

Paediatric Health Economic Evaluations: A World View

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From: Ungar W. Gesundheitsökonomische Analysen in der Pädiatrie: Historischer Überblick und Untersuchung nach Art der Interventionen. In: Gerber A, Lauterbach KW. Gesundheitsökonomie und Pädiatrie. Stuttgart, New York: Schattauer 2006

Abstract

Objectives: As economic evaluation methods evolve, their applicability to special populations, such as children, has received increased scrutiny. The objective was to review paediatric health economic evaluations published over the last quarter century, comment on trends, discuss gaps between developed and developing nations, and point to future directions for research.

Methods: Data compiled for the Paediatric Economic Database Evaluation (PEDE) project to 2003 were used to describe temporal and geographic trends and evaluate the frequency of intervention categories and conditions studied.

Results: The volume of paediatric health economic evaluations rose rapidly since 1980. Studies of infective/parasitic diseases, congenital anomalies and complications of pregnancy accounted for the majority. Prevention rather than treatment was emphasized. Most evaluations performed since 1998 (78%) were cost-effectiveness analyses. Cost-utility analyses were rare. The US produced half of all publications, with the UK contributing 12%. Economic evaluations from developing countries were uncommon, despite an urgent need for evidence-based decision-making in these regions. The interventions studied reflected local health priorities; HIV and malaria prevention were more commonly studied in developing nations, whereas treatments for asthma and birth malformations were more often evaluated in developed nations.

Conclusions: Despite global initiatives to combat disease, developing nations rely on foreign research to inform implementation of local health programs. There is a need for better methods for data transfer and extrapolation. Future research must focus on paediatric models of costs and consequences and the development of tools to measure long-term effects.

Introduction

The picture of contemporary healthcare systems is one that reflects the tension between increasing investment in new technology on the one hand and the need to curtail spending on the other. As a tool to facilitate budget allocation decision-making, economic evaluations that weigh healthcare costs against health benefits have been documented in the medical literature for over 25 years and paediatric economic evaluations were among the earliest. In recent years, a rapid escalation in healthcare costs around the globe has contributed to the urgency of generating high-quality health economic evaluations to inform decision-making and ensure sustainability of our healthcare systems.

In this paper, the roots of paediatric health economic evaluation will be described. Trends in paediatric health economic evaluation over time and by global region will be presented, and the types of interventions and paediatric conditions studied around the world in recent years will be explored. The paper will reveal the gaps in international research in paediatric health economics by exposing differences between developed and developing countries, and future directions for the conduct of paediatric health economic evaluations will be highlighted.

The Origins of International Paediatric Economic Evaluations

In 1980, eight full paediatric economic evaluations (i.e., ones that included a comparator and measured both costs and consequences) were published in the medical literature. These consisted of studies of an immunization program in Indonesia (Barnum et al. 1980), prevention of dental caries (Klock 1980), prevention of tuberculosis (Koplan and Farer 1980), immunization for measles in Southern Zambia (Ponnighaus 1980), a nutritional intervention in the Philippines (Popkin et al. 1980), an intervention for problem behaviour (Siegert and Yates 1980), a management care-delivery system for children with cancer (Strayer et al. 1980) and vaccination against pneumococcal pneumonia (Willems et al. 1980). These eight studies, published in a wide array of journals that included the *Bulletin of the World Health Organization*, *JAMA*, *New England Journal of Medicine*, *Pediatrics*, *Social Science & Medicine*, *Journal of Tropical Medicine & Hygiene and Community Dentistry & Oral Epidemiology*, represent the wide therapeutic areas and geographical disparities that continue to this day to typify child health worldwide. Unlike adult medicine that emphasizes medical treatment of disease, paediatric medicine places much importance on prevention of illness. Child health is holistic in that nutritional status, dental health and school performance are emphasized as important indicators alongside good physical health. Because of the relationship between susceptibility to disease and normal child development, aspects of behaviour and learning are often integrated into the prevention and management of illness. Child health features community, school and public health interventions to a great extent. The international health economic literature reflects these unique characteristics and also reveals the difference in priorities in child health between developed and developing nations.

