources to the immunization programme are projects foregone elsewhere in the world (even their own countries), it is not unreasonable that they be asking the question. A larger perspective would allow an insight into opportunity costing of products from multinational drug companies who already consider the entire world a single market, distributing procurement of raw ingredients and manufacturing across various countries. Price discrimination takes advantage of the world market and regulatory conditions of individual jurisdictions. However, given the complex pricing strategies that are the interaction of market price optimization, insurance reimbursement policies, and government regulation, coupled with non-standardized packaging and dosages of the same compound, CEA analysts will find it difficult to ascertain opportunity costs of drugs and vaccines at the global level. Even at the national level it is difficult to ascertain opportunity costs of drugs and vaccines. Compliance with drug formulary requirements in some European countries to state a price for the purpose of CEA analysis provides some transparency; however, there is no obligation that the drugs are indeed provided at that price later and relationship between divergent prices is unclear (Lizheng et al., 2010). In Canada, where formulary pricing of drugs and vaccines is explicit and regulated by the Patented Medicine Price Review Board, prices can vary according to the individual provincial negotiated agreement (Paris & Docteur, 2006). Vaccines provided by the UN to developing nations in the past have been cheaper than market price, due in part to the monopsony powers of UNICEF and PAHO to negotiate favourable prices, but with the restructuring of the international organization of immunization funding and support, it is unclear how the buying power of the international public sector has changed.

Yet, because vaccines may be the single largest cost item in immunization programmes using new vaccines, it will be important to understand the formulation of their financial cost to arrive
at their opportunity cost. However, although it is the global nature of the vaccine industry that might justify an extra-societal perspective, the industry itself may be resistant to a global CEA of one of its products. Mandatory demonstration of cost-effectiveness is already termed “the fourth hurdle” in the UK, after the hurdles of efficacy, effectiveness and safety. As one key informant in this thesis project expressed, CEA is considered a tool of pharmaceutical cost-containment.

Perhaps the most compelling reason to adopt an extra-societal perspective might be to promote a more efficient global allocation of donor funding. Because donors and recipients have different and sometimes conflicting motivations and constraints in providing and using health assistance, health assistance does not always go to countries or health problems of the greatest need (Birdsall, 2005; Schieber, Fleisher, & Gottret, 2006). For example Schiffman (2006) showed that from 1996-2003, while acute respiratory infections accounted for 26% of the developing world’s disease burden, it received 2% of donor funding. HIV/AIDS, accounting for 31% share of the disease burden, received 46% of donor funding. However, in maximizing health gains at the lowest cost, the implications are that small countries, regardless of their health burdens, may be disadvantaged. Health aid delivery is more costly per capita in small countries, and in an econometric study of the health effects of donor aid, it was suggested that great aid efficiency could be achieved by redirecting health aid from small to large countries (Lane & Glassman, 2007). The limitations of CEA in addressing equity and prioritization issues thus pertain to sovereign countries rather than national sub-populations, and without global governance (which some define as an effective United Nations) global disparities in health may be perpetuated or exacerbated.

The tremendous data requirement of CEA is a major stumbling block for instituting an extra-societal perspective. However, in recent years two major international projects have launched to help provide good data and analysis for health planning and policy- and decision-making, as well as co-ordination of national and international health care activities. The Center for Global Development’s Global Health Resource Tracking Working Group identified data sources and methodologies to find, manage and assess data for decision-making. It also made recommendations for the creation of a harmonized tracking system of global flows of health
resources, including donor funds (Center for Global Development, 2007). The Institute of Health Metrics and Evaluation also focused on clarifying the confusing and complex global flows of donor funding in its first annual report (Institute for Health Metrics and Evaluation, 2009). The research institute has a comprehensive programme investigating health issues of developing countries, however, and importantly, provides on-line datasets for other researchers. The standardization, harmonization and creation of health and health care data systems are major focii of its work.

Although a CEA conducted with an extra-societal perspective is only conceptual, it might be useful to consider other areas in which an extra-societal perspective might be helpful in clarifying and quantifying costs and effects that are meaningful to both national and international policy-makers. These include:

- The generalizability of CEA results to multiple sites
- The collective economic evaluation of related interventions set in multinational sites
- The valuing of lost/gained productivity and personnel costs of health workers who migrate temporarily or permanently to other countries to work
- The valuing of lost/gained productivity and personnel costs of health workers who travel to deliver humanitarian and development assistance
- Valuation of costs and health outcomes of patients who travel to other jurisdictions to seek treatment (medical tourism)
- Making explicit the opportunity costs of interventions using significant amounts of imported programme inputs
- Economic evaluation of pandemic diseases infection control

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23 See http://www.healthmetricsandevaluation.org/resources/datasets.html, especially for newly available datasets.
5.3.3 A potential role for GAVI

GAVI has had a substantial role in increasing global immunization awareness and coverage. In the lowest income countries, where it has its largest representation, health gains from averted disease have the greatest potential to translate into increased human capital, so GAVI has an indirect role as a development agency, too. Through participating in the financial innovations of the IFFIm and the AMC for pneumococcal vaccine, GAVI has also helped to shape the international vaccine market by creating favourable conditions for the demand and supply of vaccines that meet the relative needs of developing nations.

In the context of this thesis, GAVI has a further potential role in advancing and promoting a more rigorous use of CEA for immunization interventions. As described in Sections 1.5, 1.6 and elsewhere, the quantity and quality of CEAs for pediatric immunization interventions set in developing countries is lacking compared to those set in industrialized countries. In a GAVI-commissioned evaluation of its work 2006-2010, the authors concluded that GAVI had contributed significantly to the evidence base for the introduction of yellow fever, pneumococcal, rotavirus and Hib-containing multivalent vaccines by funding organizations that conducted cost-effectiveness analyses for these under-utilized or new vaccines (CEPA, 2010). However, these authors did not evaluate the quality of these studies. In this thesis, it was noted that the rotavirus studies in the Data Set (which were conducted in anticipation of GAVI support) were highly prospective, given the unknown price of the vaccine, and that the emphasis on establishing a break-even price gave the impression that the objective of the study was to determine financial feasibility or indicate a potential market for the vaccine rather than to assess its value for health gain. Furthermore, it was also noted that Section 4.2.4.1 that the definition of a “societal perspective” was variable among the studies, and in most cases, very limited. Therefore, although GAVI may have contributed to increasing the quantity of CEAs, it is less clear that GAVI has contributed to the quality of CEAs for immunization in developing countries. It might be able to do so if it were to take a more active role in participating in country-level CEAs.
GAVI has a role in clarifying and defining the scope and limits of a societal perspective in order to better capture the true, broad value of immunization. As a large payer and a decision-maker (albeit unofficial) in the public health care system of many developing countries, GAVI can ask the questions that shape CEA study design. What is the best strategy to efficiently reach children at the margin, geographically and in terms of uptake and compliance? What should the mix of immunization strategies be (routine, fixed vs. mobile facilities, mass campaigns, eradication) and under what conditions should they be implemented? What level of coverage should be targeted? Should the comparator(s) include the currently less effective but much cheaper vaccines? Who is involved in care-giving of children and how do they seek healthcare? What sub-population might experience the most health gain? What is the resource utilization and budget impact of its co-paying arrangement? These questions also bring a more explicit focus to issues of equity (e.g. who gains with more coverage), affordability (e.g. which traditional cheap vaccines to replace) and allocative efficiency (e.g. what combination of vaccine interventions and/or immunization strategies minimizes opportunity costs across sectors).

GAVI may also have a role for improving the quantity and quality of CEAs at the global level if it were to use CEA more routinely for its own decision-making. The evaluation by CEPA (2010) judged that GAVI-supported activities were cost-effective compared to other health interventions, but made sure to point out that that conclusion was not based on an actual CEA. This author did not find GAVI-performed CEAs of its current or proposed interventions. Thus, in its development of its new monitoring and evaluation plan to inform decision-making (GAVI Alliance, 2010e), GAVI could make CEA an explicit and prominent part of its strategy. By virtue of its international reach, composition of multinational partners, and the relative transparency of its operations, GAVI’s decision-making example could influence other relevant international organizations as well as national governments. Even if GAVI did not have the resources to perform CEAs, it could demand better quality from those it commissions, say, by insisting on adherence to the WHO Guidelines for Standardization of Economic Evaluation of Immunization Programmes.
5.4 Limitations

Limitations regarding literature
An Ovid Auto-Alert for Medline was maintained for 12 months after the initial search to capture emerging literature, but as grey literature is not indexed in electronic databases, hand searches were conducted of the major sources (international organizations, policy and economic research institutes and think tanks) during these 12 months. This proved to be very time-consuming and yielded a considerable amount of duplicates, and after the first two hand searches in the first six months, only one more was made at the end of the period. Coverage of the grey literature, centered on donor funding, was therefore less thorough and possibly less complete than peer-reviewed literature. The long time span and irregularly timed hand searches may have threatened internal validity as the criteria for inclusion was unevenly applied. The documents used were not appraised for quality, and this was also a source of threat to the internal validity of this research.

Publication bias was introduced when document repositories of the WHO and World Bank were used exclusively to select documents about cost-effectiveness techniques and applications that had been developed by these institutions. This may have given undue weight and importance of the WHO-CHOICE data and methods and generalized cost-effectiveness in the thematic analysis, especially in the finding that the practice of CEA seemed to be divided between practitioners in industrialized countries and developing countries settings.

Researcher bias occurred as not all the guidelines that are officially produced were located and used. It is possible that other guidelines, such as that from Australia, an early and comprehensive set, could have provided some guidance for developing countries. It would have altered the conclusion that only the WHO-CHOICE guidelines were pertinent to developing countries.

An important document was not included in the Data Set, the “WHO Guide for Standardization of Economic Evaluations of Immunization Programmes”, which were published in December 2008 (World Health Organization, 2008b). Being grey literature it was not captured by the Ovid
automatic alert, and an electronic hand search of pre-designated key web sites in December 2008 (the end of the inclusion period) also did not turn it up. It is unknown when the document was made available on the WHO website, but it was found there by this author in May 2009.

The consequences for the assessment of the guidelines for developing countries is that it would have qualified the conclusion for Section 4.3, Guidelines for CEAs in developing countries. It had been found that is only one comprehensive CEA guide for developing countries, but although the omitted guide was developed for immunization evaluations, it was a comprehensive guide in the style of Gold et al. (1996) and made specific methodological recommendations. Meant for global use, the guidelines explicitly mentioned developing countries, using literature and examples set there and addressing analytical issues relevant to developing countries. Of note is the discussion on the use of modeling in economic evaluations, and which is particularly useful for analyzing public health interventions. This set of guidelines was more practically oriented than the “Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis” (Tan-Torres Edejer et al., 2003), which figured in the conclusion of Section 4.3 as the only set of CEA guidelines for developing countries. The conclusion, in hindsight, would have been that the immunization guidelines should be considered as a companion to this volume for a complete application of guidelines in a developing country context.

Additionally, had the immunization guidelines been included in the thematic analysis, modeling methodology would have been given heavier weight in the analysis. As modeling for immunization intervention is an emerging topic area, it was only sparingly captured in the Data Set, and was not identified by authors as a methodological issue for developing countries. Again, in hindsight, this would have prompted identifying the lack of modeling guidelines as a gap in methodology in the context of immunization evaluations.

Limitations regarding key informants

The sample of key informants was a convenience sample, limited by the time-consuming effort of finding global health researchers active in developing countries and by the logistics of coordinating interview times across time zone barriers and with the travel that is characteristic
many global health researchers’ work. Many of the key informants were located in Asia and in economies that were middle-income rather than low-income. Only one informant had experience in Africa, and it was not directly related to immunization decision-making. Therefore, there is a deficiency of insights into the lowest-income countries, which are undoubtedly most in need of tools for thoughtful allocation of resources.

Although there was an explicit attempt not to bias the discussion to economic evaluation and cost-effectiveness analysis, all the interviewees knew that that was the subject of this thesis from the study description provided with the consent-for-participation forms. It is possible that there was response bias, resulting in the relative importance of economic evaluation being over-emphasized.

The key informants were all trained researchers and are all currently active in research, so they provided a research-oriented perspective, which upheld the importance of evidence and the role of the researcher, but may have added to a response bias. Non-researchers may not have placed as much emphasis on evidence. However, because most of the researchers conducted primary research at the patient and community level, they also provided meaningful insight into other non-evidence factors (e.g. politics, health care system organization) that have great influences on decision-making. The strong and articulate input from the policy analyst key informant, couched in a stakeholder framework, was particularly helpful for weighing the relative importance of various types of evidence used by decision-makers, balancing the medically dominated perspective of the other key informants.

Selection bias was present due to the reliance on personal contact to obtain interviews; all of the key informants were in similar fields, resulting in overwhelming agreement for the types of evidence needed for decision-making. Selection bias may have been reinforced by using a “snowball method” to generate further referrals for key informants, so that three of the participants, although from different countries, knew each other and had worked together in various economic evaluation components under a regional project examining the introduction of new vaccines. Selection bias may be combined with volunteer bias as in the recruitment meeting.
of two of these key informants, the third had been present (inadvertently) and had volunteered out of interest for the thesis project and for collegial participation.

Because more than half of the interviewees did not speak English as a first language, there may have been some misunderstanding on both the parts of the interviewer and the interviewee. This may have, furthermore, limited the depth of the discussion. The term “evidence” was deliberately never explicitly defined, so as to prevent guiding the discussion towards cost-effectiveness, but this may have been added to some misinterpretation on both sides as to the true meaning of the discussion.

**Limitations regarding analysis**

The literature used for this thesis was drawn from researchers and analysts predominantly based in industrialized countries, even if their focus was on developing countries, and was written in English. The views and analysis of developing nations in regards to the adequacy of the Washington Panel reference case for their own needs is a therefore a large omission. Future research should also examine the publications of the pharmacoeconomic agencies now emerging in middle-income countries and the health economics institutes and organizations based in all developing countries.

A researcher bias was introduced in avoiding examining equity-related issues in regards to CEA application to developing nations. This was deliberate as in the field of health economics this topic is controversial and large, requiring and deserving much more attention than would be warranted in this thesis. However, this is an area of particular relevance to developing countries given the more extreme health disparities that exist there and the inequitable access even to basic immunization (Hardon & Blume, 2005; Mooney & Wiseman, 2000; Waddington, 2004).

An international political economy view was introduced by the literature pertaining to donor funding, but the thematic analysis did not employ approaches normally used in examining topics in political economy (e.g. the role of institutions, power relationships, stakeholder analysis).
(Goddard, Hauck, Preker, & Smith, 2006). However, these approaches would have been inappropriate for the bulk of the literature, based on health economics, and so a limited use of a stakeholder’s approach was used to examine the role of donors-as-decision-makers.

5.5 Conclusions

This thesis project sought to discover possible improvements at the conceptual level in the application of cost-effectiveness analysis for developing countries. Focusing on the donor funding for immunization, which creates issues unique to developing countries, it was found that the reference case developed by the Washington Panel on Cost-effectiveness in Health and Medicine was not specific enough in the guidance of costing for immunization inputs for which the opportunity costs are difficult to ascertain. Guidance in the valuation of effectiveness did not recognize the importance of health systems nor indirect outcomes, as in the case of pediatric immunization, the effects on caregivers and the community (e.g. schools). Methodological developments have occurred in these areas since the reference case was established, however, and increasing attention by health economists in assessing immunization programmes in developing countries as a result of expanded resources for immunization, have addressed and provided clarification on these issues. Most importantly, it was found that the World Health Organization has established CEA guidelines that mirror the Washington Panel guidelines, but differ in the important aspect of enabling sector-wide analysis rather than by-intervention analysis. This approach is especially useful for identifying current inefficiencies in the health sector and has application for all cost-conscious economies, but especially for extremely resource-scarce economies. It was concluded thus that the Washington Panel reference case needs updating, but not replacing, to include these developments so health economists share a common methodological understanding and basis to enable dissemination of economic evidence and to prevent a division between industrialized and developing countries in the use and application of cost-effectiveness analysis.

A donor funding focus of the thematic analysis provided a wider political economy point of view compared to a strictly health care view and illuminated the global aspects of immunization programming in developing countries. On the other hand, some of the insights provided by the
key informants demonstrated the importance of using local data and local analysis suitable to the local decision-making environment. To promote evidence-based decision- and policy-making, it is concluded that the Washington Panel reference case should incorporate guidance on the translation of CEA results for end-users, particularly those untrained in health economics. To enable developing countries to use economic evidence established in industrialized countries, guidelines for generalizing and contextualizing results should also be included. The world-wide proliferation of health technology assessment agencies and attending pharmacoeconomic guidelines point to a growing global emphasis on technical efficiency and market-orientation. This biases against public health interventions. It is concluded that the Washington Panel reference case continue to be motivated by broad objectives of improving population health and should make allocative efficiency even more central in its guidance.

