

**The Hospital for Sick Children  
Technology Assessment at SickKids (TASK)**

**FULL REPORT**

**WILL THE GROWTH SPURT CONTINUE? TRENDS IN CHILD HEALTH  
ECONOMIC EVALUATION: 1980 TO 2013**

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## **CONFLICTS OF INTEREST**

The authors have no conflicts of interest to disclose.

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## **ABBREVIATIONS**

PEDE	Pediatric Economic Database Evaluation
CBA	cost benefit analysis
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CUA	cost-utility analysis
HIV	human immunodeficiency virus
HPV	human papilloma virus
ICD	International Classification of Diseases
QALY	quality adjusted life year
QOL	quality of life
RSV	respiratory syncytial virus
WHO	World Health Organization

# SUMMARY

## Introduction

Economic evaluations conducted as part of health technology assessments in pediatric populations have unique features compared to those conducted in adults. The Pediatric Economic Database Evaluation (PEDE) project includes a comprehensive database of pediatric health economic evaluations published since 1980. The objective was to identify significant trends over time as well as methodological gaps to improve the quality of future studies and evidence for decision-making.

## Methods

Medical and grey literature were searched for pediatric economic evaluations, key characteristics were extracted, frequencies were tabulated and selected cross-tabulations were performed. Differences in study characteristics between early (1980 and 1999) and late (2000 and 2013) pediatric economic evaluations were assessed using a chi-squared statistic.

## Results

A total of 2630 pediatric economic evaluations were published between 1980 and 2013 with an average annual growth rate of 15%. Substantially more cost-effectiveness analyses (CEAs) and cost utility analyses (CUAs) were published compared with cost benefit analyses (CBAs) and cost minimization analyses (CMAs) (64.5% and 24.0% versus 7.7% and 3.7%, respectively). This trend was consistent regardless of the type of intervention, disease or age group studied. A trend toward higher proportions of CUAs and CEAs was evident in the later period ( $\chi^2$   $p < 0.0001$ ). Other significant trends included more publications in health economics/policy journals and sub-specialty journals in the later period ( $\chi^2$   $p < 0.0001$ ), a higher proportion of studies of preventive interventions in the later period ( $\chi^2$   $p < 0.0001$ ), and more studies in children and fewer in perinates in the later period ( $\chi^2$   $p < 0.0001$ ). Overall the most common disease class studied was infectious diseases (29%).



## **Conclusions**

The field of pediatric economic evaluation continues to grow in volume and methodologic complexity. While CUAs have increased, the quality of CUAs remains unknown. Although most studies are in infectious disease, the volume of publications may not align with emerging child health priorities and target populations, such as adolescent health, injury, developmental disabilities, mental health, and the use of personalized medicine. Increasing economic evaluations in these areas will enhance pediatric decision-making.

# 1 INTRODUCTION

Health economic evaluations provide a comparison of the costs and health consequences of various interventions in a specified population. Results of economic evaluations are used by health practitioners and decision makers to assist with both clinical treatment and health policy decisions(1, 2). However, economic evaluations conducted in pediatric populations have unique features and challenges when compared with those conducted in adults. This includes the impact of child growth and development on disease processes and intervention effectiveness; a reliance on care-giving adults such as parents and teachers to facilitate access to healthcare services and act as a proxy for reporting health outcomes; the inability to accurately measure preferences for health states for very young children and infants; and the importance of considering lost productivity of caregivers and over a child's lifetime(3-6).

The Pediatric Economic Database Evaluation (PEDE) project was developed to identify methodological gaps in order to improve the quality of pediatric economic evaluations. PEDE is a publicly available, searchable, comprehensive database of pediatric economic evaluations published since 1980(7, 8). An initial analysis of pediatric economic evaluations in the database covering the period from 1980 to 1999 indicated that the annual volume of studies was growing but that cost utility analyses were infrequently conducted, suggesting the need for greater methodological developments in ascertaining child health utilities(9).

Continuing to monitor trends in pediatric economic evaluations will highlight areas of recent growth in the field as well as identify areas for future methodological developments in pediatric health economics. This could help advance methodologies in child health economic evaluation and ultimately enhance pediatric healthcare decision-making. Although globally infectious diseases have been a key focus in pediatric populations (10), in recent years shifts in priorities in child health include a greater policy emphasis on chronic non-infectious diseases, mental health, and conditions resulting from prematurity of birth(11, 12). There has also been a recent growth in the fields of genetics and personalized medicine for primary and secondary prevention of conditions affecting children over their lifetime (13-15). Economic evaluations of emerging technologies are essential to inform budget allocation decision-making, but it remains unclear whether shifts in child health priorities are reflected in the pediatric health economic literature.

The objectives of this study are to report and evaluate trends in pediatric health economic evaluation over the period of 1980 to 2013. The analysis compared study characteristics between two periods: 1980 to 1999 (early period) and 2000 to 2013 (late period).