The benefits of programs that focus on prevention are sometimes fully valued in monetary terms. As such, the emphasis on prevention in paediatric medicine has led to the publication of a number of cost-benefit analyses (CBAs), wherein both costs and benefits are expressed in monetary units. This is in contrast to more conventional analytic techniques such as cost-effectiveness analysis (CEA), which measures outcomes in natural health units. The occurrence of CBAs among paediatric economic evaluations belies the notion that CBAs are rare in the health sector. Among the eight pioneering studies cited above, three were CEAs, three were CBAs and two were cost-minimization analyses (CMAs) that compared costs only, given evidence of equal effectiveness between the interventions.

Not only were paediatric health economic evaluations among the earliest, they have also been among those at the methodological forefront. The 1980 study of a preventive treatment for tuberculosis (Koplan and Farer 1980) featured decision analysis, a sophisticated mathematical modelling technique that integrates data from multiple existing sources to derive the expected utility of comparator interventions (Detsky et al. 1997). In 1983, Boyle et al. published one of the first cost-utility analyses (CUA), calculating the incremental cost per quality-adjusted life year (QALY) gained for neonatal intensive care for very low birth weight babies. A QALY is a unit of health benefit that adjusts

expected survival expressed as life years gained, by decrements in health-related quality of life. This paper, regarded as a classic in the health economics literature, presented the results in both CEA and CUA frameworks. As neonatal intensive care continues to be among the costliest forms of medical care, this paper continues to have relevance for today's decision-makers. Paediatric studies were also at the forefront of the development of utility scores that reflect preferences for diverse health states for the calculation of QALYs. The Health Utilities Index (HUI), an instrument based on a multi-attribute classification system, is among the most common methods for determining utilities (Drummond et al. 2005). The HUI was developed through a systematic survey of parents of children with cancer regarding their preferences for diverse paediatric health states (Drummond et al. 2005).

International Trends in Comparative Paediatric Economic Evaluations

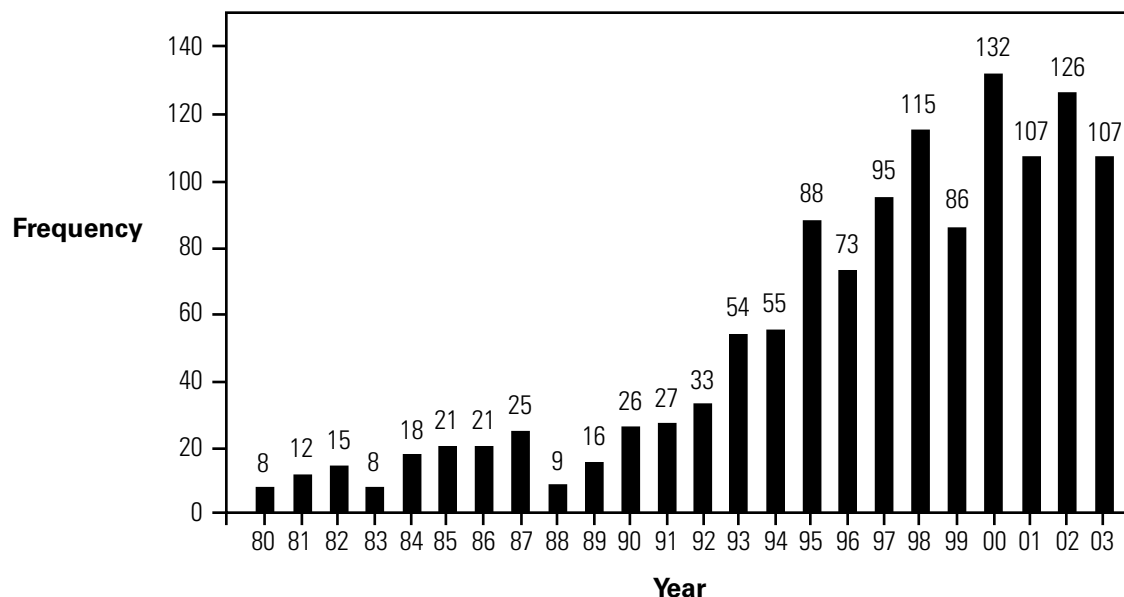
The data compiled for the Paediatric Economic Database Evaluation (PEDE) project were used for all descriptive analyses of trends. The PEDE database is an inventory of full paediatric economic evaluations, where both costs and consequences were measured for two or more comparators, published globally since 1980 (Ungar and Santos 2003). Details of the methods used to build and evaluate the PEDE database have been described elsewhere (Ungar and Santos 2004; Ungar and Santos 2002). Analyses were undertaken to examine trends over time and by region with respect to ICD-10 disease categories (World Health Organization 2003) and types of intervention studied. All experimental interventions described in published papers were classified in one of the following categories: Dental, Detection/Screening, Diagnosis, Educational, Healthcare Delivery, Health Program, Treatment, Prevention or Surgical. The Treatment category included pharmacological agents as well as devices. The great majority of interventions in the Prevention category were immunizations for primary prevention of communicable disease.