5.6 Lessons and implications

This section outlines the key messages for the four main decision-makers identified from this research project: policy- and decision-makers from developing countries, donor funding agencies, producers of CEAs, and pharmaceutical companies (particularly vaccine manufacturers).

Policy- and decision-makers in developing countries

Donor funding should be considered a source of health financing that affects the budget constraint for health. Donor funding may expand the budget through cash payments or in-kind payments of goods and services but also possibly tighten it if government health expenditures are consequently diverted to other sectors. Efficiencies gained by using donor funds can be considered a creation of more fiscal room, allowing possible decisions to be made that encourage allocative efficiency. That is, a more efficient immunization programme may allow investment in a nutrition programme. However, accepting funding incurs costs, too, which should be more comprehensively included in cost-effectiveness analysis. Obvious recurrent costs, such as the yearly purchase of vaccines, are typically included in analysis, but large
recurrent costs incurred by the administration and management of donor funding (e.g. project management, regular meetings with donors and evaluation/reporting to donors) can be overlooked. Additionally, the opportunity costs of resources, like personnel, that are diverted from provision of healthcare in other interventions or even from provision of non-health services are not, but should be included in CEA. The quantification of these opportunity costs is difficult; nevertheless the identification and reporting of these resource changes is helpful in evaluating the resource allocation impact of donor-funded programmes. However, information derived from the epidemiological and economic situation specific to the local jurisdiction, instead of adapted from other jurisdictions, is necessary for accurate evaluation of technical efficiency. Thus, national governments need to invest in their own data and technical capacity. This furthermore allows a lessening of dependence on external analytical and technical assistance and in turn, may permit a closer adherence to national healthcare objectives and priorities.

**Donor funding agencies**

While it is indisputable that donor funding fill an unmet need for additional health financing in many of the lowest income countries, donors, when assessing the cost-effectiveness of their supported programmes, also need to take account of the costs to the recipient countries of accepting that funding. Large inflows of funds, supplies, and technical personnel from donors can overwhelm low-resource countries, disrupting national health priorities and health systems, and even other sectors in the economy. This is especially true if the healthcare infrastructure is unable to smoothly accommodate or absorb the influx. Thus donors, like national governments, must recognize the opportunity costs incurred when resources are realigned or diverted from non-funded interventions or non-health sectors to apply to the donor-funded interventions. Similarly, transaction costs such as those incurred for rigorous record-keeping and reporting to fulfill donor funding conditions need to be accounted for in CEA studies. Consensus building and negotiating with other international partners to coordinate funds and inputs for provision to recipient countries also incur transaction costs to donors, and should also be included when making allocation decisions. A CEA with a global framework, using a extra-societal perspective, could be coupled with global burdens of disease information to help guide maximizing health outcomes at the global level.
Producers of CEA

The current flow of resources for healthcare improvement in developing countries result in more diverse variables for CEA modeling and estimation and more variable uncertainty. These variables reflect the greater diversity of healthcare provision and the greater extremes of health in developing countries compared to industrialized countries, which may make national averages unrepresentative of the target population of an intervention. Identifying variables appropriate to a particular health system and the plausible, policy-relevant variation around its mean value is critical. Variables for pediatric patients should reflect, for example, refinements to capture sub-divided population groups that have different epidemiological profiles depending on their region of residence, family income, and utilization patterns of healthcare service and facilities (i.e. traditional healers to leading-edge tertiary hospitals). The analyst must then use more judgment and assumptions. Furthermore, the practice of differential pricing of vaccines for developing countries makes social opportunity costs difficult to discern, and the CEA results non-transferable even between low and middle-income countries. With the price of new vaccines unknown, supplemental break-even analysis is thus valuable information for decision-makers. Transaction costs, not normally counted, are also critical in the context of donor funding for immunization interventions. Likewise, it is important to recognize that the fixed budget assumption of CEA is violated by flexible, volatile, unpredictable donor funding. To be truly useful for decision-making, a thorough understanding of the local decision-making environment is necessary.

Pharmaceutical companies, vaccine manufacturers

As a growing producer and consumer of specialized CEA (pharmacoeconomics), methodological research and CEA practice should share a focus on the needs of developing countries. Joining in the provision of a global public good like the provision of vaccines and vaccination demands corporate responsibilities in transparency in pricing vaccines, the key driver of cost-effectiveness in new vaccine interventions.
5.7 Directions for future research

From key informant interviews it was clear that cost-effectiveness analysis seemed to be more of an academic exercise than a useful policy-making aid to health ministries in developing countries. Future research could explore the decision-making environment to better understand the barriers and facilitators to CEA’s use. One of the barriers revealed by the key informants was that it was felt to be a “donor” statistic. It is thus important to understand the role of donors in disseminating CEA methodology and results to developing countries and how they have been received. It is also important to understand why policy and decision-makers don’t feel that CEA was applicable to them and what instead is available and/or is more useful as a decision-making aid. DeRoeck (2004) had found that influential individuals outside the health ministries were also important decision-makers, and this was borne out by the key informants. Therefore, identification of how the decision-making is done and by whom would help to assess the audience that CEAs need to address. Another area that could be explored is understanding the trade-offs that decision-makers must make when making healthcare decisions.

An extra-societal perspective needs geographical and other delimitations (i.e. by disease, by population) to make it feasible and practical to capture associated costs and effects. Further research is thus needed to examine the linkages of health systems and the extent of externalities, costs and effects, and the identification of new variables and indicators. Methods to value these resources are also needed. End-users or audiences and stakeholders for such a perspective would also need to be identified.

Finally the issue of affordability, central to the concerns of developing countries needs to be better integrated into CEA reporting. While budget impact analysis can answer questions of affordability, it is too demanding of data for data-strapped developing countries. In current health economics literature affordability curves are being explored to make CEA results more relevant to decision-makers (Kim et al., 2007; Sendi & Briggs, 2001; Shillcutt, Walker, Goodman, & Mills, 2009). It is necessary to discover if these are useful to decision-makers and how to improve them if not.
6 APPENDICES
## Appendix 1: Selected Health and Development Indicators

<table>
<thead>
<tr>
<th>Country</th>
<th>GNI per capita, 2009</th>
<th>Population (mil), 2009</th>
<th>Life expectancy at birth, 2008 (female and male)</th>
<th>Under-5 mortality rate, per 1000, 2009</th>
<th>DPT3 coverage rate (%), 2008</th>
<th>Population 0-4 years old (% total), 2009</th>
<th>Total health expenditure per capita, 2007</th>
<th>Public expenditure as % of total health expenditures, 2007</th>
<th>Out-of-pocket payment as % of private health expenditures, 2007</th>
<th>External resources for health as % of total health expenditures, 2007</th>
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<td>30</td>
<td>44</td>
<td>199</td>
<td>85</td>
<td>46</td>
<td>42</td>
<td>23.6</td>
<td>99</td>
<td>20.2</td>
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<td>95</td>
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<td>44</td>
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Notes:
1. All monetary figures in current US dollars.
2. Definitions of health expenditures (World Bank):
Public health expenditure consists of recurrent and capital spending from government (central and local) budgets, external borrowings and grants (including donations from international agencies and nongovernmental organizations), and social (or compulsory) health insurance funds. Total health expenditure is the sum of public and private health expenditure. It covers the provision of health services (preventive and curative), family planning activities, nutrition activities, and emergency aid designated for health but does not include provision of water and sanitation.

Out-of-pocket expenditure is any direct outlay by households, including gratuities and in-kind payments, to health practitioners and suppliers of pharmaceuticals, therapeutic appliances, and other goods and services whose primary intent is to contribute to the restoration or enhancement of the health status of individuals or population groups. It is a part of private health expenditure.

Appendix 2: Main Recommendations of the Washington Panel Reference


1. Nature and limits of a CEA:
   1.1. Societal perspective
   1.2. Time horizon long enough to capture all benefits and costs
   1.3. Comparator is next best or most feasible low-cost alternative

2. Components of cost-effectiveness ratio
   2.1. Numerator: costs covering health care services, patients’ own, childcare, travel, employer, ‘friction’, non-health
   2.2. Denominator: all effects of mortality and morbidity on productive time and leisure

3. Measurement of costs
   3.1. Marginal costs, adjusted opportunity costs, proxies
   3.2. Constant dollars
   3.3. Time costs, related future costs

4. Valuing health consequences
   4.1. QALYs to be used
   4.2. Community based preferences

5. Estimating effects
   5.1. From best-designed, least biased sources
   5.2. Models necessary in some circumstances

6. Time preferences
   6.1. Use 3%; 5% for comparison with older studies
   6.2. Review over time

7. Uncertainty
   7.1. One-way and multi-way sensitivity analysis

8. Reporting
   8.1. Use reference case as foundation
   8.2. Use reference case for assessment of quality

For comparison to a summary that reflects the current methodological emphases, the reader is directed to the WPRC as summarized in Drummond et al. (2005), in Appendix 3 below.
Appendix 3: Summarized Recommendations of the Washington Panel Reference Case

1. The societal perspective should be adopted;
2. Effectiveness estimates should incorporate benefits and harms;
3. Mortality and morbidity consequences should be combined using QALYs;
4. Effectiveness estimates from best-designed and least-biased sources should be used;
5. Costs should include health care services, patient and care-giver time and costs of non-health impacts;
6. Comparison should be made with existing practice and (if necessary) a viable low-cost alternative;
7. Discounting of costs and health outcomes should be undertaken at a real rate of 3% per annum (plus 5% for comparison with existing studies);
8. One-way and multi-way sensitivity analysis (for important parameters) should be undertaken;
9. Comparison of the incremental cost-effectiveness ratio should be made with those for other relevant interventions.

From Drummond et al. (2005, p. 46).
Appendix 4: Relevant Controlled Vocabulary for Databases

1. Medline MeSH Terms

Health Care Economics and Organizations
Economics
Costs and Cost Analysis
Cost Benefit Analysis
Cost Effectiveness Analysis – Related term
Developing Countries
Immunization
Immunization schedule
Immunization active
Vaccination
Program evaluation
Adolescent
Child
Infant
Rotavirus
Vaccines
Viral Vaccines
Rotavirus Vaccines
Quality Adjusted Life Years

2. CINAHL Subject Headings List keywords

Cost-benefit analysis, health care costs, health resource allocation, developing countries, immunization, rotaviruses, vaccines, child: preschool, infant

3. Embase Emtree Subject Headings

Economic evaluation (and the associated terms cost benefit analysis, cost effectiveness analysis, cost utility analysis) pharmacoconomics (associated term utilization review), immunization, vaccination, mass immunization, vaccines, child, adolescent, rotavirus, developing country, economic development, resource allocation

4. EconLit Thesaurus terms (English)

Cost effectiveness, cost benefit, funds flow, developing countries, health: government policy, regulation and public health, health production: nutrition, mortality, morbidity,
disability, and economic behaviour, aid, multilateralism, modeling, willingness to pay, sustainability, globalization, health care, children, discount rate, discounting, disease

5. Centre for Reviews and Dissemination Databases

(Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database, Ongoing Reviews Database)

Search by MeSH terms or by EconLit keywords, as outlined above.
Appendix 5: Sample Literature Search Strategies

Database: Ovid MEDLINE(R) <1950 to September Week 3 2007>
Search Strategy:
-------------------------------------------------------------------------------------------------------------------------------------
1 immunization/ec or immunization, passive/ec or immunotherapy, adoptive/ec or immunization schedule/ec or immunization, secondary/ec or immunotherapy, active/ec or vaccination/ec or mass immunization/ec or exp Vaccines/ec (2855)
2 exp Vaccines/ or immunization/ or immunization, passive/ or immunotherapy, adoptive/ or immunization schedule/ or immunization, secondary/ or immunotherapy, active/ or vaccination/ or mass immunization/ (184212)
3 exp Economics/ (382679)
4 2 and 3 (3954)
5 1 or 4 (4942)
6 Developing Countries/ or exp africa/ or exp caribbean region/ or exp central america/ or latin america/ or mexico/ or exp south america/ or asia/ or exp asia, central/ or exp asia, southeastern/ or exp asia, western/ or far east/ or china/ or hong kong/ or tibet/ or korea/ or macao/ or mongolia/ or taiwan/ or exp indian ocean islands/ or pacific islands/ or melanesia/ or fiji/ or new caledonia/ or papua new guinea/ or vanuatu/ or micronesia/ or guam/ or palau/ or polynesia/ or pitcairn island/ or exp samoa/ or tonga/ (473687)
7 5 and 6 (1038)
8 limit 7 to humans (861)
9 from 8 keep 1 (1)

Database: EMBASE <1980 to 2007 Week 32>
Search Strategy:
-------------------------------------------------------------------------------------------------------------------------------------
1 Rotavirus Vaccine/ or rotavirus/ or human rotavirus/ or ((rotavirus adj2 infection:) or (rotavir: adj2 infection:)).mp. or ((rotavirus: adj2 vaccin:) or (rotavirus adj2 immuniz:) or (rotavirus adj2 immunis:)).ti,ab. or rotavirus:.mp. or rotaviral.mp. (6631)
2 exp economic aspect/ (336087)
3 1 and 2 (412)
4 Rotavirus Vaccine/pe or rotavirus/pe or human rotavirus/pe (97)
5 3 or 4 (419)
6 from 5 keep 1-199 (199)
### Objective 1 - Identifying Limitations of CEA for Developing Countries

