The Use of Cost-Effectiveness Analysis for Pediatric Immunization in Developing Countries

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Context: Developing countries face critical choices for introducing needed, effective, but expensive new vaccines, especially given the accelerated need to decrease the mortality of children under age five and the increased immunization resources available from international donors. Cost-effectiveness analysis (CEA) is a tool that decision makers can use for efficiently allocating expanding resources. Its use in developing countries, however, lags behind that in industrialized countries.

Methods: We explored how CEA could be made more relevant to immunization policymaking in developing countries by identifying the limitations for using CEA in developing countries and the impact of donor funding on the CEA estimation. We conducted a comprehensive literature search using formal search protocols and hand searching indexed and gray literature sources. We then systematically summarized the application of CEA in industrialized and developing countries through thematic analysis, focusing on pediatric immunization and methodological and contextual issues relevant to developing countries.

Findings: Industrialized and developing countries use CEA differently. The use of the Disability-Adjusted Life Year (DALY) outcome measure and an alternative generalized cost-effectiveness analysis approach is restricted to developing countries. In pediatric CEAs, the paucity of evaluations and the lack of

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attention to overcoming the methodological limitations pertinent to children's cognitive and development distinctiveness, such as discounting and preference characterization, means that pediatric interventions may be systematically understudied and undervalued. The ability to generate high-quality CEA evidence in child health is further threatened by an inadequate consideration of the impact of donor funding (such as GAVI immunization funding) on measurement uncertainty and the determination of opportunity cost.

Conclusions: Greater attention to pediatric interventions and donor funding in the conduct of CEA could lead to better policies and thus more worthwhile and good-value programs to benefit children's health in developing countries.

Keywords: cost-effectiveness, developing countries, immunization, program sustainability.

POLICYMAKING THAT IS INFORMED BY COST-EFFECTIVENESS analysis (CEA) is increasing, thanks to the growing influence of evidence-based medicine and a universal need to make the best use of scarce resources for rising health care demands. In developing countries, the relatively greater scarcity of resources, coupled with relatively greater health needs, suggests that the efficient use of those same resources is even more critical than in industrialized countries. And it is most critical for those with great health needs: children.

Worldwide, of the 11.4 million deaths in children under age ten in 2002, 90 percent occurred in those under five years old, and of these, children from developing countries accounted for 99 percent (Mathers 2009). In recognition of the scale and disparity of this problem, the international community pledged to achieve Millennium Development Goal (MDG) 4, aimed at reducing under-5 mortality by two-thirds between 1990 and 2015. Despite important gains, with global under-5 mortality dropping from one hundred to seventy-two deaths per 1,000 live births from 1990 to 2008 (United Nations Development Program 2011), the current rate of annual decline at 2.2 percent (UNICEF 2011) is too slow to meet the 2015 target.

CEA may well be important to making health care investment decisions about interventions that can contribute to achieving MDG4. For example, Tan-Torres Edejer and colleagues (2005) identified strategies for implementing bundled regional child survival interventions (combinations of micronutrient fortification, measles immunization, and pneumonia case management) that are both effective and cost-effective.

With substantially more funding focused on accelerating gains in child survival and health, particularly from international donors (Ravishankar *et al.* 2009), CEA has a role in illuminating how those extra resources might be best allocated. Yet it is unclear to what extent CEA evidence is used or, indeed, is useful in developing countries where relevant economic and effectiveness data are limited and where theoretical underpinnings (such as the concept of opportunity cost) might not be congruent with economic systems. In addition, methodological issues unique to pediatric economic evaluations, especially of preventive measures, can compromise results (Ungar 2010). Finally, donor funding as a source of health care financing is an unscrutinized entity in CEA methodology and application, as it is nonexistent in industrialized countries where the CEA technique has its roots. With new vaccines, on the one hand, promising to dramatically reduce much of the heaviest burdens of disease borne by children in developing countries (e.g., rotavirus and pneumococcal vaccines) but, on the other hand, costing several times more than older vaccines, a fuller understanding of the limitations of CEA methodology and the role of donor funding could enhance the ability of policymakers to use economic evidence to improve child health programming.

In this context, we explored how CEA might be enhanced for use in developing countries. Our specific objectives were (1) to summarize the application of CEA in industrialized and developing countries; (2) to identify the methodological limitations of conventional CEA when used in developing countries, focusing on pediatric interventions; and (3) to determine the impacts of donor funding on the conduct and use of CEA.

In this article we present an overview of the results of our thematic document analysis. First we outline our methods. Then, as an introduction, we describe the standard use of the CEA in industrialized countries and, next, its use in developing countries. We discuss some of the main issues concerning the CEA of pediatric interventions and their specific relevance to developing countries, as well as the significance of donor funding to the adoption of CEA evidence in developing nations. Finally, we summarize our conclusions and outline the policy implications.

Methods

We conducted a multistrategy search of both indexed and gray literature. We searched the PubMed, EconLit, and Medline databases using both MeSH terms (cost-effectiveness, developing countries,

immunization, child) and non-MeSH terms (preference, priority-setting, vaccine economics, vaccine markets, donor funding, global health). Our searches were limited to English-language items dated between 1980 and 2007. An Ovid Auto-Alert was maintained until December 2008. These terms were also used to keyword-search the document repositories of international organizations concerned with global and child health and to search other gray literature sources such as health technology assessment agencies, funding agencies, and global health think tanks. We hand-searched potentially productive reference lists from the selected indexed and gray literature texts. Recent documents detailing important updates or developments were captured in selective keyword searches using the preceding search terms and through publication alerts; these extended the publication profile to 2010. In the end, we chose, on the basis of relevance, 157 documents spanning health economics, epidemiology, and donor assistance. The term “developing countries” applied to low- and middle-income countries as currently defined by the World Bank: in 2010, low-income countries had a gross national income (GNI) per capita of \$1,005 or less; lower-middle-income countries, \$1,006 to \$3,975; and upper-middle-income countries, \$3,976 to \$12,275 (World Bank 2011).

We examined the selected documents according to concepts we developed from the research objectives through a process of reading, coding, information reduction, and synthesis to distill, categorize, and describe common themes (Braun and Clarke 2006; Miles and Huberman 1994; Sandelowski 2000).

The Use of Cost-Effectiveness Analysis in Industrialized Countries

Cost-effectiveness analysis compares the economic costs and health consequences of two or more interventions in order to identify the best use of resources within the constraints of a finite budget (Gold et al. 1996). For example, analysts may compare a standard treatment of diarrheal disease and a new intervention using a rotavirus vaccine in a public health system. The difference in the two interventions’ net costs is divided by the difference in the interventions’ outcomes 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 are available, it is possible to rank them so as to prioritize and maximize health gains in a population. A crucial aspect of a CEA study is identifying the “perspective,” an analytical framework that determines the resource utilization scope or boundary. Equally crucial is the setting of a temporal scope, or a time horizon, that is sufficient to capture the relevant costs and benefits flowing from the intervention. Since decisions are made in the present, future costs and benefits are converted to present values through the application of a discount rate. The choice of the discount rate can have a profound impact on present values, for the higher the rate is, the more diminished the values attached to future health gains will be (Drummond et al. 2005). Data and model uncertainty and robustness are tested through sensitivity analysis of key variables, increasingly with probabilistic analysis to reveal plausible, policy-relevant ranges of the incremental cost-effectiveness ratio (ICER) (Briggs 2000).