Temporal Trends in Paediatric Economic Evaluations

As seen in Figure 1, there has been significant growth in the number of full comparative paediatric economic evaluations published globally over time, particularly since the early 1990s. In 1996, the total volume of all published health economic evaluations, including adults, was estimated at 518 (Elixhauser et al. 1998), thus the paediatric literature accounts for approximately 15% of the total. Between 1980 and 2003, a total of 1,277 paediatric studies have been published with just over half of the papers (673) published since 1998. In latter years, the annual volume has begun to plateau, with an average of 112 papers published per year since 1998. Among the paediatric papers published since 1998, the largest proportion (35%) appeared in medical journals devoted to paediatric or perinatal medicine. Thirty-three per cent were published in other types of sub-specialty journals, 11% in public health journals, 9% in general medicine journals and 8% in health economics, health policy or methods journals.

Of the various types of paediatric interventions studied around the globe in the last few decades, those for prevention were the most common, with medical treatments appearing to grow as a proportion of the total in later years. Over time, the majority (63%) of health prevention interventions were for infectious disease, including hepatitis B, *Hemophilus influenzae* type B, measles, varicella and general vaccination strategies. Economic evaluations of interventions to prevent complications of pregnancy were also common and increased in later years. Among studies of treatments, the largest proportions were for infectious disease and for perinatal conditions. Common pregnancy and perinatal conditions that were treated included cardiac abnormalities, low birth weight, prematurity, respiratory conditions, Down's syndrome and congenital hip dislocation. Detection/diagnostic interventions were focused mostly on congenital anomalies, complications of pregnancy and infectious diseases. Studies of health programs were devoted to general health as well as perinatal conditions and complications of pregnancy. Over one third of assessments of surgical interventions were directed at congenital anomalies. Surgical interventions were also common for digestive and genitourinary conditions in children. By 2003, infective and parasitic diseases, congenital anomalies and complications of pregnancy, childbirth and the puerperium together accounted for 58% of all publications.

Figure 1



Volume of Published Paediatric Economic Evaluations, 1980-2003. Adapted from Ungar and Santos 2003.

With regard to the precise analytic technique employed in the economic evaluation, CEA was the most common technique used overall since 1980. Over time, the proportion of studies using CEA has been increasing, while the prevalence of CBA has been decreasing. This may reflect the increasing emphasis in the literature on treatment rather than prevention of disease. It may also reflect an improved specification of analytic technique, as cost-effectiveness analyses are sometimes mislabelled as CBAs, particularly in publications that pre-date health economic guidelines (Zarnke et al. 1997). CUA, despite being regarded as the gold standard in health economic analytic approaches (Siegel et al. 1996), remains rare in the paediatric health economics literature, accounting for only 15/107 (14%) of papers published in 2003. The scarcity of CUAs may be related to the particular challenges associated with measuring utility as well as obtaining accurate estimates of life years gained for various interventions in children. CEA was the most common technique for all intervention types. CBAs tended to be used to evaluate health prevention and detection/diagnostic strategies. Although rare, CUAs that were conducted were usually applied to evaluations of prevention strategies and treatment interventions.