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>child</td>
<td>Childhood interventions</td>
<td>General, non-specific interventions</td>
</tr>
<tr>
<td>comp</td>
<td>Comparator</td>
<td>Baseline case, existing intervention</td>
</tr>
<tr>
<td>cost</td>
<td>Cost</td>
<td>Non-specified costs</td>
</tr>
<tr>
<td>cost-fut</td>
<td>Future costs</td>
<td>Costs arising from the implementation of the new intervention</td>
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<tr>
<td>cost-indir</td>
<td>Indirect costs</td>
<td>Costs not directly attributable to new intervention (e.g., lost productivity)</td>
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<tr>
<td>data</td>
<td>Data</td>
<td>Any issues of data availability, quality</td>
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<tr>
<td>disc</td>
<td>Discount</td>
<td>Discounting, discount rate</td>
</tr>
<tr>
<td>disc-child</td>
<td>Discount-child</td>
<td>Discounting for childhood interventions</td>
</tr>
<tr>
<td>disc-cost</td>
<td>Discount-cost</td>
<td>Discounting cost values</td>
</tr>
<tr>
<td>disc-eff</td>
<td>Discount-eff</td>
<td>Discounting effectiveness values</td>
</tr>
<tr>
<td>disc-time</td>
<td>Discount-time</td>
<td>Discounting horizon (length of time)</td>
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<tr>
<td>effect</td>
<td>Effectiveness</td>
<td>Effectiveness values, measures, variables</td>
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<td>eff-adjust</td>
<td>Effectiveness adjustment</td>
<td>Adjustments/substitutions of variables, values</td>
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<td>eff-age</td>
<td>Effectiveness-age</td>
<td>Age-related impacts on effectiveness estimation</td>
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<td>eff-BOD</td>
<td>Effectiveness-Burden of Disease</td>
<td>Burden of disease measurement of effectiveness</td>
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<td>eff-DALY</td>
<td>Effectiveness-DALY</td>
<td>DALY metric for effectiveness</td>
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<td>Effectiveness measurement</td>
<td>General issues of measures for or estimation of effectiveness</td>
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<td>eff-opin</td>
<td>Effectiveness-expert opinion</td>
<td>Expert opinion generated measures of effectiveness</td>
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<td>eff-pref</td>
<td>Effectiveness-preferences</td>
<td>Preference based measures of effectiveness</td>
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<td>eff-QALY</td>
<td>Effectiveness-QALY</td>
<td>QALY metric for effectiveness</td>
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<tr>
<td>eff-vacc</td>
<td>Effectiveness-vaccines</td>
<td>Vaccine effectiveness (actual protection under implementation conditions of target population)</td>
</tr>
<tr>
<td>efficacy</td>
<td>Efficacy</td>
<td>Vaccine efficacy</td>
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<tr>
<td>decis</td>
<td>Decision-making</td>
<td>Application of CEA to decision and policy-making</td>
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<td>effic</td>
<td>Efficiency</td>
<td>General economic efficiency issues</td>
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<td>effic-allo</td>
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<td>Efficiency-technical</td>
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<td>evid</td>
<td>Evidence</td>
<td>General economic evidence</td>
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<tr>
<td>gen</td>
<td>Generalizability</td>
<td>Generalizability or transferability of CEA results</td>
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<td>interven</td>
<td>Intervention</td>
<td>Non-specified interventions</td>
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<td>interven-imm</td>
<td>Intervention</td>
<td>Immunization and vaccine interventions</td>
</tr>
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<td>perspect</td>
<td>Perspective</td>
<td>Perspective of cost-effectiveness study; general issues of perspective</td>
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<td>pop</td>
<td>Population</td>
<td>General developing world population issues</td>
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<tr>
<td>pop-child</td>
<td>Population</td>
<td>Pediatric population</td>
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<td>sens</td>
<td>Sensitivity analysis</td>
<td>Sensitivity analysis</td>
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<td>sens-stoch</td>
<td>Sensitivity-stochastic</td>
<td>Stochastic sensitivity analysis</td>
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<td>sens-uncert</td>
<td>Sensitivity uncertainty</td>
<td>Other treatments of uncertainty through sensitivity analysis</td>
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<td>sens-var</td>
<td>Sensitivity-variables</td>
<td>Variables used for sensitivity analysis</td>
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<td>stats</td>
<td>Statistical analysis</td>
<td>Statistical analysis</td>
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<tr>
<td>Code</td>
<td>Name</td>
<td>Description</td>
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<td>-------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>uncert</td>
<td>Uncertainty</td>
<td>General uncertainties, unspecified uncertainty</td>
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<tr>
<td>valu</td>
<td>Valuation</td>
<td>Valuation and estimation</td>
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<td>var</td>
<td>Variables</td>
<td>Any variable used for CEA</td>
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<td>vary</td>
<td>Variation</td>
<td>Variations of CEA results</td>
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<tr>
<td>vary-source</td>
<td>Variation-source</td>
<td>Sources of variations</td>
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<td>best</td>
<td>Best-buy intervention</td>
<td>Identified by the DCCP as a cost-effective intervention for developing countries</td>
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<td>barr</td>
<td>Barrier</td>
<td>Barriers to immunization or vaccine uptake</td>
</tr>
<tr>
<td>bundle</td>
<td>Bundle</td>
<td>Bundled interventions, based on their collective cost-effectiveness and burden of disease addressed</td>
</tr>
<tr>
<td>context</td>
<td>Context</td>
<td>The programmatic or implementation context of the intervention. Also, the adjustment of costs/effects to reflect the context (contextualization).</td>
</tr>
<tr>
<td>league</td>
<td>League table</td>
<td>The ordering of interventions based on their cost-effectiveness</td>
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<tr>
<td>length</td>
<td>Length</td>
<td>Study horizon or length</td>
</tr>
<tr>
<td>loc</td>
<td>Location</td>
<td>The setting of the CEA study.</td>
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<tr>
<td>opin</td>
<td>Opinion</td>
<td>Opinion-derived valuations, estimations of costs/effects</td>
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<tr>
<td>policy</td>
<td>Policy</td>
<td>Policy implications of CEA study.</td>
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<tr>
<td>recomm</td>
<td>Recommendations</td>
<td>Author recommendations for methodological changes, within study</td>
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<td>rev</td>
<td>Reviews</td>
<td>Categorization of source of methodological recommendation</td>
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<td>target</td>
<td>Target</td>
<td>Intended audience of data piece</td>
</tr>
<tr>
<td>Type-(CEA, CUA, CM)</td>
<td>Type</td>
<td>Type of economic evaluation (CEA, CUA, Cost minimization)</td>
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<tr>
<td>user</td>
<td>User</td>
<td>User-related issues (relevance, usefulness)</td>
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<tr>
<td>prior</td>
<td>Priority-setting</td>
<td>The use of CEA for priority-setting</td>
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**List of Codes 1: Objective 2 - Identifying CEA Guidelines for Developing Countries**

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<th>Description</th>
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<td>CADTH</td>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health.</td>
</tr>
<tr>
<td>CHOICE</td>
<td>WHO-CHOICE project</td>
<td>Recommendations based on the WHO designed framework for CEA</td>
</tr>
<tr>
<td>WHO</td>
<td>WHO other</td>
<td>Manuals and guidelines published by the WHO for programme managers and practitioners</td>
</tr>
<tr>
<td>NICE</td>
<td>NICE</td>
<td>UK National Institute of Clinical Excellence recommendations and guidelines</td>
</tr>
<tr>
<td>Wpanel</td>
<td>Washington Panel</td>
<td>Washington Panel Reference Case recommendations mentioned in data items</td>
</tr>
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<td>synth</td>
<td>Synthesis</td>
<td>Synthesis of guidelines</td>
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<tr>
<td>guidance</td>
<td>Guidance</td>
<td>General recommendations, suggestions</td>
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<tr>
<td>manual</td>
<td>Manual</td>
<td>Hands-on, specific instructions</td>
</tr>
<tr>
<td>consensus</td>
<td>Consensus</td>
<td>Consensus statements from experts</td>
</tr>
<tr>
<td>guideline</td>
<td>Guideline</td>
<td>Formal guidelines from authoritative sources</td>
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</table>
### List of Codes 2: Objective 3 - Identifying Donor Funding Impacts on CEA Estimation

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<th>Description</th>
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<td>afford</td>
<td>Affordability</td>
<td>Affordability of entire or individual components of intervention to national government</td>
</tr>
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<td>aid</td>
<td>Aid</td>
<td>General development assistance provided from industrialized countries to developing countries</td>
</tr>
<tr>
<td>aid-effec</td>
<td>Aid effectiveness</td>
<td>The impact of development assistance</td>
</tr>
<tr>
<td>aid-health</td>
<td>Aid for health</td>
<td>General issues of development assistance for health care activities</td>
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<td>budg</td>
<td>Budget</td>
<td>Health care budget</td>
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<td>fund-cost</td>
<td>Donor funding-cost</td>
<td>Donor funding impacts on CEA cost estimation</td>
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<td>fund-donor</td>
<td>Donor funding</td>
<td>Author-specified issues pertaining to donor funding for health</td>
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<td>fund-econeval</td>
<td>Donor funding-economic evaluation</td>
<td>Any mention of any type of health care economic evaluation in conjunction with donor funding</td>
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<tr>
<td>fund-eff</td>
<td>Donor funding-effectiveness</td>
<td>Donor funding impacts on CEA effectiveness estimation</td>
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<td>fund-impact</td>
<td>Donor funding-impacts</td>
<td>Any author-mentioned types of impacts on health care</td>
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<td>fund-risk</td>
<td>Donor funding-risks</td>
<td>Any author-mentioned risks of donor funding</td>
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<td>fund-time</td>
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<td></td>
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<td>fund-trend</td>
<td>Donor funding-trends</td>
<td>Any trends of health care funding/expenditures by donors</td>
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<td>fund-volatil</td>
<td>Donor funding-volatility</td>
<td>Impacts of donor funding volatility on health care sector/programme/decision-making</td>
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<td>health-finan</td>
<td>Health financing</td>
<td>The provision/generation of funds for health care expenditures</td>
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<tr>
<td>sust</td>
<td>Sustainability</td>
<td>Sustainability of donor funded health care interventions</td>
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<tr>
<td>vac-econ</td>
<td>Vaccine economics</td>
<td>The supply/demand and distribution of vaccines</td>
</tr>
</tbody>
</table>
Appendix 7: Data Set


Bishai, D., McQuestion, M., Chaudhry, R., & Wighton, A. (2006). The costs of scaling up vaccination in the world's poorest countries-regional rather than national vaccine programs could vaccinate the greatest number of children at the lowest cost. Health Affairs, 25(2), 348-356.


Bowden, A., & Fox-Rushby, J. A. (2003). A systematic and critical review of the process of translation and adaptation of generic health-related quality of life measures in Africa, Asia, Eastern Europe, the Middle East, South America. Social Science & Medicine, 57(7), 1289-1306.


Schiffman, J. (2006). Donor funding priorities for communicable disease control in the developing world. London School of Hygiene and Tropical Medicine, 10.


1-192.


Waddington, C. (2004). Does earmarked donor funding make it more or less likely that developing countries will allocate their resources towards programmes that yield the greatest health benefits. *Bulletin of the World Health Organization,* 82(9), 703-708.


Appendix 8: Cover Letter to Key Informants

Cindy Gauvreau
PhD Candidate, University of Toronto
Tongji University Guest House
69 Zhangwu Road
Building 359, Apartment 401
Shanghai 200092, China

Dear XXXXX,

Thank you for agreeing to participate as a key informant in my doctoral research project. As you know, I aim to investigate decision-making tools in developing countries in regards to pediatric immunization. The role of the key informants will be to help me understand the information needs that are particularly relevant to developing countries in this context. Our interview will take about 30-40 minutes. I will be contacting you soon by email to schedule the interview at your convenience.

I want to reiterate that your responses will be kept in the strictest confidence, conforming to the ethical practices of the Hospital for Sick Children in Toronto and the University of Toronto, who are sponsoring this research. The information you provide would be used only for completing my dissertation and for any subsequent publications. I include here a study participation consent form, an audio-recording consent form and also an interview guide to give you an idea of the questions that I will be asking during the interview. Please return the signed consent forms to me at the address above.

I very much appreciate your expertise and time to help with my research. If you have any questions please do not hesitate to email me at cindy.gauvreau@utoronto.ca.

Sincerely,
Appendix 9: Research Consent Form

SickKids
THE HOSPITAL FOR
SICK CHILDREN
Research Ethics Board

RESEARCH CONSENT FORM

Title of Research Project:
Toward an Adapted Reference Case for Developing Countries: Incorporating Donor Funds in Cost-Effectiveness Analysis.

Investigator(s):
Principal investigator: Dr. Wendy Ungar, Senior Scientist, Child Health Evaluative Services, SickKids, Toronto, Canada +1 (416) 813–8519
Co-Investigator: Cindy L. Gauvreau, PhD Candidate, Dept. of Health Policy, Management & Evaluation, University of Toronto, Canada
Supervisor: Dr. Wendy Ungar

Purpose of the Research:
To extend the methodology of cost-effectiveness analysis (CEA) to better reflect economic factors important to developing countries, as applied to pediatric immunization.

Description of the Research:
This study will investigate the issues of applying conventional cost-effectiveness analysis to health care evaluation in developing countries, particularly for pediatric immunization. It will suggest a framework for making the CEA methodology more appropriate to decision-makers who make choices among competing interventions in the context of very scarce local resources on the one hand and substantial external funding from donors on the other. This will be a qualitative study relying on multi-disciplinary literature analysis and expert opinion and perspectives.

The “reference case” is an established set of guidelines for the standardization of estimation methods and presentation of results of economic evaluations. However, it does not address some issues that are specific to developing countries, such as donor funds which form a significant part of health care resources but which may have unintended impacts on health care systems and health outcomes. Relevant literature will be analyzed to formulate a
conceptual framework for the adaptation of the cost-effectiveness analysis reference case. These recommendations will focus on capturing the impacts of donor funds on the use and allocation of health care resources. An application of the adapted reference case to a CEA study of the introduction of rotavirus immunization into a routine schedule will be used as an example.

Experts in global health will be interviewed to provide complementary information on the decision-making environment, in order to better understand the role that such an adapted reference case might have in developing countries. Ten to fifteen key informants will be asked to provide their opinions and perspectives on certain decision-making factors in developing countries, with particular reference to pediatric immunization.

The informants will be drawn from a network of researchers and practitioners from universities, research centres, international aid agencies and developing country health ministries. Recruits will be adults, English-speaking, and will be interviewed in person or by telephone, at the mutual convenience of the participants and the investigator. The interviews will be audio-recorded, and an additional consent form is included here for audio-recording. Notes by the investigator will also be made. Transcripts will be made of the recordings and returned to the participants for verification.

This study has policy implications for countries that are trying to harmonize health care efficiency and financing objectives, especially in the developing world. It may contribute to improving the generalization of cost-effectiveness analysis.

**Potential Harms:**

We know of no harm that taking part in this study could cause you. You may decline to participate at any point in the study.

**Potential Discomforts or Inconvenience:**

You will not experience any discomforts. The time anticipated for the interviews will be 30-40 minutes.

**Potential Benefits:**

**To individual subjects:**

You will not benefit directly from participating in this study.

**To society:**

This research aims to make a research tool that is widely used in industrialized countries more suitable for use in developing countries. The tool will help to provide more evidence for better decision-making for health care.

**Confidentiality:**
Your decision to participate or not will be kept completely confidential. We will respect your privacy. No information about who you are will be given to anyone or be published without your permission, unless required by law. SickKids Clinical Research Monitors, employees of the sponsor (SickKids Research Training Centre), or the regulator of the study may see your research records to check on the study. By signing this consent form, you agree to let these people look at your records.

The data produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe those individuals described above) will have access to the data. This could include external research team members. Following completion of the research study the data will be kept as long as required then destroyed as required by SickKids policy. Published results will not reveal your identity. A summary of the anonymous, compiled results will be made available to you at the conclusion of the study.

**Reimbursement:**

We will give you a thank you letter for your participation. There will be no reimbursement.

**Participation:**

The data that will be collected will be used only for this research and will not affect employment relations with SickKids.

New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will you about this new information. And we will ask you again if you still want to be in the study.

If you become ill or are harmed because of study participation, we will refer you to treatment for free. Your signing this consent form does not interfere with your legal rights in any way. The staff of the study, any people who gave money for the study, or the hospital are still responsible, legally and professionally, for what they do.

**Sponsorship:**

The sponsor of this research is the Research Training Centre of the Hospital for Sick Children (SickKids), Toronto, Canada.

**Conflict of Interest:**

I, and the other research team members, have no conflict of interest to declare.

**Consent:**

By signing this form, I agree that:
1) You have explained this study to me. You have answered all my questions.
2) You have explained the possible harms and benefits (if any) of this study.

3) I know what I could do instead of taking part in this study. I understand that I have the right not to take part in the study and the right to stop at any time. My decision about taking part in the study will not affect my health care at SickKids.

4) I am free now, and in the future, to ask questions about the study.

5) I have been told that my research records will be kept private except as described to me.

6) I understand that no information about who I am will be given to anyone or be published without first asking my permission.

7) I agree, or consent, to take part in this study.

____________________________________
Printed Name of Subject & Age

Subject’s signature & date

____________________________________
Printed Name of Person who explained consent
& date

Signature of Person who explained consent

____________________________________
Printed Witness’ name (if the subject/legal guardian does not read English)

Witness’ signature & date

If you have any questions about this study, please call Dr. Wendy Ungar at +1 (416) 813-8519.

If you have questions about your rights as a subject in a study or injuries during a study, please call the Research Ethics Manager at +1 (416) 813-5718.
Appendix 10: Audio Consent Form

Research Ethics Board
Video/audio taping & photography consent form

**Title of Research Project:**
Toward an Adapted Reference Case for Developing Countries: Incorporating Donor Funds in Cost-Effectiveness Analysis

**Investigator(s):**
Dr. Wendy Ungar, Senior Scientist, Child Health Evaluative Services, SickKids, Toronto, Canada
Cindy Gauvreau, MA, Doctoral Candidate, University of Toronto, Canada, Dept. of Health Policy, Management & Evaluation

**Confidentiality:**

The audio tapes produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe the SickKids monitor or the regulator e.g., Health Canada) will have access to them. Following completion of the study the tapes will be kept as long as required in the SickKids “Records Retention and Destruction” policy. They will then be destroyed according to this same policy.

**Consent:**

By signing this form,

1) I also agree to be audio-taped during this study. These tapes will be used to provide a deeper understanding of the health-care decision-making environment in developing countries that is being investigated in this study.

2) I understand that I have the right to refuse to take part in this study. I also have the right to withdraw from this part of the study at any time. eg., before or even after the tapes are made. My decision will not affect my health care at SickKids.

3) I am free now, and in the future, to ask questions about the taping.

4) I have been told that my study records will be kept private. You will give no one information about me, unless the law requires you to.

5) I understand that no information about me (including these tapes) will be given to anyone or be published without first asking my permission.
6) I have read and understood pages 1 to ___ of this consent form. I agree, or consent, to being audio-taped as part of the study.