Using cost-effectiveness analysis to inform health care policy has become increasingly common in some industrialized countries. It is considered a tool of payer decision making and health technology assessment and is the analytical backbone of pharmacoeconomics, a field examining the economics of drugs and related technologies. The most extensive, explicit, and influential use of CEA for policy and decision making is found at the United Kingdom’s 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 (NICE 2008). National practice guidance rests on formal recommendations that integrate clinical guidelines with cost-effectiveness evidence, and recommendations for public funding of technologies rely on CEA studies. In Canada, the Canadian Agency for Drugs and Technology (CADTH) provides formalized guidelines for the voluntary integration of CEA into evidence for third-party insurers as well as for the mandatory pharmacoeconomic studies required for including new drugs in government-funded drug plans or formularies (CADTH 2006).

In 1996, guidelines to standardize methodology and improve quality were introduced by the U.S. Panel on Cost-Effectiveness Analysis (Gold et al. 1996; Weinstein et al. 1996). A structured set of methodological and operational recommendations, often referred to as the “Washington Panel Reference Case,” was proposed as a base-case scenario for a variety of study designs and as a possible base for comparative studies (Gold et al. 1996).

The rise in CEAs published in high-impact medical journals (Greenberg et al. 2010) may indicate the growing use of CEA, enough that it warranted editorial guidelines on quality (Drummond and Jefferson 1996; Spier, Jefferson, and Demicheli 2002). It is unclear exactly how, and how much, policymakers actually use CEA results, however. The lack of consistency in execution, reporting, and interpretation, as well as a suspicion of industry-sponsored studies, has detracted from CEA's value and impeded its fuller integration into decision making (Jefferson, Demicheli, and Vale 2002; McGregor 2006; Neumann 2005). Furthermore, the progressive, systematic integration of CEA into the setting of priorities 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) proposed that to increase CEA's generalizability, and therefore its potential as a major input into policymaking, decision makers and analysts together should streamline and harmonize CEA methods and guidelines across jurisdictions.

The Use of Cost-Effectiveness Analysis in Developing Countries

In the past, developing countries lacked good-quality cost-effectiveness studies specific to their own national epidemiologic and socioeconomic characteristics (Iglesias et al. 2005; Mulligan, Walker, and Fox-Rushby 2006; Walker and Fox-Rushby 2000). Walker and Fox-Rushby (2000) found only 107 economic evaluations of communicable disease interventions in developing countries published between 1984 and 1997, of which 26 targeted vaccine-preventable diseases. They judged the quality of these as generally poor, based on poor adherence to accepted technical criteria. Another study examining noncommunicable diseases found that only 32 economic evaluations aimed at developing countries were published between 1984 and 2003 and that the general quality was poor, with many studies so opaque that the details could not be assessed (Mulligan, Walker, and Fox-Rushby 2006).

In the mid-1990s, however, the World Health Organization (WHO) and the World Bank together developed CEA methodology for specific application to developing countries and have since coordinated large-scale efforts to produce CEA evidence for policy and decision

making on a global basis. Their 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 in the WHO-CHOICE project (Murray et al. 2000; Tan-Torres Edejer et al. 2003).

The DALY was conceived to measure the population-level burden of disease and to provide a measure of effectiveness in cost-effectiveness studies (Murray and Acharya 1997). Like Quality-Adjusted Life Years (QALYs), a universal metric of health outcomes for diverse interventions (Weinstein, Torrance, and McGuire 2009), DALYs are a composite measure of health effects, summing mortality (years of life lost, or YLL) and morbidity (years of life lived with disability, or YLD), and thus allow comparisons across disparate interventions. In both DALYs and QALYs, adjustments to a fully healthy life are made through the attachment of quality-of-life weights that are numerical expressions of “preferences” or “utilities.” Opposite 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, so a desired goal of interventions is to avert or minimize DALYs. Thus, in cost-effectiveness analysis, it is favorable to maximize DALYs-averted or QALYs-gained relative to costs.

Although the DALY is not without controversy (Anand and Hanson 1997; Arnesen and Kapiriri 2004; Arnesen and Nord 1999; Barker and Green 1996; Murray and Acharya 1997), its use has grown since its inception. Consequently, researchers have attempted to delineate more clearly the differences between and implications of using the QALY versus the DALY (Airolidi 2007; Gold, Stevenson, and Fryback 2002; Sassi 2006) and to provide criteria and instructions for calculating DALYs (Fox-Rushby and Hanson 2001). In practice, there is a division in the use of the two metrics, as the DALY is used predominantly in analyses pertaining to developing countries and for global comparisons. Kim and Goldie (2008) reported that from 2002 to 2007, the QALY was the more common outcome measure used in industrialized countries, whereas the DALY was the more common in developing countries. The Global Burden of Disease Study uses 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, thereby making the DALY pertinent to global health researchers and epidemiologists. Of note, in response to earlier criticisms of the DALY, the 2010 version

of the Global Burden of Disease Study, due for release in 2012, will employ disability weighting revised with preferences elicited from a large population diverse in geography, culture, and economic level of development rather than from a single panel of experts (Institute for Health Metrics and Evaluation 2010; Salomon 2010, WHO 2012). Using non-age-weighted DALYs with region-specific life expectancies, the multi-institution Disease Control Priorities Project (DCPP) conducted CEAs to formulate a database of results for interventions that address disease burdens of particular significance to developing countries, such as insecticide-treated nets for malaria control (Jamison et al. 2006). This work followed up and updated that initiated by the DCPP in 1996 and by the WHO Commission on Macroeconomics and Health (CMH) in 2001 to identify and recommend “best health buy” interventions based on the most DALYs averted at the lowest cost (Sachs and Commission on Macroeconomics and Health 2001; WHO 2010c). The DCPP maintains ongoing research and updates of its CEA database, regarding CEA results as relevant not only to health care but also to economic and social development decisions (Disease Control Priorities Project 2010).

A second major CEA development pertinent to developing countries is the WHO-CHOICE (CHOosing Interventions that are Cost-Effective) methodology of sectoral analysis, termed “generalized cost-effectiveness analysis” (GCEA) to indicate its broader application compared with that of conventional CEA (Tan-Torres Edejer et al. 2003). Generalized cost-effectiveness analysis was developed to allow broad-based decision making and priority setting at the national level, as opposed to conventional CEA, which focuses on the patient level (WHO 2010a). It aims to develop standardized, global methodologies; region-specific cost databases; and models that can be further adapted at the national level, as well as to build capacity in developing countries with limited resources and technical depth (Hutubessy et al. 2002, 2003; Tan-Torres Edejer et al. 2003). GCEA is also meant to address the shortcomings of conventional CEA in guiding allocative efficiency. For example, although a “do nothing” case can be counted among the feasible options, the supremacy of incremental analysis in conventional CEA emphasizes the study of new interventions, compared with standard-of-care interventions. Implicitly, this presupposes that the standard of care incurs costs and produces benefits. In contrast, GCEA is conducted from the standpoint that there might be a misallocation of resources in

existing interventions (Hutubessy et al. 2003; Murray et al. 2000), thereby supplying an analytical framework for a reexamination of those interventions and for a “clean slate” approach of programming. In other words, in conventional CEA, the options open to decision makers are constrained by the interventions already in place, whereas in GCEA, every feasible intervention can be considered for introduction, and inefficient standard interventions may be discarded. The GCEA approach may also be used to simultaneously analyze a mix of multiple interventions in the entire health sector, thus moving closer to allocative efficiency and allowing a wider perspective for prioritization on the basis of cost-effectiveness.

World Health Report 2002 first presented a summary of results generated from the WHO-CHOICE Project for forty-two interventions, focusing on interventions addressing the main risk factors according to the burden of disease defined by DALYs (WHO 2002). Updated and expanded summary cost-effectiveness results by region and disease/risk factor are currently available through the WHO website (WHO 2010b). WHO researchers have also identified cost-effective interventions consistent with strategies to reach the Millennium Development Goals. These include artemisinin-based combination treatments to address malaria; zinc and vitamin A fortification and measles immunization to address global child health; mass media campaigns, interventions for sex workers, and treatment for sexually transmitted disease infections to address HIV/AIDS; and twenty-one interventions in various combinations to improve maternal and neonatal health in sub-Saharan Africa and Southeast Asia (Adam et al. 2005; Evans et al. 2005; Hogan et al. 2005; Morel, Lauer, and Evans 2005; Tan-Torres Edejer et al. 2005).