Overall, the observed temporal trends may be explained by several factors. In the 1980s, many paediatric economic evaluations were sponsored by governmental organizations, including the US Center for Disease Control (CDC), the World Health Organization and governments of developing countries investigating screening and prevention program, and were performed by trained economists. The CDC pioneered the use of cost-effectiveness analysis to assess the economic benefits of health programs. This was consistent with the CDC's public health goals to promote prevention and early intervention in American children. A growth in managed care healthcare systems, whether as for-profit organizations or as government sponsored public plans, came with an increased awareness of the need to manage costs. Many government jurisdictions as well as managed care organizations began to use formularies to control pharmaceutical benefits. Attenuating costs within the healthcare system by restricting access to or limiting use of medications listed on a single budget formulary was relatively easy compared to achieving savings in other healthcare sectors that were funded by more complex mechanisms. Emphasis on assessing the cost-effectiveness of pharmaceuticals began

to grow, and in the early 1990s, a number of guidelines for the conduct of pharmacoeconomic evaluations were published (Siegel et al. 1996; Torrance et al. 1996; Jacobs et al. 1995; Australian Commonwealth Dept of Health, Housing, Community Services 1992). Academic health services researchers, private sector researchers and clinicians joined economists in efforts to produce economic evaluations. Over the years, the increased availability of guidelines in countries and agencies around the world (Hjelmgren et al. 2001) and an increasing demand by payors for evidence of cost-effectiveness of treatments, particularly pharmaceuticals, spurred rapid growth in the conduct of comparative health economic evaluations. This trend is apparent from the large increase in studies devoted to medical treatments for children over the last two decades. The growth in paediatric economic evaluation may also be ascribed to a growth in new technologies related to maternal and foetal health, such as ultrasound screening for foetal abnormalities. Currently, third-party payors, managed care organizations and international agencies that sponsor healthcare programs are increasingly demanding evidence of the cost-effectiveness of not only health treatments and prevention strategies, but also of medical and surgical procedures, services and programs.

Regional Trends in Paediatric Economic Evaluations

As portrayed by the global map in Figure 2, paediatric health economic evaluations are being conducted all over the world. Among the 673 publications that appeared from 1998 to 2003, almost half (49%) were conducted in the US. European countries were studied in 27%, with the largest European contribution delivered by researchers in the UK. Other important locations for the conduct of paediatric health economic research included Canada, Africa and Australia. The scarcity of paediatric economic evaluations in developing countries is striking. Regions such as sub-Saharan Africa and South Asia face a double jeopardy. The limited resources available hamper the production of paediatric health economic evaluations, and it is precisely in countries with limited healthcare resources that the need for high quality health economic evidence to ensure careful and efficient resource allocation is greatest.

Figure 2



Global Distribution of Paediatric Economic Evaluations, 1998-2003. The numbers represent the total number of published paediatric health economic evaluations conducted in the indicated region between 1998 and 2003. Percentage of total in parentheses.

Table 1. Type of Intervention by Region, 1998-2003

Region	Detection/ Screening	%	Health Care Delivery	%	Health Program	%	Health Treatment	%	Prevention	%	Other	%	Total
Africa	3	9%	1	3%	2	6%	4	13%	20	63%	2	6%	32
Central & South America & Mexico	1	8%	2	17%	0	0%	4	33%	4	33%	1	8%	12
South & Southeast Asia	2	8%	1	4%	3	12%	9	36%	10	40%	0	0%	25
Far East	3	21%	0	0%	1	7%	2	14%	5	36%	3	21%	14
Middle East & Turkey	2	17%	1	8%	0	0%	5	42%	1	8%	3	25%	12
Canada	3	9%	5	14%	6	17%	7	20%	11	31%	3	9%	35
US	59	18%	42	13%	41	12%	63	19%	60	18%	64	19%	329
UK	26	33%	0	0%	2	3%	27	35%	12	15%	11	14%	78
Australia & New Zealand	2	8%	0	0%	3	12%	6	23%	11	42%	4	15%	26
Eastern Europe	2	29%	0	0%	0	0%	0	0%	4	57%	1	14%	7
Scandinavia	2	15%	0	0%	0	0%	4	31%	4	31%	3	23%	13
Netherlands & Belgium	7	41%	0	0%	0	0%	2	12%	4	24%	4	24%	17
Western & Central Europe*	14	21%	1	1%	2	3%	16	24%	27	40%	8	12%	68
Other	1	20%	0	0%	0	0%	1	20%	2	40%	1	20%	5

* excluding UK

Percentage represents the proportion of the regional (row) total.