_________________________________
Printed Name of Subject
Subject’s signature & date

_________________________________
Printed Name of person who explained consent
Signature & date

_________________________________
Printed Witness’ name (subject does not read English)
Witness’ signature & date

In addition, I agree or consent for this tape to be used for:

1. Other studies on the same topic
2. Teaching and demonstration at SickKids.
3. Teaching and demonstration at meetings outside SickKids.
4. Not to be used for anything else.

In agreeing to the use of the tape(s) for other purposes, I have been offered a chance to hear the tape(s) and view the transcriptions. I also have the right to withdraw my permission for other uses of the tape(s) at any time.

_________________________________
Printed Name of Subject
Subject’s signature & date

_________________________________
Printed Name of person who explained consent
Signature & date

_________________________________
Printed Witness’ name (subject does not read English)
Witness’ signature & date
Appendix 11: Interview Guide

INTERVIEW GUIDE FOR KEY INFORMANTS

Dear Participants,

This guide outlines the general questions that will be asked during our interview, representing the themes that I would like to discuss with you. However, they will be more specifically tailored to your individual circumstance and professional experience. I will also ask more detailed questions following each general question as I try to understand your answers in more depth. The interview will take 30 – 40 minutes.

Your participation is greatly appreciated.

Cindy Gauvreau
PhD Candidate, University of Toronto

Representative questions:

1. Would you please describe your role/experience in pediatric immunization decision-making in your country or in the global health field?

2. Would you please describe an aspect of the decision-making process that influences whether or not a pediatric immunization program would be carried out in your country or by your organization?

3. What do you think are the types of information that are used for decision-making in pediatric immunization in a developing country?

4. Could you please tell me how this information is used for pediatric immunization decision-making?

5. Who takes part in deciding whether new immunization programs are introduced?
6. You might be aware that there are new vaccines proposed for introduction into the routine immunization schedules of developing countries. What do you think are the uncertainties of adopting a new vaccine (for example, rotavirus vaccine) in your country?

7. What kinds of information or tools are needed to address the uncertainties of adopting new vaccines?

8. How do you think the decision-making for pediatric immunization has been affected by developments in global health in the last ten years?

9. What would you like to see or would you do to help make better decisions for adopting new vaccines in your country?

10. Do you have any other comments or suggestions?
SUMMARY OF SALIENT POINTS FOR THESIS

To illustrate the use of evidence in decision-making in India, KI-1, a clinician-researcher, described a research project assessing the effect of the random delivery of an information package to decision-makers. The information includes the cost-effectiveness of internationally recommended basic health care interventions coupled with relevant “actionable” (operationalizable) messages to facilitate their adoption.

Significantly, the project illuminates what recommended interventions might be most successfully taken up, that is, what the “best-buys” are not only from a cost-effectiveness point of view, but also from a knowledge translation point of view.

An important part of the project was first understanding the complex decision-making environment for the implementation of new interventions in a setting of health care reform and expanding budgetary commitment. This required intensive study to understand the local facilitators as well as constraints in the realms of financing and budgeting, politics, health system infrastructure, human resources, jurisdictional authority, budget mobility, and political/community awareness. Also requiring intensive study was identifying and locating the decision-maker most likely to facilitate adoption of a particular intervention. Associated with this challenge is correctly identifying and utilizing the channels, including influential opinion-makers, through which to deliver the information packages. For example, in the decentralized health care system of India, local level governments enjoy discretionary decision-making for the implementation of central government recommended policies such as immunization. However, even at the intervention delivery point it can be difficult to discern the path of decision-making; although “district collectors” have the responsibility to allocate resources (often among many sectors, not only health), Chief Medical Officers may make the final decision.

Deep understanding of the decision-making environment is important in creating promotional/enabling messages specifically tailored to each intervention and project site, and most importantly, to the relevant decision-maker. The targeted use of evidence is, thus, critical in ensuring the uptake of new interventions.

PARAPHRASED INTERVIEW

We discussed one of KI-1’s current projects in India that concerns the implementation of interventions that were recommended for adoption as a basic package of services for all citizens. The recommendations are based on their cost-effectiveness, as established by an international and multidisciplinary panel of experts (the Disease Control Priorities Project and an India-specific document “Choosing Health”). One of the aims of the project is to find out from among
the recommendations “what is applicable, what’s scalable, and what’s going to have a significant health impact.” This requires an in-depth examination of the decision-making process in a setting of health care reform and expanding budgetary commitment. The project explores how decision-making might be affected when two rigourously developed sets of information are delivered together to decision-makers: the cost-effectiveness evidence associated with the recommendations and secondly, “actionable” (operationalizable) messages tailored for each group of decision-maker. In a random control design, the information and actionable message will be disseminated to decision-makers at all levels of the health care system, but particularly at the district level. This level includes local politicians, health ministry officials (e.g. chief medical officers) and local civil organizations.

Developing the actionable messages themselves requires intensive research, but locally appropriate evidence is considered by KI-1 to increase the likelihood of a successful introduction of the intervention:

So we're trying to take this, you know, because the package (of interventions), it's hard to go from that to a budget line, to a budget item. To go from an intervention to a budget item is quite difficult. And so we're trying to break it down into messages or things that are actually actionable at that level, at the level of that decision maker.

And so to develop these messages, we're now doing a bunch of qualitative work, looking at, so interviewing these different actors to try and understand if our messages are sensible and the things that they can actually act upon.

For example, one type of an actionable message is an audit report of the performance of the local health care jurisdiction, a “report card”, that would allow decision-makers to identify areas of needed attention.

The project also explores constraints to the implementation of the recommendations, including prioritization constraints. For recommended interventions that coincide with national level priorities, such as the National Rural Health Mission programme, there are fewer constraints. Two factors that affect decisions are examined: the allocation of funding in the context of increased funding and discretionary spending. In the first instance, local decision-makers may have little authority because the increased funding has been allocated at the national level, for vaccination, for example. In that case, the actionable message may be a letter to reinforce a national recommendation to add a new antigen. In regards to discretionary spending, even if funding has been allocated there may be other constraints to acting upon the health care message, such as a lack of manpower. Furthermore, money may be allocated preferentially in certain areas, opening up the possibilities of corruption and diversion. “So that’s a sort of … a personal priority setting.”

Priority setting is further complicated by the fact that some of the recommended interventions are already national budget line items, while others are not. In the latter case, to improve the uptake of an intervention requires making actionable messages more specific and meaningful to
the decision-makers. Furthermore, in introducing the poly-pill\textsuperscript{24} for example, multiple approaches may be needed: developing new (clinical) guidelines, training for cardiovascular disease management, adopting new drug procurement practices. The budget impact and financing modes of introducing a poly-pill would also need to be examined.

Another component of the project is to discover the channels through which information can be delivered, which is related to finding the truly effective decision-makers in health care delivery. KI-1 believed that the project team needed “a channel, first of all, for information…. We’re going through a lot of trouble to identify who these people are … just trying to contact them, identify who they are and how to reach them, is a fairly monumental task.” Even when an appropriate decision-maker is identified, he may be subject to competing priorities:

… to the Chief Medical Officer, health is always an issue, that's their only issue, right…. But for all these other actors, health may actually not be a big priority for them. And you know we haven't maybe thought carefully enough about how the…because we're, you know telling them information about how to spend this money, which obviously is to some degree important, but if they don't care about health because roads and all these other areas are more important, we may be losing just at the outset.

As another example, district collectors are highly influential in the decentralized health care system of India. They allocate resources at the regional government level, where health care is delivered, but they are responsible for disbursements across all sectors, not only health. Consequently, they are “inundated by supplicants throughout the day” for individual requests, and “we (the researchers) were one among many supplicants.” They are also subject to demands from members of the (national) Parliament and Assembly to effect personal favours at the district level (“Can you get me a car?”). There may also be a mis-match between responsibility and authority. So, while district collectors have the responsibility to make resource allocation decisions, final authority rests with Chief Medical Officers.

KI-1 felt that there are still many things to understand about the decision-making process and how to engage the decision-makers: how to “market” the health messages; how to motivate actors; and how to use the health care evidence gathered. Measuring the impact of the intervention is also uncertain, especially in sorting out the individual or combined impact of the ten recommended interventions in the essential package.

To KI-1 trying to effect small incremental changes is manageable goal of the project, and if successful, then is “scalable” to a wider population. Speaking to this point then, the heart of this project is the discovery of what are the “best buys” from a knowledge translation perspective. That is, identifying the interventions that have the best chance of being taken up.

Appendix 12-b: INTERVIEW SUMMARY FOR KI-2

\textsuperscript{24} Interviewer’s note: a proposed combination of aspirin, statin, ACE inhibitor, beta-blocker in one pill.
SUMMARY OF SALIENT POINTS FOR THESIS

A medical doctor and an official with a donor agency, KI-2 provided a wide perspective from a health care system point of view. From his experience with many developing countries in most regions of the world, he felt that governments make health care intervention decisions with inadequate evidence. Cost is the single most important factor in decision-making, and even if cost-effectiveness is considered, the focus is on the cost side. Consequently, ministries of finance are sometimes the key decision-maker for health care decisions.

The mismatch of scarce budgetary resources to disease burden is a major inefficiency, especially given the financial constraints of developing countries. KI-2 discussed how this mismatch might be overcome, using as an example a successful primary health care project in selected districts in Tanzania that explicitly developed the data and information base at the implementation level for intervention targeting. Evidence is needed on a sector-wide basis to illuminate and match disease burden with sources and flows of funding, as decisions are more often needed for a redistribution of budgetary resources than for an expansion of resources. Better targeting of funding, including donor funding, at the health care delivery level could lead to a more efficient use of current resources that obviates a need for expanded resources and, as shown in Tanzania, improved likelihood for better health outcomes. This approach requires a long-term perspective, but resulting cost/benefit information could provide an evidence base for extension of similar basic services to other jurisdictions.

Investments in information systems are therefore “critical” to evidence-driven policy, planning and implementation. Methods for deriving evidence that specifically addresses needs at the health care delivery level are required. The timeliness and circulation of information, the aggregation of disparate data (including that generated by external/donor agencies), the active use of this evidence, as well as the cost of obtaining information all need attention. Donors, too, require good evidence to supplement other measures of increasing aid effectiveness, such as longer term perspective and more stable funding, that ultimately contribute to better health outcomes and allocation of resources.

PARAPHRASED INTERVIEW

In KI-2’s work, projects are multi-dimensional, comprised of various facets such as human resources for health, health information and financing. Potential projects for donor support are examined from a health-systems approach: what stakeholders are involved and how, the linkages between service delivery components, “the voices from the ground”, the ethical issues, the policy implications, and ultimately how research can “actually involve improvement in care provision.”

Currently, main “research targets” for his agency’s funding are human resources for health and health information systems. The latter is critical for both documenting the impact of the
intervention and for identifying the gaps in evidence for formulation policies and planning. Financing is also a research target, critical in a severe resource constraint environment. In KI-2’s view, interventions in lower-income countries are often made without adequate evidence.

KI-2 discussed the importance of evidence in the context of a successful primary health care project in three districts of Tanzania that had implemented an integrated health systems approach to providing basic services. Results from this project demonstrated that the closer that budget allocations were matched with disease burden, the more likely the health outcome objectives would be reached. However, the information needed to enable this type of analysis is generally very limited, available only “to some extent” from government budgets, but not from donors or faith-based organizations. Once a “contribution matrix” of funders and supported interventions is established, the distribution between the disease burden and the budgetary allocation can be examined, and a re-distribution can be considered. Sharing resources and building upon existing capacities are also considered, all with a view to dealing with neglected diseases, and diseases of high burden and mortality. From project experience in Tanzania, this type of approach has resulted in health benefits for the population. However, it required a long-term, 5-8 years in this case, perspective.

Having the relevant data (e.g. health surveillance data) establishes a baseline, and allows evaluation of programming decisions and allocation decisions at the district level as well as the central government level. However, there are issues of aggregation of disparate sources of data (including that generated by external organizations), of information flow between levels of jurisdiction, of timeliness in getting information to decision-making point, and of proactive use of the information. For example, immunization coverage rates could be better used to identify and find patients who are not covered.

In Tanzania use of information from demographic surveillance sites in two separate districts have been used for impact studies and targeted advocacy. Cost information has been paired with health data to show potential investment benefits, specifically declines in mortality rates and disease burdens, and to demonstrate that an expansion of critical health interventions to other districts is financially feasible:

What’s important is that often it can be shown a redistribution of spending will suffice, not an increase of spending….The main thing is trying to see by prudent utilization of existing resources how can one make those impacts on health services that one requires. Particularly when you want to tackle the issue of infant and child health and maternal health on that level because those are good indicators for systems that are failing.

Cost data may overshadow health data, however, for decision-making:

But very quickly, very quickly the government wanted to know how much it costs, what’s the implications for budget. So that's a question that comes from central government and most time you need to lobby not the health people, you need to lobby finance, Ministry of Finance.
With decentralization of health care delivery in Tanzania, districts manage their own budget and set their own priorities. Developing a relevant information system was critical in improving evidence-based priority-setting, but experience shows that the cost of information must be weighed, too. KI-2 felt that the initial capital cost of implementing an information system is high (and hard to justify to government) but the incremental annual cost is low compared to the benefits gained from the longitudinal and good quality data generated. Nevertheless, budget implications persist in being the most meaningful factors in policy and planning and the prioritization of sub-populations for targeted interventions.

Donors’ priorities vary. KI-2 suggests that donors, too, need a good evidence base for making sound investment decisions and to harmonize their efforts. A bilateral agency like CIDA supports countries based on their basic needs, but also on strategic and trade interests. It is accountable to Parliament and tax-payers. Private foundations, on the other hand, have more flexibility, being accountable only to their boards. While there has been a large increase in health funding overall, it is streamed into a few “donor-identified priorities”. At question is, “how to better synchronize priorities and ensure that funding that's coming in go to these priorities beyond simply the sexy terms of AIDS, TB and malaria.”

Increased [global] funding for immunization is a welcome development, but information is still needed to know how to maximize the efficacy and efficiency of immunization and remove barriers. The barriers (to uptake) vary from place to place and need to be understood to target programmes specifically. Donors must also balance their accountability to boards and their own priorities with those of recipient countries. To improve immunization outcomes donors need to take a longer perspective to allow effects to take place. KI-2 points out that while donor funding needs to be more stable and longer termed, long-term sustainability of programmes also requires funding from the national governments themselves.

To KI-2, effective decision-making in the future rests critically on locally pertinent evidence:

How can one develop a better mechanism of deriving the evidence that speaks more to the need on the ground, you know, in more specific ways? And I think that's what's critical, and countries need to be able to invest in information gathering and evidence based derivations so that this can truly drive policy and planning and intervention in a specific way.

Appendix 12-c: SUMMARY FOR KI-3

SUMMARY OF SALIENT POINTS FOR THESIS

KI-3 provides research and management support to economic and epidemiological studies for the introduction of several new vaccines in Asia. She has noted a remarkable increase in awareness of economic evidence among government partners of the International Vaccine Institute in the last three to four years. Although governments may not be very familiar with
cost-effectiveness methodology itself, they are very aware of the importance of having economic evidence for decision-making. However, in international vaccine-focused meetings, including that for rotavirus, cost-effectiveness is a major topic, due to the number of new, expensive vaccines close to introduction as well as to the wide acceptance of evidence-based medicine.

From her experience in both industrialized and developing countries, she feels that in the former cost-effectiveness analysis emphasizes vaccine production (value for investment), and in the latter, where financial resources are limited, the focus is on vaccine use (sustainability and affordability). To better ensure sustainability in developing countries KI-3 felt that national governments should participate in the negotiation of new vaccine prices rather than leaving it solely to international organizations to negotiate with manufacturers on their behalf.

Nevertheless, international organizations are important in the decision-making process as they increase the evidence base for vaccine introduction as well as fund new vaccines. IVI is an important partner of several Asian countries. In Vietnam for example, it is assisting in the collection of disease burden, economic evaluation and clinical trial data for the rotavirus vaccine, all of which can be used as a “package” for application to GAVI for funding assistance. Other international organizations such as the WHO also assist in increasing local technical and manpower capacity for conducting economic evaluations.