National income levels greatly affect the pattern of resource use and health system development. Middle-income countries, especially those that are expanding their local resources for health care or that are undergoing health care reforms and have more local analytical capacity, are more squarely focused on CEA for local priority setting. Low-income developing nations, in contrast, have less control over their priority setting, owing to their need for external resources, and are more concerned with affordability. The identification of cost drivers and cost impacts on related services (e.g., a vaccine supply chain for new vaccines) through CEA is thus more important to low-income nations (Griffiths, Hutton, and Pascoal 2005; Shepard et al. 2004). Reflecting the heterogeneity

of health systems needs, guidance for cost-effectiveness thresholds in developing countries are based on gross domestic product (GDP). Interventions with cost-per-DALY-averted values 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).

Cost-Effectiveness Analysis of Pediatric Interventions

Whether in industrialized or developing countries, pediatric interventions are a neglected focus of economic evaluation methodology (Ungar 2010). That is, pediatric health economic evaluations generally do not explicitly address how the distinctiveness of children compared with adults might challenge the valuation of costs and benefits. For example, not only are children’s life spans, and therefore time horizons, longer, but also pediatric interventions are predominantly preventive, with benefits accruing further in the future than costs. This makes adequately and sufficiently capturing future benefits more important, as constant and nondifferentiated (between costs and effects) discount rates may result in a greater discounting of benefits relative to costs. Consequently, compared with acute care interventions, pediatric interventions, like other preventive interventions, may be undervalued (Bos et al. 2004; Cairns 2006). In addition, because the biology of children differs from that of adults, interventions developed for and/or tested on adults may have different impacts. Medications, for instance, may have different pharmacodynamic and pharmacokinetic properties (Keren, Pati, and Feudtner 2004). Some interventions may even have unintended opposite effects, as Keren, Pati, and Feudtner (2004) also pointed out, citing the decrease in cost-effectiveness for dual air bags in cars, given their fatal deployment on front-seat child passengers.

Cognitive ability differences between children and adults and between children of different age groups contribute to issues concerning the elicitation of children’s preferences in measuring health status and subsequently to weighting effectiveness measures (Petrou 2003; Ungar 2011). Parents’ and caregivers’ preferences often stand as proxies

for very young children, but it is not clear that their preferences are the same as children's or whose preferences are more important (Cairns 2006; Keren, Pati, and Feudtner 2004). Generic utility instruments derived from adult instruments or those not validated for children, for example, the adult EQ-5D, may also degrade the measurement of health states (Petrou 2003). Furthermore, according to Petrou (2003), because children's development is so rapid and divergent, it may be hard to assign a common set of dimensions to each age group, so using descriptions of static health states is inadequate. Survey-based methods (e.g., contingent valuation) to derive willingness-to-pay for cost-benefit analyses are inappropriate for children, as unbiased responses require a grasp of monetary values, time horizons, and health states beyond the experience and comprehension of children, especially younger ones (Ungar and Gerber 2010). Substantial work is continuing in pediatric outcome measurement, however. In a literature review of quality-of-life measurement instruments for children, Solans and colleagues (2008) found rapid development, with fifty-one new instruments published between 2001 and 2006 meeting their quality and inclusion criteria. They noted that the multiplicity of dimensions captured in these instruments might reflect attempts to capture health states that rapidly evolve along with a child's development. Prosser, Hammitt, and Keren (2007) have also proposed that separate age-appropriate measures might better capture children's unique age-related health states.

These challenges in conducting economic evaluations in children may have contributed to the poor methodological quality of the studies that have been conducted. For example, 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. In particular, data and model uncertainties were very poorly addressed. In 52 percent of the studies no sensitivity analyses were performed, and in another 44 percent, only one-way analysis was performed (Ungar and Santos 2005). Other reviews of pediatric CEAs found considerable variation in QALY estimations, underdevelopment of child-specific health state measurements, and noncompliance with guidelines provided by the Washington Panel Reference Case (Griebsch, Coast, and Brown 2005; Ladapo et al. 2007).

Cost-Effectiveness Analysis of Pediatric Immunization in Developing Countries

Outstanding methodological and quality issues for pediatric CEAs may result in disproportionately felt resource allocation inefficiencies in developing countries, where studies of childhood immunization programs form the bulk of economic evaluations and where investment in child health has especially large benefits for national social and economic development (Belli, Bustreo, and Preker 2005; Bloom, Canning, and Weston 2005). Only recently have guidelines specific to economic evaluations of immunization and with an international outlook been developed (WHO 2008), and it is premature to assess their impact on future studies.

The economic evidence for vaccines and immunization is still relatively sparse for developing countries, compared with industrialized countries (Beutels et al. 2003). Kim and Goldie (2008) found that of 276 studies published between 1976 and mid-2007, only 43 were set exclusively in developing countries. In the 1980s, the cost-effectiveness of the standard six Expanded Program on Immunization (EPI) vaccines against measles, diphtheria, pertussis, tetanus, tuberculosis, and polio was firmly established (Brenzel 1990; Brenzel and Claquin 1994; Mills and Thomas 1984). New CEA evidence was generated to support increased investment in vaccines and immunization to address the stagnation of and decline in coverage rates and coverage inequalities in the 1990s (Shepard et al. 1995). More recently, CEAs have been used to inform potential additions to the core EPI programs to reduce disease burdens particularly significant to developing countries. These include vaccines against *Hemophilus influenzae B* (Hib) and hepatitis B, widely used in industrialized countries but underutilized in developing countries, and new or potential vaccines against, for example, HIV and dengue fever (Andrus et al. 2004; Bos and Postma 2001; Limcangco et al. 2001; Shepard et al. 2004). Most recently, the introduction of the rotavirus vaccine has been a major confluence of interest for global health researchers, health care providers, and health program funding agencies, due to its promise of reducing a heavy worldwide burden of disease (Walker and Rheingans 2005). Almost every child in the world has had at least one episode of rotavirus-induced gastroenteritis by age five, resulting in 25 million clinic visits and 2 million hospitalizations

per year (Parashar et al. 2003). Of the resulting 400,000 annual deaths, 82 percent occur in developing countries, where the risk of dying from rotavirus disease is 1 in 205 in the lowest-income group (Parashar et al. 2003). Rotateq, made by Merck, and Rotarix, made by Glaxo-Smith-Kline, were licensed by the U.S. Food and Drug Administration in 2006 and 2008, respectively (Glass and Parashar 2006; Kamal-Uddin and Croft 2006; Ruiz-Palacios et al. 2006; U.S. Food and Drug Administration 2010; Vesikari et al. 2006). It is significant to note that the Rotarix trials took place in Latin America and the vaccine was launched in Mexico, a departure from the usual launch in industrialized countries. This may give a more realistic and accurate idea of its effectiveness in the population to which it is targeted. Because of the rotavirus vaccine's initial high cost, the careful weighing of policy options (e.g., targeted versus universal coverage) could be helped by economic evaluation.