Despite the fact that a few large developed countries produced the majority of studies, it is remarkable to note the wide variety of countries contributing to the literature. In total, over 53 countries around the globe contributed one or more comparative paediatric economic evaluations to the medical literature between 1998 and 2003.

Between 1998 and 2003, the three most common categories of interventions studied world-wide were prevention (26%), treatment (22%) and detection/screening (19%). Most studies of prevention were for infective and parasitic diseases. On a per region proportional basis, evaluations of infective and parasitic diseases were more common in Africa, Eastern Europe and the Far East where they accounted for 75%, 71% and 57% of studies conducted in these regions respectively, compared to 22%, 15% and 20% of studies conducted in the US, UK and Canada respectively. As seen in Table 1, as a proportion of the total number of studies in the region, studies of prevention were more common in Africa (63%), Eastern Europe (57%), Australia/New Zealand (42%), Western/Central Europe excluding the UK (40%) and South/Southeast Asia (40%) compared to the US (18%) and the UK (15%). In contrast, studies of congenital anomalies were more frequent on a per region proportional basis in the US and UK, where they accounted for 11% and 15% of all studies respectively, compared to 0% in Africa and Australia/New Zealand, 6% in Canada and 4% in Western/Central Europe.

Between 1998 and 2003, most preventive interventions studied consisted of immunization strategies against a wide variety of communicable diseases, including hepatitis A, hepatitis B, *Hemophilus*

influenzae type B, measles, meningococcal disease, pneumococcal disease and varicella. While studies of these diseases were distributed across numerous countries and continents, the many studies of interventions to prevent malaria were concentrated in Africa (including sub-Saharan Africa, Gambia, Tanzania and Kenya) and Afghanistan. The US and UK contributed only one study each to the prevention of malaria. Despite the preponderance of studies evaluating immunization strategies for primary prevention of common communicable diseases, the diseases most frequently targeted for prevention were respiratory syncytial virus (RSV) and maternal-fetal transmission of HIV. The RSV studies were all conducted in the US, UK, Spain, Argentina, Australia, Germany or New Zealand. In contrast, the majority of HIV prevention studies were conducted in sub-Saharan Africa and South Africa. Only six studies of HIV prevention were conducted in the US, UK or Canada.

Studies of interventions categorized as treatments included economic evaluations of pharmacotherapy and devices. Of those that were published between 1998 and 2003, the largest proportion examined antibiotic regimens for a variety of infectious diseases. These studies were distributed across many global regions. Also common were treatments for complications of birth. These studies were conducted exclusively in the US, Canada, Sweden and Australia. Numerous economic evaluations of asthma, the most common chronic disease of childhood in developed nations (Akinbami and Schoendorf 2002; Mannino et al. 2002), were published by researchers in the US, UK, Brazil, Canada, Denmark, New Zealand and Sweden. Studies of nutritional interventions, both parenteral and oral supplements, were also common around the globe. Other studies evaluated treatments for attention deficit hyperactivity disorder, cystic fibrosis, deafness, haematological disorders, nausea and vomiting, neutropenia, optimal orthopaedic strategies and optimal anaesthesia regimens.

A majority of interventions labelled as detection/screening were for perinatal detection of birth defects. The interventions evaluated included biomarkers, genetic tests and imaging modalities. Down's syndrome was the disease for which screening interventions were evaluated most often. These studies were conducted in the US, UK, the Netherlands, France, Switzerland, Canada and Denmark. Also common were evaluations of screening for haematological disorders, including sickle-cell anaemia and thalassaemia. These studies were conducted in the UK, US, Hong Kong, Israel and Thailand. Evaluations of screening strategies for hearing and visual disorders were also common. Studies of HIV screening were conducted in the US, UK and New Zealand. Studies of antenatal screening for sexually transmitted diseases were among publications in the US, UK, sub-Saharan Africa, the Netherlands and Slovenia.