In Asia opinion leaders are very influential in accelerating the introduction of vaccines. Some of them have decision-making capacities as civil servants and medical professionals, but they also motivate public health workers in implementing new interventions and the general public in complying with immunization programmes. The strength of the public health system and its workers is thus a major factor in immunization effectiveness. Public compliance with immunization may also be important to immunization effectiveness, but its impact is hard to estimate. KI-3 observes that compliance varies among countries, and the unusually high immunization coverage rates in Vietnam, for example, might be a result of its citizens’ high compliance with government rules in general and its high cultural homogeneity. KI-3 thought that high levels of health education there might also contribute to vaccine uptake, unlike other countries where, say, public alarm might be the motivation.

There are major uncertainties in adopting new vaccines; the most important, according to KI-3, are the price of the vaccine after GAVI support is ended and the supply of vaccines. Accordingly, increasing local manufacturing capacity is critical to enabling lower prices and to ensuring vaccine supply. The actual number of rotavirus-induced diarrhea is also still uncertain, as is the number of non-hospital health care encounters with rotavirus.

As economic evaluation becomes more important to decision-makers, KI-3 feels that national governments should develop standards in methodology. She sensed that even the WHO guidelines for economic evaluation of diarrheal diseases were considered by academic health economists to be non-rigourous.

PARAPHRASED SUMMARY
KI-3 provides research and management support to economic and epidemiological studies for the introduction of several new vaccines in Asia. She is currently working in the clinical trials for rotavirus vaccines in Asia and in building associated evidence, including economic evidence, for vaccines against rotavirus and typhoid.

From her experience, KI-3 notes that there is a marked difference in the type of economic evidence required for the US market and the Asian market. Whereas in the former cost-effectiveness analysis emphasizes vaccine production (value for investment), in the latter, where financial resources are limited, the focus is on vaccine use (sustainability and affordability). “So in America, of course, the cost is one of the critical factors we were considering but it was never been [sic] the pure limiting factor.”

Nevertheless, she felt that in the Asian countries in which she has worked, CEA is very important to the decision-making process of the government.

Opinion leaders in Asia have a very strong influence on the uptake of vaccines, and “if you have sufficient information for government and opinion leaders of medical community, I don’t see that much hesitation from the general public side of the vaccine acceptance.” Opinion-leaders are located in various government agencies including infectious disease control agencies, and many of them are medically trained, such as pediatricians. They are key in accelerating the introduction of vaccines and in communicating with local health workers. In some countries the primary health care unit are also key in accelerating vaccine adoption.

The International Vaccine Institute (IVI) is an important supporting partner in the decision-making process of many countries in Asia (India, China, Vietnam, Thailand), where they participate in clinical trials, product acceleration and demonstration projects. The rotavirus project in Vietnam is an example of an integrated surveillance project collecting disease burden as well as economic data, with potential to add clinical trial components. The economic evaluation component has become a very important part of the IVI’s partnered projects in recent years:

I mean that was actually amazing change in very recent years. If it was ten years ago I never see any people who talk about economic data as important evidence to be applied for any new vaccine when I was working with different countries. But then from let’s say about three to four years in recently, whenever I meet people we talk about you know what is the economic impact of the vaccine.

Although national governments may not be very familiar with cost-effectiveness methodology, they are very aware of the importance of having economic evidence for decision-making.

In KI-3’s experience at international meetings concerning rotavirus vaccine, and vaccines in general, the awareness of and importance assigned to economic evidence is high. She thinks this is due first to the large number of vaccines in the development “pipeline”. When the new vaccines are to be added to the EPI programme, their impact on the health care resources of the countries become a concern. Secondly, since resources for public health in Asia are constrained,
better criteria for determining their use is key. Lastly, governments, physicians and opinion leaders have embraced the concept of evidence-based medicine.

Examining immunization from a broader resource-sharing view is conceptually familiar in Asia, but it is not systematically implemented. Currently, even the most advanced user of HTA in Asia, Thailand, is still developing standards in methodology. IVI is actively helping government decision-making by collating an information package of epidemiological and economic data in Vietnam.

I mean this is the, almost the first time that any Asian country has the whole package for at least the rotavirus vaccine. … So then the timing of collecting all the information and cost effective analysis will be the time when Vietnam’s government has to make a decision for GAVI money for Rotavirus vaccine support… So I’m going to, I’m encouraging the Vietnamese government actually to utilize this package information when they apply for this GAVI money.

In regards to the sustainability of the rotavirus program in Vietnam (in which Vietnam begins by co-paying the vaccine price with GAVI and then eventually assume the whole cost itself), GAVI is negotiating with the manufacturer to reduce the purchase price. It is desired to have also a verbal commitment to maintain that price even after GAVI’s support has ended. GAVI and other international organizations are currently negotiating on behalf of Vietnam, but KI-3 thinks that while it would be better if low and middle-income countries would also participate in the negotiations to better ensure future sustainability.

One of the most important factors determining the effectiveness of immunization is the public health system. KI-3 thought that Vietnam’s socialist system and cultural characteristic of compliance to government rules and policies have ensured a wide-spread and unusually high level of coverage for the EPI programme (97%). The adoption of new vaccines is made potentially successful by the current system of health education delivery through dedicated local health workers. In China where there is greater cultural diversity, the compliance to EPI policies might not be as great and public health care workers may not be as committed to carrying them out. In India, public health education is weaker and immunization is often motivated by alarm during outbreaks. KI-3’s observation is that socialist countries have better compliance than democratic countries. However, vaccine effectiveness as related to coverage rate is difficult to estimate.

There are many other uncertainties in introducing a new vaccine. The supply and price of new vaccines are major uncertainties. Increasing the manufacturing capacity for vaccines in LMICs themselves might lead to lower prices due to lower production costs, KI-3 believed. The price of vaccines after GAVI support has ended is yet another major uncertainty. Also unknown is the actual number of rotavirus-induced health care encounters taking place outside the hospital. Furthermore, by using extrapolated rather than country-specific data, the exact economic impact of illness is not accurately captured.

Although the uncertainty of vaccine supply might be reduced by vaccine production being based in developing countries, issues of regulation (for production quality) exist. Additionally,
governments would require even more information and education concerning the production aspects not only for effecting good manufacturing practices but also for more confidence in decision-making.

In general, KI-3 felt, more evidence of all kinds is needed. With economic evidence becoming more important and sought out, governments need to establish standards. KI-3 sees that there is a division between “pure” (academic) health economists and epidemiologists in the methodology and application of CEA. For example, academic economists have challenged the guidelines suggested by WHO for economic evaluation of rotavirus. “…they don’t regard the information coming from those, uhm, guideline based studies as very academic or very economic oriented information.”

Appendix 12-d: INTERVIEW SUMMARY FOR KI-4

SUMMARY OF SALIENT POINTS FOR THESIS

KI-4 is a researcher currently involved in cost-effectiveness studies of new rotavirus vaccines in South East Asia, with in-depth knowledge of the health care systems of Thailand and Vietnam. He states that the two key decision-makers in the introduction of new vaccines to Thailand’s routine immunization programme are the National Vaccine Committee and the National Health Security Office (NHSO). The former, in the Ministry of Public Health, is concerned with the technical, medical issues surrounding new vaccines. The latter, an independent governmental body, is concerned with financing issues and is the payer of the programme. Local academic researchers and researchers from international organizations take part in providing evidence.

Burden of disease and other epidemiological evidence are the primary factors in motivating the introduction of public health interventions in Thailand. However, economic evaluation is a well-known and an increasingly-used technique employed in decision-making for public health. The National Vaccine Committee is currently focused on economic evaluation aspects in considering Rotateq® rotavirus vaccine for the national immunization programme. KI-4 feels that the main uncertainty for assessing the cost-effectiveness of adopting the rotavirus vaccine is its unknown price.

Economic evaluations are required for listing on the National Drug List, and recently a national health technology assessment agency (HiTAP) was established. HTA activity is quite high in Thailand, thought KI-4; methodological guidelines and a textbook have also been published.

PARAPHRASED INTERVIEW

KI-4 is a researcher currently involved in cost-effectiveness studies of new rotavirus vaccines in South East Asia, with in-depth knowledge of the health care systems of Thailand and Vietnam.
In Thailand the Ministry of Public Health is reviewing the inclusion of rotavirus vaccine in the universal Expanded Programme of Immunization (EPI). The Ministry, principally through the National Vaccine Committee, resolves medical and implementation issues surrounding immunization programmes and submits proposals for public financing to the National Health Security Office (NHSO), an independent government agency.  

… the Ministry of Public Health right now, they focus on the technical issue. First they may introduce the technical information to the National Health Security Office and then finally the National Health Security Office they have to make decision to include, to start to have the financial support for those things or not.

In studying the incorporation of the Rotateq® rotavirus vaccine into the EPI the National Vaccine Committee will draw on a variety of evidence. Epidemiological data is given most weight, due to its familiarity to the ministerial actors currently involved in the rotavirus project. The Committee often asks researchers for input, and recently a cost-effectiveness analysis using a DALY outcome measure was requested. Along with KI-4, epidemiologists and pediatricians are meeting to develop an analysis plan and identify relevant data. Data requirements are still to be finalized by the project members, but will fall into three groups: 1) vaccine data – e.g. price, efficacy, coverage, side effects 2) epidemiological data (e.g. morbidity, incidence) 3) direct and indirect costs on a societal basis (including treatment cost of rotavirus diarrhea).

However, data availability for the rotavirus studies in South East Asia is a large uncertainty. Where there is no country-specific data, generalization from another country or expert opinion is used, which introduces a high level of uncertainty.

But in some countries, we don’t have enough specific data, country-specific data we have to introduce that data from some other countries… And what we need in the country, like the costing, even costing we don’t have the direct measurement of the cost sometime we need. Sometime we use a expert opinion for the costing. Something like this that reach a very high level of uncertainty.

On the other hand KI-4 feels there is less uncertainty in the Vietnam rotavirus project, because the data is being specifically and primarily collected alongside the vaccine trials. In that project, economic data collection is incorporated into the surveillance at hospital clinics in three provinces. Health care utilization information is collected from surveys at outpatient clinics. Inpatient care data is derived from discharge information, and follow-up care after discharge is also collected. Collection is at three levels of facilities: village clinic, district hospital and provincial hospital. Patients were interviewed for indirect costs (travel, meals, lost work time of parents), and recall bias was reduced by interview within three days of visit.

25 Interviewer’s note: The National Health Security Office administers the Universal Coverage Scheme, which covers the population not covered under the country’s other two health schemes, an employer-based and a government employee scheme. Accordingly, the population under the Universal Coverage Scheme tends be in lower-income groups.
The economic analysis for rotavirus vaccine introduction in Thailand will use modeling. The uncertainty of the vaccine price will be handled with sensitivity analysis, testing a range of prices for the rotavirus vaccine. Due to the probable high cost of the vaccine, KI-4 thought that price subsidization may be recommended. Thailand is not eligible for financial support from GAVI for this vaccine.

Other important uncertainties to resolve are the actual incidence of rotavirus disease and the cost of treatment without vaccination:

...in case if this it’s not a fatal disease so we did not [sic] invest for a vaccination. We just wait for the disease, it happen and give the treatment, okay, because the treatment is not expensive, very cheap, why invest in a vaccination?

Although KI-4 was not aware whether the National Vaccine Committee had used economic evaluation evidence before this case with rotavirus vaccine, in general economic evaluations for decision-making is increasingly used in Thailand. Drugs placed on the National Drug List require economic evaluations, for example. The infrastructure for economic evaluations is also growing; there is now an established and active national body for economic evaluations and recent development of national methodological guidelines and production of a textbook.

Appendix 12-e: INTERVIEW SUMMARY FOR KI-5

SUMMARY OF SALIENT POINTS FOR THESIS

KI-5’s work in Vietnam includes the economic evaluation of new vaccines in the context of an expansion of the EPI program and health reform in Vietnam. Some of this work takes place in international collaborative studies of typhoid and shigellosis vaccines.

Vietnam has a system of socialized and centrally planned health care, with a universal program of childhood vaccination that includes the regular EPI vaccines. Decision-making for vaccination programs does not include a formal channel for consulting non-governmental bodies, but the Ministry of Health does draw upon expertise from various sources, including academia. Scientific committees formed in the Ministry are the main structure for decision-making and prioritizing vaccine(s) adoption. The Institute of Vaccines (and Biological Substances), which also produces vaccines, sometimes initiates the decision-making process by a proactive presentation of efficacy and effectiveness evidence. International organizations are also part of the decision-making process, as they provide technical assistance in the various aspects of introducing new vaccines.

26 Interviewer’s note: The HiTAP – Health Intervention and Technology Assessment Program.
Economic evaluation is a new tool for health care decision-making in Vietnam, but there is a low level of technical capacity to perform it. “We don't have lots of people work in this area. In fact I have to fight that.” External technical assistance from international organizations is therefore still required. Data collection and availability, especially for financial data, is also a major constraint in using economic evaluation. The outcome measurement is changing from “coverage” to “lives saved” or “DALYs saved”, in line with international trends.

Currently Vietnam is collaborating with international organizations in several active vaccine studies that incorporate some form of economic evaluation. In addition to typhoid and shigellosis, vaccines against HPV, rotavirus, HIV/AIDS and rabies are being studied.

In general, evidence has become a major input in health care decision-making. “Evidence is very, very important in Vietnam now for making plans, for making decisions and for management also.”

PARAPHRASED INTERVIEW

KI-5 is a researcher in Vietnam. Some of her recent research is centered on analyzing the cost-effectiveness of typhoid vaccines, in the context of an expansion of the EPI program and health reform in Vietnam. Working on international collaborative studies of new vaccines, KI-5 is currently focused on examining the health system costs of introducing new typhoid and shigellosis vaccines to Vietnam. The impetus for the typhoid vaccine studies is the proposed introduction of a new formulation to replace the existing vaccine, with support from the International Vaccine Institute. 27

The policy-maker and main decision-maker is the Ministry of Health. Top-level scientific committees provide disease-specific guidance and expertise. The Institute of Vaccines (and Biological Substances), which produces vaccines, is also an actor in vaccine decision-making. It may initiate the introduction of vaccines, providing evidence to government for assessment. “...so for Institute, they have to show the evidence that vaccine is possible, first of all is efficacy and then they have to do the research to show that it's cost effectiveness [sic].” International organizations are also part of the decision-making process, as they provide technical assistance in the introduction of new vaccines.

Vietnam has a free universal programme of childhood vaccination that includes the regular EPI vaccines, and it is currently considering the addition of other vaccines. Previously, efficacy was the main factor considered in adopting vaccines, but cost-effectiveness has now become more important. Ongoing technical assistance from international organizations is required as there are still few local analysts. Although KI-5 finds that the cost-effectiveness technique is not difficult to use, she finds data is hard to get. “You know the record system in Vietnam before is not work [sic].” Although it is better now, it is still hard to collect data; financial data is particularly sensitive. Another limitation in using cost-effectiveness analysis (CEA) is the quality of data for effectiveness measures. For example, data on “coverage” usually count children who are

27 Interviewer note: Vi vaccine (Typhim VI (VICPS)), inactivated, injectable).
immunized, but not whether they have completed all required doses. However, these gaps are being overcome. Also, while “coverage” has been the metric predominantly used in the past, there has been a change of directions to use “lives saved” or “DALYs saved” recently.

After efficacy, effectiveness and CEA information are presented to decision-makers, they then decide the next step taken, say, a field trial. The scientific committees prioritize vaccines to include in the national programme and recommend to the Ministry of Health specific vaccine inclusion in national planning and submission for budget allocation. “We have … committee to decide which ones should be priority for the whole country. And they even decide which (vaccine] should be the first priority, the second priority.” In the case of the typhoid vaccine, the transfer of technology to Vietnam to produce it locally was also considered.

International organizations are active in assisting economic evaluations of new vaccines, including those for rotavirus, HIV/AIDS and HPV, rabies. “… normally when we apply for a new vaccine, normally it belongs to the international organization to come and help us. Because is this area is still new in Vietnam….”

In general there has been increased use of evidence for planning.

We talk about using evidence for making plans or for allocation of the budget…. Evidence is very, very important in Vietnam now for making plans, for making decisions and for management also. We need evidence for not only the vaccinations but for the other aspect in health care… like for training. Use cost data to establish fee for service. … in conclusion, evidence is very important not just in talking. In fact economic evidence is also very important.

Appendix 12-f: INTERVIEW SUMMARY FOR KI-6

SUMMARY OF SALIENT POINTS FOR THESIS

KI-6 is a senior researcher in China, working in diverse areas of community health and health care reform issues.