Cost, affordability (the ability to pay for an intervention with local resources), and sustainability (the feasibility of maintaining a program with only local resources) are major concerns, as the new and underutilized vaccines just mentioned are far more expensive than the traditional six EPI vaccines listed earlier, and many countries require funding assistance for their procurement. Additional vaccines would also require additional storage in the cold chain and may need to be combined with other antigens in a single injection to prevent prohibitively frequent visits to health facilities. Griffiths, Hutton, and Pascoal (2005) estimated that adding hepatitis B vaccine, combined with the DTP vaccine, to the routine schedule in Mozambique in 2001 increased the cost of immunization services by 56 percent, with the cost of vaccines accounting for about a third of the increase. Hutton and Tediosi (2006) found that at the high end of the price range (\$10 per dose), the cost of the malaria vaccine alone would be three times the entire EPI budget in Tanzania. Given this price reality, explorations of a rotavirus vaccine "break-even" price have led to several studies. Fischer and colleagues (2005) found routine immunization with rotavirus vaccine to be cost-effective in Vietnam at \$40 per DALY averted for vaccine prices up to \$4.52 per two-dose course. In a regional study, Podewils and colleagues (2005) estimated that 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 countries in Asia, respectively.

Donor Funding of Health Care and Immunization in Developing Countries

Although cost and affordability problems might be eased with donor funding, the recent large increases in donor assistance may exacerbate problems of program sustainability. Between 1990 and 2007, development assistance for health, consisting of officially recorded financial and in-kind contributions to low- and middle-income countries for health activities, increased from \$US5.6 billion to \$US21.8 billion (2007 U.S. dollars), with the steepest rates of increase occurring since 2002 (Ravishankar et al. 2009). As a result, external sources of support, such as the UK Department of International Development or the Global Fund to Fight AIDS, Tuberculosis, and Malaria (The Global Fund), are a significant budgetary resource for government ministries in many countries and in 2007 accounted for 17.5 percent of total expenditures on health care in low-income countries (WHO 2010d).

Besides the changes in funding volumes, substantial changes in funding sources and funding channels have attracted the attention of development economists and political scientists in regard to their overall impact on health care systems. Funding for health programs in developing countries is now characterized by a proliferation of funding entities, ranging from broad-focus development organizations to various disease-specific funds and initiatives to innovative financing mechanisms. One of the most significant changes in development assistance in health has been the formation of supranational global health funding partnerships composed of traditional bilateral and multilateral donors, large private foundations, and large multinational drug companies, as well as institutional health care research and development institutes. Of these partnerships, the two most prominent are the GAVI Alliance and the Global Fund. In 2007 the development assistance for health 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, as well as the magnitude of their funding and prominence of their activities, raises questions about their influences on national health objectives and priorities and long-term financial and operational sustainability of the supported programs—all of which can distort local

resource allocation (Birdsall 2005; Caines 2005; Garrett 2007; Schiffman 2006; Waddington 2004; Widdus 2003). These aid-effectiveness concerns are especially relevant to the most donor-dependent health systems, such as Cambodia, where donor expenditures were greater than government expenditures on health in 2003 (Michaud 2005).

Donors have traditionally strongly supported immunization because of its central role in public health and its established relative cost-effectiveness, and GAVI has become the preeminent international channel of funding for new and continuing immunization efforts. From 2000 to September 2011, GAVI disbursed US\$3.2 billion to eligible countries in cash, vaccines, and vaccine services support (GAVI Alliance 2011). In its first five years, GAVI helped increase immunization coverage, particularly in low-coverage areas (Chee et al. 2007; Lu et al. 2006), and it actively encouraged program sustainability by, for example, requiring national sustainability plans as a funding condition. However, Arevshatian and colleagues (2007) found that many sustainability plans were not used as expected. Also, in its early history, GAVI was found to have displaced government immunization expenditures and to contribute to resource allocation inefficiencies by adding to the proliferation of donors and consequent costs of donor-recipient interactions (Lane and Glassman 2007).

Attention must be paid to incorporating donor-funding effects when estimating cost-effectiveness. For example, because donor commitments are typically short term (Birdsall 2005), implementation costs tend to accrue predominantly at the very beginning of interventions. A too-short time horizon would not capture benefits occurring in the far future (as in the case of hepatitis B immunization), and the penalizing effects of discounting would be exacerbated. The volatility and uncertainty of fund disbursement may belie the smooth stream of costs and benefits usually assumed in CEA estimation. Notably, the transaction costs incurred by donor-recipient interactions (e.g., meetings, guided site visits, reporting, and accounting) are not typically included. Because these costs are unavoidable, their omission understates intervention opportunity costs. Furthermore, substantial donor funding that crowds out or overshadows government expenditures realigns resources related to national health care objectives and priorities (e.g., the training and deployment of citizens for health care work). This confuses the “next best” use of resources that underlies the concept of opportunity cost.

Implications and Conclusions

In this article, we outlined the applications of the cost-effectiveness analysis technique in industrialized and developing countries, focusing on methodological issues in pediatric interventions, particularly immunization, and donor funding in developing countries. We found that in industrialized countries, CEA studies abound, but it is unclear how influential the technique is beyond recommendations for government drug formularies. The World Bank and the WHO have been the major proponents of methodological advances to address the limitations of applying CEA in developing countries, but the development and use of the DALY has remained concentrated in developing world settings. Similarly, the WHO's alternative, generalized cost-effectiveness analysis approach is limited to use in developing countries, although a sectorwide approach might be beneficial for policymaking in all settings. In pediatric CEAs, a vicious cycle of the paucity of evaluations and poor attentiveness to overcoming the methodological limitations caused by children's special characteristics means that pediatric interventions may be systematically understudied and undervalued. This is especially problematic when considering the need for good-quality CEAs to help reduce the burden of childhood morbidity and mortality in developing countries. Finally, the ability to generate high-quality CEA evidence is further threatened by inadequate consideration of the impact of donor funding on determining opportunity cost.

Several implications might be drawn from these findings. Given that DALYs are predominantly used with analysis set in developing countries and QALYs when set in industrialized countries, a systematic bias might be created if there were a systematic difference between the two measures. DALYs and QALYs are not perfectly interchangeable, as the former was originally formulated to address population health, and the latter, patient-level health. Although few direct comparisons have been made between the outcomes of the two applications, Airoidi (2007) found that the health benefits measured by DALYs are consistently lower than those measured by QALYs. This may lead to developing countries' shouldering a higher burden of proof than industrialized countries and missing out on benefits from interventions that could be efficient if measured otherwise.

Having two prevailing generic outcome measures would also make CEA even less generalizable. Conducting CEAs is expensive and requires

technical expertise, so with a shortfall of local analytical capacity, low-income countries must rely on borrowing models and results from other jurisdictions. Variability in the outcome measure makes applicability difficult and hinders the extraction of local variations for relevant local policymaking. Using results from the two measures together yields confusing priorities for research and intervention introduction. For example, Gold and Muennig (2002) found that the rank ordering of the disease burden of five common conditions and diseases in the United States varied substantially when measured by DALYs compared with QALYs.

The use of the GCEA exclusively for developing countries means that methodological improvements for it languish, as far fewer researchers use it and those who do, do not always agree on its application. A key debating point is the use of a null comparator (i.e., starting from no existing interventions at all) with no associated costs, which gives rise to a comparison of average costs rather than marginal costs, as in the conventional CEA approach. Because marginal (incremental) cost analysis is currently considered "best practice" among health economists, it is doubtful that a null comparator would gain widespread acceptance. Yet, the value of the GCEA approach may be that it allows a reimagining of a health system built up efficiently in steps as resources expand. This may be a viewpoint that is especially attractive to developing countries for health system planning. Without resolving the differences between GCEA and CEA approaches, developing countries may be left with a tool that has unrealized potential for achieving better allocative efficiency.