The analytic approach used was often related to the type of intervention studied. Table 2 displays how each intervention type was distributed across the four principal analytic techniques for all regions and all publications between 1998 and 2003. CEA was used in a majority of publications of each intervention type. The rate was lowest, however, for prevention interventions, of which 17% used CBA. CBAs were also more common in evaluations of detection/screening strategies compared to other types of interventions. Approximately one third of all CUAs were devoted to studies of health treatments and another third to studies of prevention.

Despite the measurement challenges associated with conducting CUAs in children, they have been conducted by researchers around the world for a range of diseases, including several infectious diseases, haematological disorders and asthma. They have also been applied to the evaluation of medical devices for hearing loss and diabetes management. The largest proportion of CUAs (31%) consisted of studies of infectious diseases compared to other ICD-10 disease categories. These were most frequently studies of hepatitis A and B, HIV, meningococcal and pneumococcal disease. Sixteen CUAs of infectious disease interventions were carried out in the US (four), sub-Saharan Africa (four), India (two), the Netherlands (two), Switzerland (two), Chile (one) and the UK (one).

Regional Disparities in Paediatric Health Economic Evaluations

The above examination of the global regional distribution of published paediatric economic evaluations underscores the wide disparities in healthcare resources between developed and developing

Table 2. Analytic Technique by Type of Intervention, 1998-2003

Intervention Type	CBA	Column %	Row %	CEA	Column %	Row %	CUA	Column %	Row %	CMA	Column %	Row %	Totals
Dental	1	2%	7%	12	2%	86%	0	0%	0%	1	3%	7%	14
Detection/ Screening	15	27%	12%	105	20%	83%	3	6%	2%	4	10%	3%	127
Diagnosis	0	0%	0%	24	5%	83%	4	8%	14%	1	3%	3%	29
Educational	2	4%	10%	14	3%	67%	4	8%	19%	1	3%	5%	21
Health Care Delivery	1	2%	2%	45	9%	85%	1	2%	2%	6	15%	11%	53
Health Program	2	4%	3%	52	10%	87%	1	2%	2%	5	13%	8%	60
Health Treatment	6	11%	4%	113	22%	75%	17	33%	11%	14	35%	9%	150
Prevention	29	52%	17%	127	24%	73%	18	35%	10%	1	3%	1%	175
Surgical	0	0%	0%	33	6%	75%	4	8%	9%	7	18%	16%	44
Total	56			525			52			40			673

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CMA = cost-minimization analysis
Column and row percentages may not add to 100 due to rounding.

nations. Non-members of the Organisation for Economic Co-operation and Development (OECD) accounted for only 14% of the paediatric health economics literature but exhibit the greatest burden of disease. As a measure of burden of disease, disability adjusted life years (DALY) in children aged 14 years and under were 30,644 per 100,000 population in low- and middle-income countries, compared to 5,911 per 100,000 population in high-income countries (Mathers et al. 2005). The countries of South Asia and sub-Saharan Africa accounted for 69% of the DALY burden in children worldwide (Mathers et al. 2005). Each year, approximately 10 million children die from preventable and curable diseases (Black et al. 2003).

As mentioned above, developing countries face the double jeopardy of possessing limited resources for conducting paediatric health economic evaluations and having the greatest need for high quality health economic evidence to inform allocation of extremely limited healthcare budgets. Efforts to transfer knowledge from economic evaluations conducted in developed countries are hampered by differences in healthcare delivery systems as well as differences in healthcare priorities. Even if findings of a particular study, such as an evaluation of a tuberculosis vaccination program, were generalizable to other settings, transferability of results is hindered by difficulty identifying appropriate price sources and conversion rates. In developing countries, prices may not reflect the opportunity cost and a shadow foreign exchange rate is often required (Walker and Fox-Rushby 2000). Another concern is that for developing countries, mere evidence of cost-effectiveness of an intervention is not enough. These nations also require an indicator of *affordability* (i.e., the ability of the target payors, such as government or health agencies, to cover the costs of the program). Developing nations may have no choice but to rely on foreign economic evaluation findings when faced with the need for *ex ante* evidence to inform decisions regarding implementation of health programs. This is particularly true for wide-scale prevention programs such as national immunization schedules. A reliance on foreign economic evaluation stresses the need for better methods for transferability and extrapolation of data.