The process of decision-making is very hierarchical, with evidence being submitted to lower levels of government and then passed upwards as approval is gained at each level. Government coordinates the generation of evidence for policy-making, soliciting advice and expertise as needed. Government research institutes directly support decision-making, but “famous researchers and professors” have an especially high standing with government decision-makers. In addition to providing evidence, they often provide validity to government decision-making. Special interest groups may also initiate and drive decision-making. “And they use some famous professors to push the policy-maker to issue the policies.”
Personal relationships between researcher and decision-maker, which engender trust, make it more likely for evidence to be accepted.

The Department of Chronic Disease Control in the Ministry of Health, which is responsible for assessing and issuing immunization policy, is the key decision-maker for immunization.

In general there is an awareness of using evidence for making health care decisions, and decision-makers in China are now using more rigourously generated evidence. However, the demand for economic evidence is growing among decision-makers, the understanding of economic evaluation is very limited and usually equated with cost or budgetary analysis. The requests are motivated by budgetary concerns, so that despite efforts by researchers to introduce concepts of cost-benefit or cost-effectiveness analysis, decision-makers sometimes do not value the information. For example, in examining the nutritional fortification of flour, researchers “gave them some cost benefit ratio. They say I don't care about a ratio… I don't care about that, you just tell me how much money you need for the project.”

To the central government economic evaluation is still a low priority technique, and few resources are used to develop capacity to produce and use it. Yet within the last five years decision-makers have increasingly asked KI-6 for economic evidence, if not actual economic evaluations. Decision-makers at local levels of government are sometimes more receptive to the concepts and results of economic evaluation. She feels that the cautious approach to adopting economic evaluation is a result of a general Chinese characteristic and desire, especially among ministers who do not want to jeopardize the current economic status, to maintain stability. Therefore impetus for new ideas like economic evaluation sometimes come from the international organizations running projects in China, and collaboration with these partners on economic evaluation is a preferred approach.

Economic evaluations are also constrained by poor and missing data, and the heterogeneous sources and formats of data that are difficult to coordinate and combine. Otherwise, KI-6 felt the methodology itself presented no difficulty.

For China the largest impact that developments in global health have made is in the field of health financing protection. As the result of a successful donor agency pilot project, the Medical Finance Assistance scheme was implemented. In general, KI-6 felt, international organizations have provided positive influences and benefits to China, and this speaks well for future collaborations for the development of economic evaluation, too.

PARAPHRASED INTERVIEW

KI-6 is a senior researcher providing research support to the Ministry of Health in China on community health and health care reform issues, and has interests in health technology assessment and health care program evaluation.
In developing new community health care service, the ownership mode of the community health centers is currently being studied by the Department of Community Health of the MOH. The China Health Economics Institute (CHEI) compared the quality and quantity of health care delivered alternatively by privately and publicly run community health centers in two pilot cities. It was able to provide evidence, health outcome data, that there is no difference in health care provision between the two ownership modes.

Immunization for children under one year old is free under the National Immunization Plan and is one of the six functions of the community health centers. In introducing new vaccines, government would “want some scientific study evidence.” The Department of Chronic Disease Control in the Ministry of Health, which is responsible for assessing and issuing immunization policy, is the key decision-maker for immunization. New vaccines must be passed through the Chinese equivalent of a Federal Drug Administration, which requires biotech companies to provide evidence on efficacy and effectiveness of vaccines.

In general there is an awareness of using evidence for making health care decisions. Special interest groups rather than policy-makers might also initiate evidence gathering, and the focus of that evidence is usually health outcome related rather than economic:

And they use some famous professors to push the policy-maker to issue the policies. Say we deliver the free folic acid tablet to the pregnant woman, you know, poor area. And they have some evidence. It's scientific evidence say if we deliver the free folic acid tablet to a pregnant woman ….. But they (policy-makers) didn't ask the evidence from the cost analysis …. They just ask, give me the clinical evidence and tell me if we delivered folic acid to the pregnant woman and can prevent the NTD comes out [sic]. Okay, I can issue the new policy. So in this time we launch the new one, … the reform of the medical care system and this one become the policy.

To the government decision-makers economic issues are mostly considered in the vein of budgetary impacts, although as a researcher KI-6 felt that

… we have to persuade them to know how important economic evaluation it is. But sometimes, they don't care about that. For example, we have a meeting between the research and the policy maker talking about fortification in flour. We gave them some cost benefit ratio. They say I don't care about a ratio - one with two, one with 100 - I don't care about that, you just tell me how much money you need for the project. Tell me how much money needed for one province or for the southern part or the northern part.

In general, the focus is on the cost side and not the benefits, motivated by budgetary concerns. KI-6 thinks that there is not a full understanding of the concept of economic evaluation, especially by lesser-educated government members from the military or pure politicians. Also there is sometimes resistance from local health authorities in the dissemination of the information from the central government.
However, there is a growing understanding of economic evaluation among more highly educated personnel in the central level of the Ministry of Health. At the same time, it is being introduced to local levels of government with positive reception. For example, in the case of a swine flu prevention study, KI-6 says, “we give them the idea about a cost benefit analysis or about information from cost and the benefit. It’s a [sic] really, really wake them up.” For any government official to accept research findings a personal relationship has to be developed to engender trust in the findings, though:

If you give them scientific evidence and if your research was conducted in the rigorous methodology and if you can have the chance to talk with the policy maker face-to-face and say it kind of building up the relationship, is trusting relationship, and then they will trust your results, findings. Depend on the relationship.

Other than policy-makers, KI-6 stated that “famous researchers, famous professors” are involved in making decisions, and provide evidence as well as validity to high-level policy makers who are increasingly using evidence to inform their decision-making:

So far, before just the ten years or the seven years ago, the policy maker, they may make decisions by their own brain. They didn't take the evidence. But so far, I think they are eager to see the evidence. One is for the scientific review, another one for protecting their position because I take your (the researcher’s) results.

The process of using evidence for decision-making is very hierarchical in China. Evidence from researchers are submitted to lower levels of the MOH, say deputy director of departments, who submits it to the director, and then up for joint review with other departments, and finally to the national level. Generally, nation-wide policy is made at the central government level, and then local, provincial, city governments interpret and implement it according to the local circumstance.

KI-6 has still not seen any policy impact made by economic evaluation. Because of the wide disparity in economic development in China, a main constraint in delivering equitable health care, decision-makers at the national level are focused on budgetary issues. Therefore, there is low priority for more complex analysis and few resources to develop the capacity for economic evaluation. Yet, demand for economic analysis is growing:

For example, five years ago ... At that time, nobody wants to ask Research do some economic analysis, even though not pure economic analysis…. But so far and gradually more and more officer, they have the thought. They talk to me and they ask me to do the project, before never.

KI-6 also felt that although acceptance of economic evidence is growing, policy-makers are cautious in embracing these concepts and results as they do not want to jeopardize the current
favourable economic situation. “I see some of the ministers when they want something they do something stably, they don't want up and down.” Therefore, impetus for new ideas like economic evaluation sometimes come from the international organizations running projects in China, like DFID, World Bank, WHO:

Sometimes international organization have idea of the economic evaluations and sometimes (Chinese) officers say okay, we can plus [sic] some economic evaluation and they say okay. Then they can work together for China project.

Other constraints facing economic evaluation are incorrect or missing data. For example, in the collection of immunization cost data, researchers must go through the Division of Finance and Planning in the MOH. Not only is data quality poor, with little auditing done, it is also inappropriate, geared toward administration not research. Furthermore, multiple sources of data (hospitals, local communicable disease authorities, foreign researchers) are not coordinated, and each body has its own database system. However, methodology is not an issue, KI-6 feels.

The development in global health that has most affected China has been the focus on health financing. There are many international organizations and donor agencies working in China, and the one that has had a direct outcome is a component of a DFID project that has resulted in implementation of the Medical Finance Assistance scheme. In general, KI-6 feels, international organizations have had a positive influence in China, especially if a long-term relationship has been built:

And the international organization is kind of … kind of start up, it kind of give you a start engine and let you see how it's running the train or the car. And then the Chinese government say, oh, the train or the car is really, really good vehicle, or transportation, for Chinese people. Okay, okay stop, I can take that, I can follow your way to do for Chinese people.

KI-6 observes that economic evaluation in China is still very new, and it lacks personnel to conduct it, but foreign, outside help is welcome to come help develop the field.

Appendix 12-g: INTERVIEW SUMMARY FOR KI-7

SUMMARY OF SALIENT POINTS FOR THESIS

Speaking from wide experience in providing academic and research input into public policy and decision-making as well as direct involvement in the development of health technology assessment in India and other developing countries, KI-7 describes the role of economic evaluation in India as “scanty” and “nascent” or “latent”. Health care decision-making in India has largely relied on evidence derived from international sources, but KI-7 felt that India must
use its own tools to assess its own data to establish locally specific epidemiological data and locally appropriate medical models.

India is currently assessing the introduction of several expensive vaccines. There are several medical and technical advisory bodies assisting the government, but the well-developed vaccine industry is also a strong player.

The structure of India’s health care system is an important factor in decision-making. There is a strong private sector providing health care to high income groups, and as much as 80% of health care expenditures are paid out of pocket rather than from government funds. Consequently, there is relatively less pressure on the government to use cost-effectiveness analysis when making decisions. Decisions usually revolve around long-term financing. It is KI-7’s opinion that potential GAVI funding has affected the priority placed on assessing an expensive vaccine like pneumococcal conjugate vaccine and that requests to fund a non-GAVI supported vaccine might not be as favourably considered by GAVI.

KI-7 feels that India needs more and better-targeted disease surveillance systems and that decision-making could be improved by drawing evaluation expertise from all sectors. Data and analysis must be specific to the local population and representative of the wide population and geographical diversity of India.

PARAPHRASED INTERVIEW

KI-7 is well connected to the decision- and policy-making process for pediatric immunization in India, as a researcher and serving on various advisory committees. He describes policy-making as being determined by the Ministry of Health and Family Welfare. There is no formalized role for scientists in the process, but academics are often asked for input. There are two routes: one is an invitation from government to experts to form recommendations and the other is for professionals to form recommendations on their own and offer it to government for consideration.

The government’s main criterion in assessing recommendations, KI-7 feels, is financing, but in conjunction to expected or suspected burden of disease and need for a vaccine. Inputs are also taken from international organizations like the WHO, UNICEF, the Bill and Melinda Gates Foundation, and particularly GAVI. In India, the decision is also affected by vaccines already being produced in India, regardless of the related burden of disease.

The vaccine industry is an important factor. Established during British colonialism, it has large capacity, manufacturing many of the WHO/UNICEF EPI vaccines for domestic and export use, as well as vaccines not provided under India’s Universal Immunization Programme. There are a number of vaccines currently recommended by professional bodies which are being considered for approval by the government. The process of approval to include vaccines into the routine schedule includes meetings with the Indian Academy of Pediatrics, the Indian Medical Association, Medical Academy of Pediatrics, the India Expert Advisory Group as well as
specialists providing input on specific vaccines. This consultation was in place for the polio, hepatitis B, and pneumococcal conjugate vaccines.

Traditionally three bodies of data were considered in decision-making: international literature, locally generated data, and expert opinions. Additionally, WHO guidelines or, occasionally, American Academy of Pediatric recommendations and ACIP28 guidelines were implemented following vaccine adoption. In the last three to four years, the trend towards evidence-based decision-making includes attempts to contextualize international results or to generate local data. For example, local data for hepatitis B infection established that prevalence was half the rate previously accepted for the last 25 years based on international data.

There is a surveillance system in place for the EPI program, and another specific to polio eradication, but there is none for other vaccine-preventable diseases. The polio system is extraordinary as it is tied to global eradication efforts and is generously funded by domestic and international resources at every level. KI-7 thought that in strengthening the infrastructure for surveillance much finesse in approach is needed. Disease-specific surveillance is needed, and data collection needs to be widely situated to reflect the range of geographic, social, and population variations.

In regards to the introduction of rotavirus vaccine, data is still needed to establish its need. The local disease burden is unknown (the incidence, the severity of rotavirus infection, and whether the level of mortality and morbidity warranted public health measures).

Rotavirus vaccine is already available in India, meeting private demand. The ability of local manufacturers to produce it and the relatively loose regulatory regime allow citizens to buy the vaccine themselves. “Because there is a segment of the population in our country which can afford even very, very expensive vaccines and other pharmaceutical products.”

However, the public provision of vaccines is a much different matter, entailing more difficult decision-making revolving around long-term financing. “Now decisions, which have been a huge financial consequence, have been made in the past especially with regard to the old polio vaccine on which our country probably spends unprecedented amounts of money and has been doing so for the last 13 or 14 years with no firm end point in sight.”

Accordingly, to KI-7 the Indian government’s current serious consideration of adopting the expensive pneumococcal conjugate vaccine, which was recommended by a local scientific enquiry, with the help of GAVI is puzzling. This vaccine would need to be imported as there is no current local capacity to produce it. “What is not clear is why GAVI should be willing to finance and fund only this particular vaccine and only for a limited period of time. For example, I am given to understand, though I have no proof, that if the Indian government were to ask GAVI to fund another vaccine which we think is more important, we might not get as encouraging results as for this pneumococcal vaccine.”

28 Interviewer’s note: Advisory Committee on Immunization Practices, an American CDC body.
Other vaccines being considered by the Indian government are Hep B, Hib, and Japanese encephalitis. The evidence being used to help in decision-making are a Hib probe study, meta-analysis of a series of small studies across India.

Although the Indian government has not systematically performed cost-effectiveness analysis for immunization, K1-7 thought that it would be possible as many of the costing data is easily available. However, assessing programmes over time was difficult. “What we don’t have is some way to measure cost effectiveness or cost benefits or the net gain over a period of time at serial points in time of a vaccination. This is something we lack and therefore this is one of the important reasons why we have not included any new vaccines over the last 25 years and the fact that we continue to battle polioyelitis with no definite end point in sight.”

Nevertheless, economic evaluation should be generated using local tools and local data, and not extrapolations of evidence from external sources.

Currently, health economics and economic evaluation is “scanty” and “nascent” or “latent” in India, partly because of lack of training in it by health, finance or business professionals. Also, there is little incentive to examine health care programmes, as health funding by the government is a very small portion (20%) of the total expenditure on health, 80% coming from out-of-pocket payments. K1-7 didn’t feel that economic evaluation will become conventional until the government starts to bear more of the expenditure and has to do “some kind of accounting for every buck”.

K1-7 thinks that health care decision-making in India would be greatly improved by being able to draw on a greater pool of evaluation expertise from all sectors, especially those who had the capacity to appraise externally generated evidence for its applicability to India. Generating data locally and combining it with international data to help assess disease burden, vaccine efficacy and effectiveness, and to generate epidemiological model specific to India, are necessary. Lastly, long term monitoring and evaluation would be ideal.

Appendix 12-h: SUMMARY FOR KI-8

SUMMARY OF SALIENT POINTS FOR THESIS

KI-8 is an economist with international experience. She brought this broad perspective as well as the perspective from the research-and-development oriented pharmaceutical companies in China to the key informant interviews.

KI-8 explains that the decision-making environment in China has been evolving, reflecting the country’s change in governing and economic directions. Whereas in the past it has been centrally controlled at the national level and closed to public opinion, there is now more decentralized decision-making in the provincial and regional level, such as at provincial or
municipal ministries or departments of health. There is also more acceptance of public participation in decision-making, in some government departments more than others, although there is no formal channel for incorporating that participation in actual decisions.

In a departure from the past, expertise, evidence and commentary is being solicited from the public and fit within the central planning framework, to inform official decision-making at the national level for the health system reforms. Input from academicians carry especially heavy weight. The academic community, which has extensive connections to the public sector, is the prime provider of health care, scientific and technical evidence. Specific evidence about drugs and vaccines (especially in regards to costs, quality and market structure) is often solicited from the pharmaceutical industry. Economic information related to health care provision, in regards to hospitals, medical personnel and drugs, for example, are highly sought and analyzed by the central government to reform the financial incentives and financing of the health care system.

However, economic evaluation is still an insignificant tool for decision-making in China. KI-8 thought that it is considered by policy-makers as an academic exercise. “… some substantial research doing [sic], being done, going on, but has not been adopted for policy use yet.” There is almost no capacity outside of the academy to conduct or understand economic evaluation, and even within the academy, capacity is limited to a few well-known professors.