CEAs for child health in developing countries characteristically examine preventive interventions, most often immunization. Methodological deficiencies that might have led to undervaluing the benefits of immunization may not have been critical in the past when vaccine prices were exceedingly low, but new and underutilized vaccines are several times more expensive than those in current use. Despite the increasing scrutiny on pediatric applications, however, it is unknown whether methodological deficiencies may have caused misallocations of resources. It is difficult to measure the opportunity cost of inappropriate investment decisions; furthermore, to our knowledge there has been no direct comparison of immunization CEA evidence with and without donor funding. However, a start could be made by trying to understand the impact on opportunity costing, for example, by distinguishing between internal and external funding for vaccines. When a vaccine price is

subsidized internally by a local government, the opportunity cost may not be fully reflected by the acquisition price, as the subsidy, which is a transfer payment from one part of society to another, is not isolated. Nevertheless, the measurement of resource use remains consistent within the analytical scope of a societal perspective. In the case when there is an external funder like GAVI, the price it subsidizes reflects a transfer from one payer jurisdiction to another, and thus the resource flow is outside the analytical scope. Logically, then, benefits and costs should be traced back to the same origin as the resource flow—which would require a brand-new “extrasocietal perspective” as an analytical scope. So, even though the true opportunity cost may currently be hard to ascertain, it should nevertheless be recognized in reporting that it is surely higher than the subsidized price. Furthermore, dealing with external funders incurs transactions costs (e.g., intensive reporting, funders’ meetings) not normally associated with internal funding. An underestimated opportunity cost and excluded transaction costs lead to an inefficient allocation of resources. Finally, but not insignificantly, when there are large flows of external funds to specific interventions and not to others, say, those addressing equal or larger burdens of disease, a divergence in priority-setting objectives may arise between donors and domestic governments.

Methodologists, donors, and recipients are giving more attention to the global return for investments in immunization in terms of health benefits as large commitments, such as the \$US4.3 billion pledged in 2011 to support GAVI’s work, continue to be made by the international community. In addition to rotavirus vaccine, GAVI now funds injection safety and vaccines against hepatitis B, Hib, measles second dose, meningitis A, pneumococcal, rubella, yellow fever, and HPV (GAVI Alliance 2012). Meanwhile, new vaccines targeting dengue fever, meningitis, Japanese encephalitis, cholera, shigellosis, and pediatric HIV all are currently under development (WHO Initiative for Vaccine Research 2012). Although the recent dramatic reduction in the price of rotavirus vaccine may lead to similar drops in other vaccine prices, general immunization services will remain significant cost drivers for adopting new vaccines (Agosti and Goldie 2007; Atherly et al. 2012; Beatty et al. 2011; Sinha et al. 2007; Termrungruanglert et al. 2011). Beyond expanding the cold chain, more resources are needed for additional health workers and additional training in using new technologies, and for health education and social mobilization for unfamiliar and, especially, controversial vaccines

such as the HPV vaccine (Biellik et al. 2009; Burchett et al. 2012). To help maximize health benefits and increase policy relevance, vaccine efficacy and effectiveness are being directly assessed in developing countries (Cherian, Wang, and Mantel 2012), and tools to better understand and represent local epidemiology, health system conditions, and distributional impacts are being used (Chaiyakunapruk et al. 2011; Hutubessy et al. 2011; Jit et al. 2011a; Rheingans, Atherly, and Anderson 2012; Vanni et al. 2012).

As funders and researchers broaden their analytical perspectives to include programmatic and implementation aspects of immunization, they have various tools at their disposal. Although conceptually difficult and technically demanding to perform, cost-benefit analysis provides a superior framework to capture the externalities of immunization and its broader economic impacts on nonhealth sectors, as shown by Bärnighausen, Bloom, and Humair (2012). Supplementing conventional CEA or CBA with budgetary, return-to-investment, and planning and management analyses would give policymakers better insights into the affordability and sustainability of new interventions and would enable proactive planning for the adoption of new (and sometimes multiple) vaccines (Gordon, Jones, and Wecker 2012; Jit et al. 2011b; Kim et al. 2010). Likewise, by viewing donor funding as one resource among others being utilized and by recognizing its contribution to the opportunity cost within the CEA framework, researchers may advance the inquiry into what is good value for improving child health in developing countries.

References

- Adam, T., S.S. Lim, S. Mehta, Z.A. Bhutta, H. Fogstad, M. Mathai, J. Zupan, and G.L. Darmstadt. 2005. Achieving the Millennium Development Goals for Health Cost Effectiveness Analysis of Strategies for Maternal and Neonatal Health in Developing Countries. *BMJ* 331:1107–10.
- Agosti, J.M., and S.J. Goldie. 2007. Introducing HPV Vaccine in Developing Countries—Key Challenges and Issues. *New England Journal of Medicine* 356:1908–10.
- Airoldi, M. 2007. *Gains in QALYs vs DALYs Averted: The Troubling Implications of Using Residual Life Expectancy*. London: London School of Economics and Political Science.

- Anand, S., and K. Hanson. 1997. Disability-Adjusted Life Years: A Critical Review. *Journal of Health Economics* 16:685–702.
- Andrus, J.K., G. Tambini, J.L. di Fabio, and M.R. Periago. 2004. Anticipating New Vaccines in the Americas. *Pan American Journal of Public Health* 16:369–70.
- Arevshatian, L., C. Clements, S. Lwanga, A. Misore, P. Ndumbe, J. Seward, and P. Taylor. 2007. An Evaluation of Infant Immunization in Africa: Is a Transformation in Progress? *Bulletin of the World Health Organization* 85:449–57.
- Arnesen, T., and L. Kapiriri. 2004. Can the Value Choices in DALYs Influence Global Priority-Setting? *Health Policy* 70: 137–49.
- Arnesen, T., and E. Nord. 1999. The Value of DALY Life: Problems with Ethics and Validity of Disability Adjusted Life Years. *BMJ* 319:1423–25 [erratum appears in *BMJ* 320:1398].
- Atherly, D.E., K.D.C. Lewis, J. Tate, U.D. Parashar, and R.D. Rheingans. 2012. Projected Health and Economic Impact of Rotavirus Vaccination in GAVI-Eligible Countries: 2011–2030. *Vaccine* 30(suppl. 1):A7–A14.
- Barker, C., and A. Green. 1996. Opening the Debate on DALYs. *Health Policy Plan* 11:179–83.
- Bärnighausen, T., D.E. Bloom, and S. Humair. 2012. *Strengthening Health Systems: Perspectives for Economic Evaluations*. Program on the Global Demography of Aging Working Paper Series. Cambridge, MA: Harvard University.
- Beatty, M.E., P. Beutels, M.I. Meltzer, D.S. Shepard, J. Hombach, R. Hutubessy, D. Dessis, L. Coudeville, B. Dervaux, O. Wichmann, H.S. Margolis, and J.N. Kuritsky. 2011. Health Economics of Dengue: A Systematic Literature Review and Expert Panel's Assessment. *American Journal of Tropical Medicine and Hygiene* 84:473–88.
- Belli, P.C., F. Bustreo, and A. Preker. 2005. Investing in Children's Health: What Are the Economic Benefits? *Bulletin of the World Health Organization* 83:777–84.
- Beutels, P., E.V. Doorslaer, P.V. Damme, and J. Hall. 2003. Methodological Issues and New Developments in the Economic Evaluation of Vaccines. *Expert Review of Vaccines* 2:649–60.
- Biellik, R., C. Levin, E. Mugisha, D.S. LaMontagne, A. Bingham, S. Kaipilyawar, and S. Gandhi. 2009. Health Systems and Immunization Financing for Human Papillomavirus Vaccine Introduction in Low-Resource Settings. *Vaccine* 27:6203–9.
- Birdsall, N. 2005. *Seven Deadly Sins: Reflections on Donor Failings*. Washington, DC: Center for Global Development.