When economic evaluations are conducted in developing regions, they are often funded by international agencies such as the World Health Organization (WHO), UNICEF and the World Bank. The risk in this case is that studies funded by world health agencies, non-governmental organizations or private sector multinational corporations will reflect the priorities of these organizations, which may or may not coincide with those of the local people (Walker and Fox-Rushby 2000). If divergence in priority-setting between international organizations and local governments is present, the funding of programs and services directed toward local child health needs may suffer. Moreover, childhood diseases such as malaria, which are not deemed a worthy investment by multi-national pharmaceutical companies, remain (de Joncheere 2001), thus further limiting access to needed treatments. International funds, such as charitable organizations, can help to ensure that research will be conducted in underserved therapeutic areas (de Joncheere 2001).

Priorities for Future International Paediatric Health Economic Evaluations

In determining future directions for paediatric health economic research, it is essential that researchers who produce economic evaluations and policy decision-makers who utilize them recognize the critical differences between paediatric and adult health economic evaluation, both conceptually and methodologically.

Conceptual differences relate to the way child health is understood. Understanding child health as multi-dimensional, encompassing physical, mental, nutritional, behavioural, educational and sociological components, facilitates the design of integrated programs or interventions (i.e., those that address physical health as well as nutrition, education and family and community supports). In a Canada-Tanzania collaborative pilot project that directed limited available funds at reducing child mortality from several major causes simultaneously, death rates fell by more than 40% in the districts implementing this approach (Nolan 2005). In addition, understanding the relationship between time of exposure to an intervention and the pathway for normal development is essential for the design of appropriate outcome measures. Valid outcome measures relevant to healthy development may include physiological milestones as well as participation rates at school and academic performance. It was recognized in early economic evaluations examining nutritional interventions that chronic malnutrition in the first two years of life permanently impairs cognitive ability, with adverse consequences for productivity and earnings potential throughout life (Behrman 1993). A time horizon that captures costs and benefits into adulthood is thus often necessary. A health intervention that results in better school performance may lead to greater workforce participation in adulthood, higher income and a change in societal determinants of health such as a reduction in poverty. Even less well-recognized is that early childhood interventions may also result in greater workforce participation and increased productivity by parents and caregivers. The potential for cost-effective health interventions delivered during childhood to have far-reaching effects, such as poverty reduction and, ultimately, demographic transition, must be recognized (Belli et al. 2005).

The need to capture lifetime costs and consequences presents a difficult but not insurmountable challenge. While statistical modelling and decision analysis offer some tools for extending time horizons, the best data are empirical. Birth cohort studies that track large cohorts of children longitudinally with repeat assessments through the years of development into adulthood greatly enhance our ability to predict outcomes. Birth cohort studies typically encompass a representative sample of whole populations born in a given year, such as the UK Medical Research Council National Survey of Health and Development (Wadsworth et al. 2004) and the UK National Child Development Study (Blundell et al. 2005). Two recent initiatives, the Norwegian autism birth cohort study (Fink 2004) and the Canadian Allergy, Genetics & Environment birth cohort study (Sears 2005), will include the collection of DNA samples alongside detailed health questionnaires for studying how the relationship between genes and the environment affect the development of disease. Both studies offer opportunities for wide-scale and long-term measurement of costs and health outcomes.

Several researchers have pointed out important differences between adults and children for selecting the appropriate methodology to conduct paediatric health economic evaluations (Ungar