Drug policy is an important focus of reform because drugs are a significant out-of-pocket cost for patients, accounting for one half of total health care expenditures in China. Furthermore, they have a reputation for low quality. Drug reform includes addressing health system factors that have helped fuel the over-prescription of drugs, such as low public financing for hospitals and low health care provider remuneration. The pharmaceutical industry in China has a strong interest in the reforms, and in public consultations, it has provided advice and analysis on accommodating health care system restructuring and drug cost reduction with balanced, reasonable growth of the pharmaceutical industry. The industry is concerned with the possible use of cost-effectiveness analysis for cost-containment, even though pharmacoeconomics is in the very early stages of development in China.

Besides unknown reform-related impacts, uncertainties facing the Chinese pharmaceutical market include the world-wide financial crisis and increased global regulation.

PARAPHRASED INTERVIEW

KI-8 is an economist with international experience. She brought this broad perspective as well as the perspective from the research-and-development oriented pharmaceutical companies in China to the key informant interviews.

The R&D oriented companies in China is supported by an umbrella organization that includes in its services the conduct of evidence-based research, including economic analysis. The organization also produces evidence for government and the general public, and research projects range from pricing studies to policy and position papers to educational seminars for Chinese health care stakeholders. Although the organization mainly serves its mostly
multinational members, it also provides leadership for local manufacturers. In the recent health care reform public consultations, the organization addressed the factors contributing to unusually high national drug costs (one half of health care expenditures in China), with a view to balancing cost reductions with industry growth.

Other important stakeholders in the Chinese health system reform process included national level academicians, local health care associations and the National Development Reform Commission (NDRC). The health system reform steering committee itself is comprised of fourteen ministries. Decision-making is thus complex:

I think this is considered very challenging part of the whole process. This is … partially the reason why the reform, China, you know, health care reform results have not been released yet, because, you know, takes long time and process. Hard process to consolidate the real consensus among those key partners, among those key ministries. Because each, you know, … problem is each ministry talking about reform from their own perspective. But sometimes … the lack of effective coordination, it’s a problem.

Notably, in a departure from the past, planning for health care reform has included public consultation with all stakeholders. “You know, in the old days, you know, there’s not much open… there’s no channel for open discussion or consultation. But there has been change, significant change…”

However, there is no real, formalized channel to provide evidence to decision-makers yet. There are varying procedures and varying degrees of receptiveness by different ministries for receiving input. KI-8 feels that the NDRC, which is also responsible for pharmaceutical products and policies, is “the most upfront.”

You know, NDRC is ready or plan to cut market pharmaceutical price or maybe to make adjustment…. You know, they call for meetings, and ask industry representatives to sit at the table. And to hear their proposals but also provide their feedback and suggestions to them. And so I think, you know, NDRC is very good at doing this. And for other ministries, I think can be quite different.

Evidence, a cost survey, for example, is often solicited by the government from the pharmaceutical industry. Aside from pricing, the association is currently studying the pharmaceutical quality management system. Drug policy is currently very important to the Chinese government not only because of cost, but also of the poor local and international reputation for drug quality.

KI-8 feels that the pharmaceutical industry in China has not developed as far as others in middle-income countries, with a large quality gap for the same compound. There are 4500 local companies, and growth, she thinks, needs to be quality rather than quantity-driven. Recent regulatory changes and standards for quality and new drug registration have resulted in a large

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29 Interviewer note: Formerly the State Planning Commission, which has authority for broad macro-economic planning.
drop in product registrations. Most of the drugs produced are targeted towards the local market, with vaccines being produced only by a few companies.

The current financial crisis will cause uncertainty for the pharmaceutical industry, but the large investment (850 billion Chinese Yuan\(^{30}\)) being committed to the health care reforms should help to indirectly sustain growth in the industry. The larger uncertainty, however, will stem from increased regulation:

Definitely, you know, high pharmaceutical spending in China, in the Chinese hospitals is something very unique, when China, China compared to other countries. So, China has a very strong goal to cut excessive pharmaceutical cost over the next few years. At least in near-term reform, in the next three years. Whether that … how that’s going to impact on the pharmaceutical industry, I think we are all waiting to see what happens.

The high expenditures on drugs “.. attract so much attention …. political attention”, and are a major focus in the reform process. Decision-makers are therefore analyzing economic information such as drug price, hospital cost, hospital income, total health care costs and medical service fees. The public/private structure of the health care system and the sources and flows of financing are also being examined. Charging for drugs, with a substantial mark-up, is a form of financing for doctors and hospitals due to the low medical service fee paid to doctors and the low rate of public financing for public hospitals (only 7% of costs covered). Half of hospital incomes come from drugs. The incentives for over-prescription are therefore contributing to high drug costs. KI-8 thought that as a service economy evolves in China, better wages for medical personnel will help reduce the cost of drugs (i.e. by reducing the need to supplement the low medical fees). Although there is compelling reasons to cut drug costs, KI-8 believed that the reduction should be gradual.

Economic evaluation in the government and the pharmaceutical industry is still in the theoretical stages, due partly to a lack of technical capacity. It is being conducted predominantly by academics, and although awareness is growing, there is no substantive use of economic evaluation. KI-8 notes that, “… some substantial research doing [sic], being done, going on, but has not been adopted for policy use yet,” and that “there’s a lot of talk…ah… very little actions.” Nevertheless, the potential for expanding use of economic evaluation is considerable, since evaluations of the pilot programs inevitably resulting from reforms would need to include CEA or HTA.

Appendix 12-i: INTERVIEW SUMMARY FOR KI-9

SUMMARY OF SALIENT POINTS FOR THESIS

\(^{30}\) Interviewer note: Approximately $C 127 billion, April 2009.
KI-9 has studied the decision- and policy-making processes, data requirements, and vaccination strategies for the introduction of vaccines against cholera, typhoid, shigellosis, Japanese encephalitis, dengue fever and rotavirus by national governments in Asia (South Asia, Southeast Asia and East Asia).

Factors affecting vaccine introduction in Asia differ according to the particular country, but universally disease burden and profile are the most important according to survey and interview data. Personal relationships among decision-makers play an influential but unofficial and undocumented role. Decision-makers are mainly government employees, with national planning bodies having a dominant role in the centralized political structure of many of the countries in Asia. Ministries of finance are also powerful. Increasingly, though, national technical advisory bodies responsible for vaccine and immunization practices are being established across Asia. Local capacity for vaccine production and strong manufacturers also affect decision-making in some countries.

External funding, particularly by GAVI but also by other international organizations, is a driving force for vaccine research and introduction, significantly influencing the prioritization and accelerating the introduction of needed but highly expensive new vaccines. Programme sustainability at the finish of such support is a concern. Nevertheless, assisted nations benefit from accelerated or otherwise unattainable introduction of needed vaccines, and some funders have also proven flexible in accommodating local circumstances. The autonomy of national governments to address their own needs is not entirely curtailed by funding conditions, especially in the cases of countries that have capacity for vaccine manufacturing for themselves or for their region.

KI-9 feels that the establishment of local disease surveillance systems, preferably based on disease groups, is the most important factor in better targeting for vaccine research and introduction and in enabling national governments to control their own decision-making.

**PARAPHRASED INTERVIEW**

KI-9 has studied the decision- and policy-making processes, data requirements, and vaccination strategies for the introduction of vaccines against cholera, typhoid, shigellosis, Japanese encephalitis, dengue fever and rotavirus by national governments in Asia (South Asia, Southeast Asia and East Asia).

Among the most important factors affecting vaccine introduction are personal relationships among decision-makers. KI-9 felt that “number one is…well, you never know what happens behind closed doors and who influences who ….. the way hepatitis B vaccine got introduced in [country name]… a golfing buddy of the President had died of liver cancer …. .”

Decision-makers include ministries of finance, which tend to be very powerful. Some national planning commissions also “hold purse strings” (India, Indonesia). In Thailand parliamentarians
are decision-makers. The process of decision-making in most countries has often been ad hoc, closed to scrutiny, or subject to influential persons. Increasingly, though, countries in Asia are establishing national advisory committees for immunization practices, sometimes with encouragement and help from WHO. Some countries already have strong such bodies (Sri Lanka, Thailand, Malaysia), while others have immunization bodies that are getting stronger (India). “This is the trend and only a few countries don’t have them now in Asia.”

Survey and interview data indicate that disease burden is the main factor in the introduction of new vaccines. Other factors include whether the disease was epidemic or endemic, was urban or rural-based (“…because urban is where media and politicians are”), affected only the middle-class or cut across all class lines, affected children or not, and whether it had a high case fatality rate. Importantly, “if it's a GAVI-funded vaccine, all of a sudden it goes way up to the top of the list, even if the country can’t afford it, doesn't know they have the disease.” Also taken into account is the impact on the routine immunization programme in terms of additional number of visits and cold chain requirements.

Data requirements for decision-making include cost, affordability, and budgetary resources. Some countries use cost-effectiveness, but others are uninterested in it. “DALY doesn't mean anything. That's more of a donor driven statistic.” For the few countries using cost-effectiveness analysis, it is often defined and/or perceived as simply cost analysis.

Local capacity to produce vaccines is an increasingly influential factor in the introduction of vaccines. Some governments are reluctant to introduce vaccines unless there is a possibility that it could be wholly or partially produced (e.g. “fill finished”) locally. In one case, counter to local need, a foreign-made vaccine for Japanese encephalitis was rejected and introduction negated. “…there are a number of countries that have a national policy for local production reliance, or self-reliance in local production. In other words, if the vaccine can't be made locally, either now or in the future, near future, then they don't want to introduce. Or, you know, they are very reluctant to introduce. So that's a very powerful influence in India, in Vietnam, in China, in a number, a growing number of countries.”

Reducing vaccine cost is one of the motivations, as are national pride and the desire to target local strains, in trying to take advantage of local manufacturing capacities.

External funding greatly influences the introduction of new vaccines. KI-9 feels that “GAVI funding is an enormous factor.” In some cases the potential of GAVI funding has initiated or stimulated research and new vaccine introduction, such as for Hib and rotavirus vaccines. Many countries had previously had relatively little direct data on rotavirus-induced diarrhea, but KI-9 thought “they scrambled to do studies, or they did studies supported by GAVI or the Gates Foundation, but there's, you know a lot of pressure for them to introduce the vaccine because it's practically free for them.”

31 The GAVI Alliance, formerly the Global Alliance for Vaccines and Immunization.
KI-9 feels that a serious issue is the introduction of the rotavirus vaccine despite its comparatively low effectiveness in low-income settings, 40% in Malawi compared to 90% in the US, for example. In a country with a well-organized social system the effectiveness approaches 70% (e.g. Vietnam). Yet, despite a more effective three-dose regimen, a two-dose regimen has been recommended (globally) by SAGE\textsuperscript{32} the WHO-based Strategic Advisory Group of Experts (SAGE) on Immunization.

“And I think that's the pressure of the pharmaceutical company…. So that shows that, well it shows the power of the pharmaceutical companies and it shows the power of donor funding.”

Similarly for the very expensive pneumococcal vaccine, once Advanced Market Committment funding was announced there were more countries taking it up and there were more early adopters than had been projected in an earlier business case study. Conversely, it is extra challenging to adopt non-GAVI supported vaccines, like dengue, which is desired by most policy-makers in Asia. Thus the national prioritization of vaccine introduction is affected.

KI-9’s opinion was that at the end of GAVI funding, countries would need to discontinue the supported vaccine or find alternative solutions, “jeopardizing the sustainability of the whole programme.”

However, she also felt that, otherwise, countries would not be able to introduce needed vaccines for many years. Furthermore, neither GAVI nor the Gates Foundation has been overly “prescriptive” in their funding conditions; they have recognized local needs. For example, GAVI can make special arrangements to accommodate locally made vaccines. The International Vaccine Institute transferred technology to make cholera vaccine to India through a Gates Foundation grant that includes field trialing the vaccine, licensure, and WHO prequalification. The two organizations have therefore “changed the whole field of immunization,” with both positive and negative results.

Although vaccine introduction has been in large part donor-driven, national governments can also find their own solutions to their particular problems. Japanese encephalitis (JE) vaccine is an example of need-based rather than donor-driven introduction; its low cost and medical expediency led to its adoption by India. “India had a big outbreaks of JE and they had to do something immediately, so they actually used a vaccine from Vietnam, so that broke both their policy of just locally produced vaccines.” Some countries also desire locally appropriate evidence. “… there are a lot of countries now doing, even if a vaccine's been licensed internationally, even if it's, in some cases, offered by GAVI, they want a local efficacy and safety study done.”

To KI-9, it is imperative that disease surveillance systems be improved. Otherwise developing countries are subject to funders and product development projects defining their needs. Also, funding needs to be based on a comprehensive health system rather than disease by disease, for example, to the GEMS (Global Enteric Multi-Center, Multi-Sites) study for causes of diarrhea in children.

\textsuperscript{32} Interviewer’s note: The WHO-based Strategic Advisory Group of Experts (SAGE) on Immunization.
SUMMARY OF SALIENT POINTS FOR THESIS

KI-10 is an economist with wide experience in health care analysis. She contributed a perspective from the health care reforms in Mexico.

Economic analysis is well integrated in health care decision-making in Mexico. Comprehensive economic analyses were used in the design of Mexican health care reform, including using cost-effectiveness analysis to identify a package of assured essential, basic interventions. The high level of training and technical sophistication of policy- and decision-makers in Mexico were key to the successful understanding and application of economic evidence, both globally and locally generated. These decision-makers were also able to make the most of a well-developed surveillance and health data infrastructure. At the time, national interest in using economic evidence was bolstered by the then-groundbreaking integration of economic techniques and evidence for global health research and decision-making at the global level. Decision-making in Mexico is participatory and complex, with several health ministry bodies, the private sector, academia and the community providing input.

Health financing has long been a domestic focus, separate from the global focus on health financing. Mexico’s middle-income status makes it ineligible for the more recently created health funding initiatives and organizations, but, for low-income countries, KI-10 thought, these organizations have been important in improving access to needed drugs and vaccines. The organizations generally base their funding priorities on evidence, although implementation may not always be locally appropriate.

KI-10 felt that, in general, developing countries have some capacity for generating data and evidence, and some have made impressive efforts to generate disease burden and cost-effectiveness evidence. The quality of the evidence and the ability to appropriately use it are issues, though. Globally generated economic evidence has allowed a wide comparative basis, and for countries lacking the expertise to take advantage of this evidence for decision-making, technical assistance from international organizations is available.

The next phase in evidence-based decision-making beyond using disease burden and cost-effectiveness, KI-10 believes, will be to develop more illuminating indicators to capture complicated attributes such as effectiveness.

PARAPHRASED SUMMARY

Economic evidence is “essential” to the work of the Ministry of Health and was extensively used to design health reform in Mexico. Although health economics had been used in Mexico
for some time, it and other forms of economic analysis were used intensively in the reform period, where there was a conscious coordination of economic analysis, to “base decisions on evidence, precisely so that you’re not doing a leap of faith.”

“For decision making? Well there was a substantial amount of economic analysis that we did about financial protection, impoverishment from health spending, and then also on more specific projects, in terms of changing taxes, taxes around tobacco. So a variety of mostly economics related evidence, or economics evidence around what was going to be used for designing the health reform.”

The intensive use of economic analysis was due, in part, to the readiness and competence of a technocratic leadership in the Ministry of Health. Furthermore, the World Health Report of 2000 and the Commission on Macroeconomics and Health, which in turn had resulted in a Mexican Commission on Macroeconomics and Health, had also generated an interest in economic evidence.

Very importantly, Mexico already had a good infrastructure of health data collection and storage, within a system unified under the INEGI\(^33\), and included the National Income and Expenditure Surveys and the National Health Surveys.

“You know there was…and the other piece that was important I think was actually the existence of data with which we could work, which made the evidence substantially stronger.”

Data from national surveys dated back to the 1950’s, and the health reform team used data from the 1980’s onwards. The team also designed data collection processes for a formal evaluation of the reform.

Decision-making for health in Mexico is sophisticated and participatory. In the Ministry of Health itself “there are multiple decision-making bodies and that’s really what the Ministry is in fact all about.” A Minister, several Vice-Ministers, two Under-Secretaries, and the National Health Council are the key bodies, with varying prominence depending on the disease area being considered. Outside of government, the INEGI, academics, advocates, NGOs, clients, users, and patients all have a say via various channels including the Internet. This participatory process is not unique to the reform process, but is in place for the development of national health programmes every 6 years.