- Bloom, D.E., D. Canning, and M. Weston. 2005. The Value of Vaccination. *World Economics* 6:15–39.
- Bos, J.M., P. Beutels, L. Annemans, and M.J. Postma. 2004. Valuing Prevention through Economic Evaluation: Some Considerations Regarding the Choice of Discount Model for Health Effects with Focus on Infectious Diseases. *Pharmacoeconomics* 22:1171–79.
- Bos, J.M., and M.J. Postma. 2001. The Economics of HIV Vaccines: Projecting the Impact of HIV Vaccination of Infants in Sub-Saharan Africa. *Pharmacoeconomics* 19:937–46.
- Braun, V., and V. Clarke. 2006. Using Thematic Analysis in Psychology. *Qualitative Research in Psychology* 3:77.
- Brenzel, L. 1990. *The Costs of EPI: Lessons Learned from Cost and Cost-Effectiveness Studies of Immunization Programs*. Boston: John Snow.
- Brenzel, L., and P. Claquin. 1994. Immunization Programs and Their Costs. *Social Science & Medicine* 39:527–36.
- Briggs, A.H. 2000. Handling Uncertainty in Cost-Effectiveness Models. *Pharmacoeconomics* 17:479–500.
- Burchett, H.E.D., S. Mounier-Jack, U.K. Griffiths, and A.J. Mills. 2012. National Decision-Making on Adopting New Vaccines: A Systematic Review. *Health Policy and Planning* 27:ii62–ii76.
- CADTH. 2006. *Guidelines for the Economic Evaluation of Health Technologies: Canada*. 3rd ed. Ottawa: Canadian Agency for Drugs and Technologies in Health.
- Cairns, J. 2006. Discounting of Children's Health: Conceptual and Practical Difficulties. In *Economic Valuation of Environmental Health Risks to Children*, ed. P. Scapecchi, N. Johnstone and C. Delecourt, 187–205. Paris: Organization for Economic Co-operation and Development.
- Caines, K. 2005. Background Paper: Key Evidence from Major Studies of Selected Global Health Partnerships (High Level Forum on the Health MDGs Working Group on Global Health Initiatives and Partnerships, April 25–26, 2005). London: DFID Health Resource Centre.
- Chaiyakunapruk, N., R. Somkruea, R. Hutubessy, A.M. Henao, J. Hombach, A. Melegaro, J. Edmunds, and P. Beutels. 2011. Cost Effectiveness of Pediatric Pneumococcal Conjugate Vaccines: A Comparative Assessment of Decision-Making Tools. *BMC Medicine* 9:53.
- Chee, G., N. Hsi, K. Carlson, S. Chankova, and P. Taylor. 2007. *Evaluation of the First Five Years of GAVI Immunization Services Support Funding*. Bethesda, MD: Abt Associates.
- Cherian, T., S. Wang, and C. Mantel. 2012. Rotavirus Vaccines in Developing Countries: The Potential Impact, Implementation Challenges, and Remaining Questions. *Vaccine* 30(suppl. 1):A3–A6.

- Disease Control Priorities Project. 2010. <http://dcp2.org/page/main/Home.html> (accessed September 24, 2010).
- Drummond, M.F., and T.O. Jefferson. 1996. Guidelines for Authors and Peer Reviewers of Economic Submissions to the BMJ. *BMJ Economic Evaluation Working Party. BMJ* 313:275–83.
- Drummond, M.F., M.J. Sculpher, G.W. Torrance, B.J. O'Brien, and G.L. Stoddart. 2005. *Methods for the Economic Evaluation of Health Care Programs*. 3rd ed. New York: Oxford University Press.
- Evans, D.B., T. Tan-Torres Edejer, T. Adam, and S.S. Lim. 2005. Methods to Assess the Costs and Health Effects of Interventions for Improving Health in Developing Countries. *BMJ* 331:1137–40.
- Fischer, T.K., D.D. Anh, L. Antil, N.D.L. Cat, P.E. Kilgore, V.D. Thiem, R. Rheingans, L.H. Tho, R.I. Glass, and J.S. Bresee. 2005. Health Care Costs of Diarrheal Disease and Estimates of the Cost-Effectiveness of Rotavirus Vaccination in Vietnam. *Journal of Infectious Diseases* 192:1720–26.
- Fox-Rushby, J.A., and K. Hanson. 2001. Calculating and Presenting Disability Adjusted Life Years (DALYs) in Cost-Effectiveness Analysis. *Health Policy and Planning* 16:326–31.
- Garrett, L. 2007. The Challenge of Global Health. *Foreign Affairs* 86(1):13.
- GAVI Alliance. 2011. <http://www.gavialliance.org/results/disbursements/> (accessed January 9, 2012).
- GAVI Alliance. 2012. New and Underused Vaccines Support. Available at <http://www.gavialliance.org/support/nvs/> (accessed July 4, 2012).
- Glass, R.I., and U.D. Parashar. 2006. The Promise of New Rotavirus Vaccines. *New England Journal of Medicine* 354:75–77.
- Gold, M.R., and P. Muennig. 2002. Measure-Dependent Variation in Burden of Disease Estimates: Implications for Policy. *Medical Care* 40:260–66.
- Gold, M.R., J.E. Siegel, L.B. Russell, and M.C. Weinstein. 1996. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press.
- Gold, M.R., D. Stevenson, and D.G. Fryback. 2002. HALYS AND QALYS AND DALYS, OH MY: Similarities and Differences in Summary Measures of Population Health. *Annual Review of Public Health* 23:115–34.
- Gordon, W.S., A. Jones, and J. Wecker. 2012. Introducing Multiple Vaccines in Low- and Lower-Middle-Income Countries: Issues, Opportunities and Challenges. *Health Policy and Planning* 27:ii17–ii26.
- Greenberg, D., A.B. Rosen, O. Wacht, J. Palmer, and P.J. Neumann. 2010. A Bibliometric Review of Cost-Effectiveness Analyses in

- the Economic and Medical Literature: 1976–2006. *Medical Decision Making* 30:320–27.
- Griebsch, I., J. Coast, and J. Brown. 2005. Quality-Adjusted Life-Years Lack Quality in Pediatric Care: A Critical Review of Published Cost-Utility Studies in Child Health. *Pediatrics* 115(2):1407.
- Griffiths, U.K., G. Hutton, and E.D.D. Pascoal. 2005. The Cost-Effectiveness of Introducing Hepatitis B Vaccine into Infant Immunization Services in Mozambique. *Health Policy and Planning* 20: 50–59.
- Hogan, D.R., R. Baltussen, C. Hayashi, J.A. Lauer, and J.A. Salomon. 2005. Cost Effectiveness Analysis of Strategies to Combat HIV/AIDS in Developing Countries. *BMJ* 331:1431–37.
- Hutton, G., and F. Tediosi. 2006. The Costs of Introducing a Malaria Vaccine through the Expanded Program on Immunization in Tanzania. *American Journal of Tropical Medicine & Hygiene* 75:119–30.
- Hutubessy, R.C., R.M. Baltussen, T. Tan-Torres Edejer, and D.B. Evans. 2002. Generalised Cost-Effectiveness Analysis: An Aid to Decision Making in Health. *Applied Health Economics & Health Policy* 1: 89–95.
- Hutubessy, R.C., D. Chisholm, T. Tan-Torres Edejer, and WHO-CHOICE. 2003. Generalized Cost-Effectiveness Analysis for National-Level Priority-Setting in the Health Sector. *Cost Effectiveness and Resource Allocation* 1:8.
- Hutubessy, R.C., A.M. Henao, P. Namgyal, V. Moorthy, and J. Hombach. 2011. Results from Evaluations of Models and Cost-Effectiveness Tools to Support Introduction Decisions for New Vaccines Need Critical Appraisal. *BMC Medicine* 9:55.
- Iglesias, C.P., M.F. Drummond, J. Rovira, and N.P. Group. 2005. Health-Care Decision-Making Processes in Latin America: Problems and Prospects for the Use of Economic Evaluation. *International Journal of Technology Assessment in Health Care* 21:1–14.
- Institute for Health Metrics and Evaluation. 2010. Global Burden of Diseases, Injuries, and Risk Factors 2010 Study. Available at <http://www.healthmetricsandevaluation.org/research/project/global-burden-diseases-injuries-and-risk-factors-2010-study> (accessed May 31, 2012).
- Jamison, D.T., J.G. Breman, A.R. Measham, G. Alleyne, M. Claeson, D.B. Evans, P. Jha, A. Mills, and P. Musgrove, eds. 2006. *Disease Control Priorities in Developing Countries*. 2nd ed. New York: Oxford University Press.
- Jefferson, T., V. Demicheli, and L. Vale. 2002. Quality of Systematic Reviews of Economic Evaluations in Health Care. *JAMA* 287:2809–12 [see comment].