and Santos 2005; Keren et al. 2004; Nujiten 2004; Tilford 2002). In addition, there have been three critical appraisals of the paediatric health economics literature (Griebsch et al. 2005; Ungar and Santos 2005; Walker and Fox-Rushby 2000). Some of the same deficiencies that compromise the quality of adult studies can be seen in the paediatric literature, namely, poor specification of perspective, incomplete costing, omission of productivity costs, reliance on intermediate outcome measures, lack of sensitivity analyses and lack of transparency. A key limitation is the lack of child-specific outcome measures and the inadequacy of adult measures for assessing health outcomes in children. In particular, there does not exist a valid and reliable measure of utility for calculating QALYs in children. To make matters worse, researchers often rely on parent proxies to report preferences and health status in very young children. Numerous studies have demonstrated a lack of agreement between parent and child reports of quality of life (Brunner et al. 2003; Eiser and Morse 2001; Saigal et al. 1998). The use of an adult measure to solicit a parent proxy report of child health status is a flawed approach to measuring outcomes in children. Given the importance attributed to CUAs as the gold standard analytic approach in international health economic guidelines, several researchers have called for the development and validation of child-specific measures of utility (Griebsch et al. 2005; Tilford 2002). Alternatively, it may be sensible to acknowledge the limitations of QALYs and seek better approaches to valuing health outcomes in all age groups. Because of the emphasis on lifetime disease prevention and the need to include family and community in valuing paediatric outcomes, alternative approaches, such as willingness-to-pay, which incorporate externalities and intangible benefits related to improved child school performance and increased productivity in caregivers may be preferred to utility assessment, which focuses on patient preferences alone. By capturing overall improvements in social welfare, a willingness-to-pay approach remains consistent with welfare economic theory and presents a result within the framework of CBA.

While there may be a shortage of high quality paediatric economic evaluations, there is no shortage of general guidelines on conducting health economic evaluations. None of the 25 independent guidelines that have been generated by various jurisdictions and agencies (Hjelmgren et al. 2001) provides insight on the application of health economic methods to the paediatric population. Rather, there is an implicit, if not flawed, assumption that these methods can be applied to all age groups. In addition, many of the guidelines lack a recommendation to include time costs. Failure to do so will bias the results when the inclusion of caregiver productivity gains is significant enough to move an intervention from cost-generating to cost-saving (Hjelmgren et al. 2001). This is illustrated by the example of intravenous immune globulin for the treatment of respiratory syncytial virus. When the newer drug palivizumab, administered by intramuscular injection, was introduced to the market, the use of intravenous immune globulin all but disappeared, despite similar direct costs, due to the much greater caregiver time required for the administration of intravenous immune globulin (Tilford 2002). Similarly, an economic evaluation of a varicella vaccination program in the US revealed that the program actually saved money when parental productivity gains were included in the analysis (Lieu et al. 1994).

In addition to inadequacies in existing guidelines, there is no single set of harmonized international guidelines, despite the need for standardized methods for transferring cost and outcome data across borders. With the maturation of the field of health economics, the time has come for the development of guidelines that focus on the paediatric population and that point out the directions for much needed methodological research.

Conclusion

The volume of publications in the international medical literature devoted to paediatric health economic evaluations has risen rapidly in the last two decades. Publications in the areas of infective and parasitic diseases, congenital anomalies and complications of pregnancy, childbirth and the puerperium accounted for the majority of publications. Disease prevention rather than treatment was the most common category of intervention. The majority of economic evaluations (78%) performed since 1998 were in the form of CEA. CUAs remained rare (less than 8%), despite being

promulgated by guidelines. The US alone produced almost half of all publications, with the UK contributing another 12%. Not surprisingly, economic evaluations from developing countries were rare, despite the urgent need for evidence-based informed decision-making to guide the allocation of limited healthcare budgets in these regions. To a certain degree, the types of interventions studied were reflective of the health priorities of particular regions. On a per country proportional basis, studies of prevention of HIV and malaria were more common in developing nations, whereas studies of treatments for asthma and birth malformations were more common in developed nations. There is evidence that the WHO is beginning to shift its focus to chronic rather than communicable diseases. Recently, emphasis has been placed on containing the burden of illness in developing countries due to chronic disease such as asthma (World Health Organization 2005).

Despite increasing global initiatives to combat disease, developing nations continue to rely on foreign economic evaluations to inform decisions regarding implementation of health programs. There is thus a great need for better methods for transferability and extrapolation of data. Future research must focus on accurate conceptual definitions of paediatric costs and consequences and in developing the tools and methods necessary to conduct high quality studies. In particular, tools that facilitate long-term measurement of cost and consequences are vital. The future of paediatric health economic evaluation would greatly benefit from an international effort to harmonize guidelines and to recognize the special needs of children.

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Acknowledgements

This research was supported by a Canadian Institutes of Health Research New Investigator Career award. I am grateful for technical assistance provided by Ms. Deirdre Snelgrove and Ms. Sara Quirk and for useful comments provided by members of The Health Economics Network of the University of Toronto.