“Around…not just around the reform, but with every national health plan, there’s an effort to have cons…well not consensus, there’s an effort to have discussion groups and offer the possibility, via internet and others, to be able to hear the thoughts of different groups as well as users of the system. And I would say that’s probably the most organized way when those national health programmes are developed every six years. And then, other than that, there’s you know constant dialogue between the Ministry and particular agencies. And in the National Health Council, major NGOs and all the different actors within the system are represented.”

For a hypothetical decision to be made to introduce a new vaccine into Popular Health

\(^33\) Interviewer’s note: Instituto Nacional de Estadística y Geografía, National Institute of Statistics, Geography and Informatics.
Insurance\textsuperscript{34}, for example, the National Health Council, itself a multi-institutional group, would base its decision on a number of factors, including “cost effectiveness, ethics and the burden of disease and the availability of funds as to whether or not it will be included every year in a constantly expanding package of services.” Adding its weight, an under-secretariat responsible for health promotion would examine the necessity of adding the vaccine. The vaccine producer would be heard through its membership in the Council, and otherwise would lobby government in support of its product after having won approval for its registration.

The focus on health financing has been present in Mexico for some time, and was not the result of international focus in this area. Because of its higher income level and particular disease burden, Mexico is not a target of some of the global health financing initiatives like the Bill and Melinda Gates Foundation and the Global Fund (for AIDS, TB, and Malaria). Mexico has long been a participant in the PAHO (Pan American Health Organization) Revolving Fund (for Vaccine Procurement), which has allowed it to benefit from favourable prices on vaccines and various drugs.

Nevertheless, KI-10 believes that the major global health funds have increased access to drugs for AIDS, malaria, TB in lower-income countries. KI-10 believes that there should be an evidence-based process for establishing national health priorities, but that might not be done at the local level either. Although it may be argued that the priorities of the international organizations may be considered “heavy” they are generally based on evidence. The issue comes in whether they are implemented in a locally appropriate manner.

Developing countries do have the ability to produce evidence. Although some have been “completely closed” to participating in the generation of evidence, those who have been open “there’s been, you know, pretty impressive effort to be able to produce at least some of the basic evidence in terms of burden of disease, cost effectiveness of certain interventions.” Additionally, with much of the work in this area being done globally, there is a good comparative framework, and “it’s more or less considered a public good.”

The issues of this economic evidence are the quality of the basic data, the methodology (although there has been “impressive” work done on both the development and the critiquing of those methodologies), and whether there is enough capacity at the local level to understand it.

A good example of the use of this global evidence was the Mexican package of covered services that resulted from the reform; it was “precisely based on that kind of evidence, of cost effectiveness, of burden, of need.” The limitations are that sometimes the “numbers” are often difficult to understand and require “training to understand what’s particularly useful for a country and what’s not. Mexico was fortunate to have among its decision-making team some of the best economists and epidemiologists in the world and so had an excellent understanding of the evidence. Some of them had participated in developing Mexico’s databases.

For countries that don’t have that level of expertise in the decision-making body, there are nevertheless opportunities to ask technical assistance from international organizations to help

\textsuperscript{34} Interviewer’s note: the Seguro Popular, the Mexican universal health insurance programme initiated by the health reforms to extend insurance and health services to low-income and otherwise uninsured citizens.
explain and utilize the evidence. The forms of assistance could be in the interpretation of the evidence, the training of local staff, to identify a package itself, to look at the data and results more closely.

As for limitations, KI-10 thought that there is still probably a gap in the quality and quantity of the data. Another issue is how to “homogenize” the data.

KI-10 believes that there is a new generation of evidence is emerging that is an improvement over the “round two” indicators of burden of disease and cost-effectives. Indicators like “effectiveness” will be more difficult to estimate but would give a better picture of the local health care situation. There is already wide-spread work on new and more complex indicators, including work done at the Institute for Health Metrics. However, for countries that are still relying on round two indicators, developing the analytical capacity of local agencies would be preferable.

In closing, KI-10 thought that in regards to the use of evidence for decision-making, a key factor for countries like Mexico is the long-term evaluation of programmes.

Appendix 12-k: INTERVIEW SUMMARY FOR KI-11

SUMMARY OF SALIENT POINTS FOR THESIS

KI-11 is a medical doctor and academic researcher studying community health in both the extremely advanced urban health care systems and the very basic rural systems in China. He works with all levels of governments as well as with international collaborators.

KI-11 spoke from the perspective of using research evidence to inform or influence decision and policy-making, emphasizing that policy-makers do not consider evidence alone, so that decision-making could be a “long and very unpredictable process.” Politics, for example, explicitly plays an important role in policy- and decision-making.

The decision-making environment is hierarchical but also decentralized and very diverse in China. The central government makes “generic” national policy and the provinces/municipalities funds, interprets and implements national policies and regulates practice. Health care services are delivered at the county level. Consequently, there are many levels of administration and there is also a great unevenness in Chinese health care provision according to interpretation differences and the technical and financial capacity of provincial and local governments. Less economically developed regions depend more on central government financial transfers.

For example, the national immunization (EPI) programme is broadly determined by the central government, the provinces decide how to achieve the coverage targets and how to co-finance it,
and then the county level governments deliver and evaluate it. Provincial health authorities have substantial flexibility in implementing the EPI programmes, with powers to decide the spread of financing between levels of government and private citizens as well as to decide the composition of the antigens delivered.

Although disease profiles and local disease burdens are taken into consideration for immunization decisions, politics and influential persuasion by opinion leaders, both inside and outside government, add an unpredictable element.

KI-11 believes that, in general, health care decision-making in China is not evidence-based. Instead, the government often reacts to issues made known by special interest groups like academic or professional organizations. The response is usually to strike a committee to study the problem and to advise its funding. Evidence-based decision-making is seen more at the provincial level, where interpretation and implementation of national policies may be guided by the health needs of the local populace.

Nevertheless, KI-11 believes that researchers should provide government with evidence, preferably from several points of views: effectiveness, cost, training, monitoring and evaluation. Also, there is a need for a formal channel to work with policy-makers from the inception of the programme. For research evidence to have an impact it is important to engage with the right decision-maker at the right level of decision-making and to provide appropriate and relevant evidence to the respective decision-maker.

KI-11 sees that there are many decision-making tools that can be transferred from developed countries, but that each one has its “own route for the translation” to be made useful. International guidelines like those for TB treatment, for example, need to be systematically and rigourously adapted and incorporated, and not used as is.

International medical guidelines have a growing importance in China, KI-11 has noted. They are now gaining wide acceptance and adoption, due in part to a leadership that is more aware of the concept of evidence-based medicine. It is also due to the improved working relationships formed with international organizations, especially those that have long-term experience in China. Yet, politics also affect these relationships, lessening the impact of some organizations that do valuable work, but are at political odds with the central government.

Funding per se, however, is not an overly important part of the international organizations relationship with the Chinese government, KI-11 felt, due to the country’s relatively improved economic resources.

PARAPHRASED INTERVIEW

KI-11 is a medical doctor and academic researcher studying community health in both the extremely advanced urban health care systems and the very basic rural systems in China. He works with all levels of governments as well as with international collaborators.
KI-11 provided insights into research-evidence informed (or influenced) decision and policy-making. His research include migrant workers’ access to health care, community health impacts of decentralizing the treatment base from county-run to township-run facilities, and knowledge translation tools that convert national policies to clinical or treatment guidelines.

In the current policy environment of health care reform, KI-11 feels that policy makers would consider broad-based evidence:

I think in the evidence mostly regarding two things. One is effectiveness of that programme. So, for example, like for TB, you have to say that, to say decentralization [sic], if they can increase the treatment, the success rate, and increase the case detection rate, et cetera. Another is to the resources have to be input into the new initiative, that regarding the money, how much that will cost for the government. And how much that cost compared with the routine practice. And also, you have to look at how much, how many people have to be involved at different levels and how much work they have to carry under the new initiatives.

However, decision-makers also consider factors outside of evidence, so that decision-making and policy change can be a “long and very unpredictable process”. According to KI-11 decision-makers usually have to just have to “face facts”,

(b)ut on the policy maker’s side, I think politics are very important. For example, who are you talking to and how you can demonstrate it’s needed so? you can bring more political resources of the decision maker and how do they think about the relationship of doing this with others, et cetera

Decision-making and health care provision is very hierarchical in China, with each lower level of government having increasingly more specific functions. However, there is great unevenness in Chinese health care provision due to differing interpretations of the general policies and the varying resources available to provincial governments.

….So for the national health, public health policy, it can have different interpretations under the provincial level. And we find more and more that the central level makes very … kind of generic policies, and then that is the decision for the provincial government, how to get the money and how to implement, and how to monitor and evaluate, et cetera.

….But in general, we can say that the central government makes the general, uh, general health policies and also form new initiatives. And then, the provincial government are more to regulate how to implement the policy from central government and then how to make a province-specific, specific policies. And then the county level are most the unit for implementation.

….China is very big and provinces are in different development stages. So that it varies. For the rich provinces in the eastern part of China, like Shanghai, Zhejiang, Shandong, they are going to cover their own financing, uh finance. But for the, I
know western provinces in China like Guangxi there is a big amount covered by the central government transfer.

KI-11 generates evidence that goes to all levels of government, depending on which policies are to be affected. It is important to engage with the right decision-maker and provide appropriate and relevant evidence to the respective decision-maker. For example, in the development of TB practice guidelines for front-line doctors at the county level, he says that…we work with the central level to make sure it can be used the nation wide, but we work … lots of details into it at the provincial level because they are more flexible and they want to bring more evidence to, for their, for example, local policy making of local initiatives.

KI-11 provided a few more insights into the EPI programme, which is centrally administered. The China Centre for Disease Control takes part in immunization decision-making at the national level, and KI-11 believes that the impact, the prevalence and the preventability of the disease as well as the financing are taken into consideration. However, politics creates uncertainty: …I think the most unpredictable thing is that the politics, it depends what they’re, for example, what they’re concerned about, who are doing a better social marketing in terms of illustrating the, you know, selling this disease should be prevented, et cetera.

There are opportunities for provinces to make substantive decisions in the EPI programme. For example, Guangxi was able to introduce a targeted programme for the prevention of rabies in addition to the mandatory EPI childhood diseases.

KI-11 is not familiar with the particular uncertainties faced in introducing new vaccines, but in general he doesn’t believe that government decisions are evidence-based. He observes that special interest groups bring issues to the attention of the government. Once government is made aware, an expert committee is then struck to look at the issue, and government undertakes a financing exercise to decide the allocation of the funds. Yeah, I don’t think it is very much evidence-based….The usual way about a government making a decision is to, first you should have some kind of organizations from universities or from the some kind of say like, say for example, in our [High Tech] Park there is a kind of associations of different, different professionals. They can lobby the government for example. For example, this disease should be prevented, and then the government would form a kind of experts committee to look at each, this issue and report back to the government. Then they will go into the financing procedure to look at how much money would be allocated for the next year for this and how much spend they have, et cetera.
KI-11 believes that researchers should provide government with evidence from several points of views: effectiveness, cost, training, monitoring and evaluation etc. Also, there is a need for some kind of formalized channel to work with policy-makers from the inception of the intervention. He described a research project that is unique for China not only in its inclusion of policy- and decision-makers throughout, but also its comprehensive design of an inception stage, a pilot, revision provisions, and scaling-up plans.

KI-11 sees that there are many decision-making tools that can be transferred from developed countries, but that each one has their “own route for the translation”. He cites a successful project for producing a tuberculosis desk guide for front-line doctors. The guide was developed at the University of Leeds in the UK, incorporated the implementation experiences of Pakistan, Uganda, and Swaziland, and then was translated to China through local practitioners to be finally developed as nation-wide guidelines. On the other hand, KI-11 believes that some WHO guidelines are unsuccessful examples of translated tools. In reality, he thought, having guidelines themselves is just a beginning and there are various ways to make them useful. Sometimes only a few of them need to be implemented locally, sometimes they can work in parallel with local guidelines, and sometimes they can be used to improve local guidelines. But it is necessary to systematically adapt and incorporate new guidelines, and not use them as is.

The increasing frequency of adaptation of international guidelines, KI-11 thought, is due to an improved receptiveness for international organizations in the research environment of China:

I can see there are more and more adaptation right now, at the national level. … That is because, for example, there are different factors. One is that as the leaders are always changing, so you can base more kind of the timing for leaders who, who know the evidence and who, for example, have to look at evidence or appreciate the international guidelines. The secondly [sic], you can also say there’s a change, there’s a way of changing the working relation between the international organizations with China. For example like, for example like the Bill Gates Foundation in China, the Darmiane Foundation in China, and so they work with programme people and for a long time, so that they know each other and they know how to improve. So I think there are lots of factors affect that result, but it is very hard to say now is the most optimal stage.

For international organizations to succeed, KI-11 thought, they should understand the wide diversity between provinces in China, they should be technically strong, and that they should form a good working relationship with their partner at the central or provincial level and be prepared to work with them for a long time.

The efficient use of resources overshadows the source, external or domestic funding, of those resources:

I think money is just one part. …It’s the most important thing is how to use the money. To be honest, I think the China government has lots of money, has lots of resources. And also lots of, for example, research funds are misallocated. Overlaps, two projects overlaps, et cetera. There are lots of those examples.
KI-11 is uncertain as to the appropriate tools for more efficient allocations of resources:

I think the tool is...I don’t, honestly I don’t know how to develop the tools, but the tools are more related to the governance and I think governance is also not an easy topic. You have to work within the system rather than from outside of the system.

According to KI-11, using evidence in China consists of, first, identifying the topics of interest, identifying the recipient of the evidence, and then developing a plan for implementation with collaborators, recognizing that it will need to be a long collaboration with lots of uncertainties. Furthermore, it must be recognized that there are many different routes to achieve targets.
Appendix 13: Glossary

*Allocative efficiency* – the use of the least combination of resources to achieve the best combination of outputs. This wider definition of efficiency implies that resource use for health interventions can be compared to those of, say, education interventions. Cost-benefit analysis is the technique that best makes these comparisons, as valuation of costs and effects are made in a neutral and common metric, a monetary unit.

*Cost-effectiveness threshold* – a single value per QALY gained (often termed *lambda* in methodological literature) that is a decision-making break-point. More theoretically debated than practically implemented or empirically observed, the notion implies that decision-makers have predefined levels of acceptable ICERs beyond which they would not commit resources. In the literature, the critical values have often been identified as US$50,000 or £25,000.

*DALY (Disability-adjusted life years)* – a variant of the QALY that differs in preference elicitation, life expectancy assumptions and treatment of patient age. Although not as widely used as the QALY (below), it is the metric preferred by international organizations concerned with global health, such as the WHO and the World Bank, especially for international comparisons of burdens of diseases.

*Development Assistance for Health (DAH)* – transfers of financial and in-kind resources (e.g. donations of drugs and vaccines, technical assistance, training) for health care to developing nations. The sources of DAH include donor governments, private foundations, multilateral institutions (UN organizations, development banks). These flows are difficult to trace, as reporting is variable and inconsistent, with no one international repository of information.

*League table* – an ordered ranking of incremental cost-effectiveness ratios (ICERs), from most cost-effective (lowest ICER) to least cost-effective (highest ICER), in aid of presenting and interpreting cost-effectiveness evidence for decision-making

*Opportunity cost* – the value of an object defined by the opportunity forgone in choosing that object. In health care, for example, it may be defined as the value of the next best choice of
intervention. Often, the financial cost, or market price, is used as a proxy for specific cost items based on the assumption that perfect markets prevail.

**QALY (Quality-adjusted life years)** – a widely used measure of consequences incorporating patient preferences for a particular health state, which provides a more generic measurement of consequences than that based on a natural, biological/physiological outcome (e.g. mortality). The QALY is therefore especially useful for evaluating health interventions that affect morbidity. Economic evaluations that use this measure are termed cost-utility analysis, although in this thesis we include them in the general term, cost-effectiveness analysis.

**DALY (Disability-adjusted life years)** – an alternative measure of consequences that also combines mortality and morbidity. It differs from the QALY in preference elicitation, life expectancy assumptions and treatment of patient age. Although not as well-known as the QALY it is the main metric used in CEA’s set in developing countries and is heavily used by international organizations concerned with global health.

**Technical efficiency** – the use of the least resources to produce the same single output, or alternatively expressed, incurring the lowest opportunity cost to achieve a specified outcome. Cost-effectiveness analysis results imply technical efficiency, comparing resource use within one sector only (e.g. health) for a relevant outcome (e.g. QALY, immunization coverage rate).
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