- Jit, M., N. Demarteau, E. Elbasha, G. Ginsberg, J. Kim, N. Praditsithikorn, E. Sinanovic, and R. Hutubessy. 2011a. Human Papillomavirus Vaccine Introduction in Low-Income and Middle-Income Countries: Guidance on the Use of Cost-Effectiveness Models. *BMC Medicine* 9:54.
- Jit, M., R. Yuzbashyan, G. Sahakyan, T. Avagyan, and L. Mosina. 2011b. The Cost-Effectiveness of Rotavirus Vaccination in Armenia. *Vaccine* 29:9104–11.
- Kamal-Uddin, S., and N.M. Croft. 2006. Rotavirus Vaccines: The Wheel Has Turned. *Gastroenterology* 131:1352–54.
- Keren, R., S. Pati, and C. Feudtner. 2004. The Generation Gap: Differences between Children and Adults Pertinent to Economic Evaluations of Health Interventions. *Pharmacoeconomics* 22:71–81.
- Kim, S.-Y., and S.J. Goldie. 2008. Cost-Effectiveness Analyses of Vaccination Programmes: A Focused Review of Modelling Approaches. *Pharmacoeconomics* 26:191–215.
- Kim, S.-Y., S. Sweet, D. Slichter, and S. Goldie. 2010. Health and Economic Impact of Rotavirus Vaccination in GAVI-Eligible Countries. *BMC Public Health* 10:253.
- Ladapo, J.A., P.J. Neumann, R. Keren, and L.A. Prosser. 2007. Valuing Children's Health: A Comparison of Cost-Utility Analyses for Adult and Paediatric Health Interventions in the US. *Pharmacoeconomics* 25:817–28.
- Lane, C., and A. Glassman. 2007. Bigger and Better? Scaling Up and Innovation in Health Aid. *Health Affairs* 26:935–48.
- Limcangco, M.R., C.L. Armour, E.G. Salole, and S.J. Taylor. 2001. Cost-Benefit Analysis of a Haemophilus Influenzae Type B Meningitis Prevention Programme in the Philippines. *Pharmacoeconomics* 19:391–400.
- Lu, C., C.M. Michaud, E. Gakidou, K. Khan, and C.J.L. Murray. 2006. Effect of the Global Alliance for Vaccines and Immunisation on Diphtheria, Tetanus, and Pertussis Vaccine Coverage: An Independent Assessment. *The Lancet* 368:1088–95.
- Mathers, C. 2009. Global Burden of Disease among Women, Children, and Adolescents. In *Maternal and Child Health: Global Challenges, Programs, and Policies*, ed. J.E. Ehiri, 19–42. New York: Springer-Verlag.
- McGregor, M. 2006. What Decision-Makers Want and What They Have Been Getting. *Value in Health* 9:181–85.
- Michaud, C. 2005. *Donor Flows in Cambodia, Indonesia and Sri Lanka: Synthesis of Key Findings*. Geneva: World Health Organization.
- Miles, M.B., and A.M. Huberman. 1994. *Qualitative Data Analysis: An Expanded Sourcebook*. 2nd ed. Thousand Oaks, CA: Sage.

- Mills, A., and M. Thomas. 1984. *Economic Evaluation of Health Programmes in Developing Countries: A Review and Selected Annotated Bibliography*. London School of Hygiene and Tropical Medicine.
- Morel, C.M., J.A. Lauer, and D.B. Evans. 2005. Cost Effectiveness Analysis of Strategies to Combat Malaria in Developing Countries. *BMJ* 331:1299 [erratum appears in *BMJ* 332:151].
- Mulligan, J., D. Walker, and J. Fox-Rushby. 2006. Economic Evaluation of Non-Communicable Disease Interventions in Developing Countries: A Critical Review of the Evidence Base. *Cost-Effectiveness and Resource Allocation* 4:7.
- Murray, C., and A.K. Acharya. 1997. Understanding DALYs. *Journal of Health Economics* 16:703–30.
- Murray, C., D.B. Evans, A. Acharya, and R.M. Baltussen. 2000. Development of WHO Guidelines on Generalized Cost-Effectiveness Analysis. *Health Economics* 9:235–51.
- Neumann, P.J. 2005. *Using Cost-Effectiveness Analysis to Improve Health Care: Opportunities and Barriers*. New York: Oxford University Press.
- NICE (National Institute for Health and Clinical Excellence). 2008. *Guide to the Methods of Technology Appraisal*. London.
- Parashar, U.D., E.G. Hummelman, J.S. Bresee, M.A. Miller, and R.I. Glass. 2003. Global Illness and Deaths Caused by Rotavirus Disease in Children. *Emerging Infectious Diseases* 9:565–72.
- Petrou, S. 2003. Methodological Issues Raised by Preference-Based Approaches to Measuring the Health Status of Children. *Health Economics* 12:697–702.
- Podewils, L.J., L. Antil, E. Hummelman, J. Bresee, U.D. Parashar, and R. Rheingans. 2005. Projected Cost-Effectiveness of Rotavirus Vaccination for Children in Asia. *Journal of Infectious Diseases* 192(suppl. 1):S133–S45.
- Prosser, L.A., J.K. Hammitt, and R. Keren. 2007. Measuring Health Preferences for Use in Cost-Utility and Cost-Benefit Analyses of Interventions in Children: Theoretical and Methodological Considerations. *Pharmacoeconomics* 25:713–26.
- Ravishankar, N., P. Gubbins, R.J. Cooley, K. Leach-Kemon, C.M. Michaud, D.T. Jamison, and C.J.L. Murray. 2009. *Financing of Global Health: Tracking Development Assistance for Health from 1990 to 2007*. Seattle: Institute for Health Metrics and Evaluation.
- Rheingans, R., D. Atherly, and J. Anderson. 2012. Distributional Impact of Rotavirus Vaccination in 25 GAVI Countries: Estimating Disparities in Benefits and Cost-Effectiveness. *Vaccine* 30(suppl. 1):A15–A23.
- Ruiz-Palacios, G.M., I. Perez-Schael, F.R. Velazquez, H. Abate, T. Breuer, S.C. Clemens, and H.R.V.S. Group. 2006. Safety and

- Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis. *New England Journal of Medicine* 354:11–22.
- Sachs, J., and Commission on Macroeconomics and Health. 2001. *Macroeconomics and Health: Investing in Health for Economic Development. Report of the Commission on Macroeconomics and Health*. Geneva: World Health Organization.
- Salomon, J.A. 2010. New Disability Weights for the Global Burden of Disease. *Bulletin of the World Health Organization* 88:879–80.
- Sandelowski, M. 2000. Whatever Happened to Qualitative Description? *Research in Nursing & Health* 23:334–40.
- Sassi, F. 2006. Calculating QALYs, Comparing QALY and DALY Calculations. *Health Policy and Planning* 21:402–8.
- Schiffman, J. 2006. Donor Funding Priorities for Communicable Disease Control in the Developing World. *Health Policy and Planning* 21:411–20.
- Sculpher, M., and M.F. Drummond. 2006. Analysis sans Frontières: Can We Ever Make Economic Evaluations Generalisable across Jurisdictions? *Pharmacoeconomics* 24:1087–99.
- Shepard, D.S., J.A. Suaya, S.B. Halstead, M.B. Nathan, D.J. Gubler, R.T. Mahoney, D.N.C. Wang, and M.I. Meltzer. 2004. Cost-Effectiveness of a Pediatric Dengue Vaccine. *Vaccine* 22:1275–80.
- Shepard, D.S., J.A. Walsh, E. Kleinau, S. Stansfield, and S. Bhalotra. 1995. Setting Priorities for the Children's Vaccine Initiative: A Cost-Effectiveness Approach. *Vaccine* 13:707–14.
- Sinha, A., O. Levine, M.D. Knoll, F. Muhib, and T.A. Lieu. 2007. Cost-Effectiveness of Pneumococcal Conjugate Vaccination in the Prevention of Child Mortality: An International Economic Analysis. *The Lancet* 369:389–96.
- Solans, M., S. Pane, M.D. Estrada, V. Serra-Sutton, S. Berra, M. Herdman, J. Alonso, and L. Rajmil. 2008. Health-Related Quality of Life Measurement in Children and Adolescents: A Systematic Review of Generic and Disease-Specific Instruments. *Value in Health* 11:742–64.
- Spier, R., T.O. Jefferson, and V. Demicheli. 2002. An Editorial Policy Statement: Submission of Economic Evaluations of Vaccines. *Vaccine* 20:1693–95.
- Tan-Torres Edejer, T., M. Aikins, R. Black, L. Wolfson, R. Hutubessy, and D.B. Evans. 2005. Cost Effectiveness Analysis of Strategies for Child Health in Developing Countries. *BMJ* 331:1177.
- Tan-Torres Edejer, T., R. Baltussen, T. Adam, R.C. Hutubessy, A. Acharya, D.B. Evans, and C.J. Murray. 2003. *Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis*. Geneva: World Health Organization.

- Termrungruanglert, W., P. Havanond, N. Khemapech, S. Lertmaharit, S. Pongpanich, C. Khorprasert, and S. Taneepanichskul. 2011. Cost and Effectiveness Evaluation of Prophylactic HPV Vaccine in Developing Countries. *Value in Health* 15:S29–S34.
- Ungar, W.J. 2010. *Economic Evaluation in Child Health*. Oxford: Oxford University Press.
- Ungar, W.J. 2011. Challenges in Health State Valuation in Paediatric Economic Evaluation: Are QALYs Contraindicated? *Pharmacoeconomics* 29:641–52.
- Ungar, W.J., and A. Gerber. 2010. The Uniqueness of Child Health and the Challenges to Measuring Costs and Consequences. In *Economic Evaluation in Child Health*, ed. W.J. Ungar, 3–32. Oxford: Oxford University Press.
- Ungar, W.J., and M.T. Santos. 2005. Quality Appraisal of Pediatric Health Economic Evaluations. *International Journal of Technology Assessment in Health Care* 21:203–10.
- UNICEF. 2011. Trends in Under-Five Mortality Rates (1960–2010). Available at http://www.childinfo.org/mortality_ufmrcountrydata.php (accessed December 15, 2011).
- United Nations Development Programme. 2011. Millennium Development Goals. Available at http://www.beta.undp.org/content/undp/en/home/mdgoverview/mdg_goals/mdg4.html (accessed December 15, 2011).
- U.S. Food and Drug Administration. 2010. Background on Rotavirus Vaccines. Available at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm205543.htm> (accessed May 22, 2012).
- Vanni, T., P. Mendes Luz, A. Foss, M. Mesa-Frias, and R. Legood. 2012. Economic Modelling Assessment of the HPV Quadrivalent Vaccine in Brazil: A Dynamic Individual-Based Approach. *Vaccine* 30: 4866–71.
- Vesikari, T., D.O. Matson, P. Dennehy, P. Van Damme, M. Santosham, Z. Rodriguez, M.J. Dallas, J.F. Heyse, M.G. Goveia, S.B. Black, H.R. Shinefield, C.D.C. Christie, S. Ylitalo, R.F. Itzler, M.L. Coia, M.T. Onorato, B.A. Adeyi, G.S. Marshall, L. Gothefors, D. Campens, A. Karvonen, J.P. Watt, K.L. O'Brien, M.J. DiNubile, H.F. Clark, J.W. Boslego, P.A. Offit, and P.M. Heaton for the Rotavirus Efficacy and Safety Trial (REST) Study Team. 2006. Safety and Efficacy of a Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine. *New England Journal of Medicine* 354:23–33.
- 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* 82:703–8.

- Walker, D., and J.A. Fox-Rushby. 2000. Economic Evaluation of Communicable Disease Interventions in Developing Countries: A Critical Review of the Published Literature. *Health Economics* 9: 681–98.
- Walker, D., and R. Rheingans. 2005. Cost-Effectiveness of Rotavirus Vaccines. *Expert Review of Pharmacoeconomics & Outcomes Research* 5:593–601.
- Weinstein, M.C., J.E. Siegel, M.R. Gold, M.S. Kamlet, and L.B. Russell. 1996. Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 276:1253–58 [see comment].
- Weinstein, M., G. Torrance, and A. McGuire. 2009. QALYs: The Basics. *Value in Health* 12:S5–S9.
- Widdus, R. 2003. Public-Private Partnerships for Health Require Thoughtful Evaluation. *Bulletin of the World Health Organization* 81:235.
- WHO (World Health Organization). 2002. *The World Health Report 2002: Reducing Risks, Promoting Healthy Life*. Geneva.
- WHO (World Health Organization). 2006. *New Vaccines against Infectious Diseases: Research and Development Status*. IVR, WHO, April 2005, updated February 2006 ed. Geneva.
- WHO (World Health Organization). 2008. *WHO Guide for Standardization of Economic Evaluations of Immunization Programmes*. Geneva: WHO, Department of Immunization, Vaccines and Biologicals, Initiative for Vaccine Research.
- WHO (World Health Organization). 2010a. WHO-CHOICE. Available at <http://www.who.int/choice/en/> (accessed September 24, 2010).
- WHO (World Health Organization). 2010b. Cost-Effectiveness Results. Available at <http://www.who.int/choice/results/en/> (accessed September 24, 2010).
- WHO (World Health Organization). 2010c. Macroeconomics and Health (CMH). Available at <http://www.who.int/macrohealth/background/en/> (accessed September 24, 2010).
- WHO (World Health Organization). 2010d. *World Health Statistics, 2010*. Geneva.
- WHO (World Health Organization). 2012. Global Burden of Disease. Available at http://www.who.int/healthinfo/global_burden_disease/en/index.html (accessed May 31, 2012).
- WHO (World Health Organization) Initiative for Vaccine Research. 2012. Vaccine Research and Development. Available at http://www.who.int/vaccine_research/en/ (accessed June 1, 2012).
- World Bank. 1993. *World Development Report 1993: Investing in Health*. Vol. 1. Washington, DC: World Bank.

World Bank. 2011. *How We Classify Countries*. Available at <http://data.worldbank.org/about/country-classifications> (accessed December 15, 2011).

Acknowledgments: Cindy Gauvreau was supported through a studentship by the Matching Funds / Hospital for Sick Children Foundation Student Scholarship Program. Funding was also provided by the University of Toronto, the Canadian Institutes for Health Research, and Dr. Susan Horton (University of Waterloo, Canada).