## **2 METHODS**

### **2.1 Data Source and Study Selection**

The analysis was conducted using the PEDE database, a comprehensive database of all pediatric economic evaluations published since January 1, 1980. A publication is eligible to be included in PEDE if one or more comparators exists and descriptions of both costs and health outcomes are present. Eligible studies examined interventions directed at children of any age, or at pregnant or breastfeeding women as long as outcomes were measured in the offspring. The economic evaluation did not have to be the primary objective of the study to be eligible for the database. Detailed inclusion and exclusion criteria for determining eligibility are provided elsewhere (7). Because the database focuses on patient health outcomes rather than the structures and processes of health care, studies of interventions consisting of a guideline, a quality improvement process, or a new operating procedure or policy targeted toward improving practice or efficiency were excluded. Inter-rater reliability training is performed for all reviewers performing citation selection and data extraction to achieve a high level agreement (kappa values >0.9).

### **2.2 Search Strategy**

PEDE is updated annually using custom search strategies for retrieval of citations designed to achieve high sensitivity. Economic and medical literature citation databases routinely searched include MEDLINE, CINAHL, EMBASE, IPA, EconLit, the Cochrane Collection, NHS EED, DARE, HTA, and ERIC. Over 73 web sites of HTA agencies and research groups are also searched for inclusion of eligible grey literature. The full search strategy for each citation database is available on request.

### **2.3 Data Collection**

The database includes characteristics for each citation and is linked to a searchable bibliographic database containing the full citation information and abstract. Variables extracted for each citation include:

- year
- journal type (dentistry, general medicine, health economics/policy/methods, pediatrics/perinatal medicine, pharmacology, public health, sub-specialty medicine, other)
- target population (free-text)

- disease classification (based on International Classification of Diseases (ICD)-9 Clinical Modification (CM) or ICD-10 schema)
- age group (perinate, neonate, infant, child, adolescent, adult)
- intervention(s) studied
- intervention category (dental, detection, diagnosis, educational, health care delivery, health program, health treatment, health prevention, surgical)
- health outcome(s) (free-text)
- analytical technique (CMA, CEA, CUA, CBA)

For free-text variables, summary categories are used when possible and recorded in the database. On-line data entry is performed using REDCap, a secure, web-based application designed to support data capture for research studies (16), and data are managed using Microsoft Access (Redmond, WA) and EndNote (Philadelphia, PA). Additional details on the development of the database and variable definitions are provided elsewhere (7, 17).

## **2.4 Data Analysis**

Trends in the pediatric economic evaluations were explored by performing one-way frequency distributions and two-way cross-tabulations on variables within the database. Descriptive statistics were used to describe the key characteristics of publications including publication year, disease category, intervention type, outcome measures, age group and target population. Data analyses were performed using Microsoft Excel (Redmond, WA).

The trend analysis considered two main periods: 1980 to 1999 (early period) and 2000 to 2013 (late period). Study characteristics were compared between periods using a chi-squared statistic. For the purposes of analysis, only the primary study outcome was considered.

### 3 RESULTS

Trends over time and difference between early and late intervals are presented for volume of publications, analytic technique, journal type, intervention type, outcome measures, age group, disease category and target population. Select cross-tabulation by age group and by analytic technique are also presented.

#### 3.1 Volume of Publications

Between 1980 and 2013, a total of 2630 pediatric economic evaluations were published, with numbers steadily increasing over time (Table 1). Between 1980 and 1989, there were 154 studies published (5.9% of the total), rising to 655 (24.9%) between 1990 and 1999, and increasing again to 1335 (50.8%) between 2000 and 2009. Between the four-year period of 2010 and 2013, there were 486 publications (18.5%). The average annual increase in publication volume between 1980 and 2013 was 15.2%.

Table 1. Publications per 10-year period (n=2630)

Year	n	%	% change
1980-1989	154	5.9%	--
1990-1999	655	24.9%	325.3%
2000-2009	1335	50.8%	103.8%
2010-2013	486	18.5%	--
TOTAL	2630	100.0%	

### **3.2 Analytic Technique**

Economic evaluations are often classified based on the analytic technique. The four main types are cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), or cost-minimization analysis (CMA). Of the 2,630 economic evaluations included in PEDE, 64.5% are CEAs, 24.0% are CUAs, 7.7% are CBAs, and 3.7% are CMAs.

The distribution of the types of analyses have changed significantly over time ( $X^2$   $p < 0.0001$ ). Both CEAs and CUAs have increased over time while the CMAs and CBAs have decreased. This trend can be observed by looking at 10-year periods and when comparing early (1980 to 1999) versus late (2000 to 2013) periods (Table 2 and Table 3). More recently there has been a trend of decreasing CEAs between 2010 and 2013 compared with earlier decades. This decrease in CEAs was offset by an increase in CUAs during the same period (Figure 1). In 2009, CUA, the approach recommended by economic evaluation guidelines (1, 2), overtook CEA as the most common type of analytic technique for the first time.

Table 2. Publications per 10-year interval by analytic technique (n=2630)

Analytic Technique	1980-89			1990-99			2000-2009			2010-2013			TOTAL	
	n	col%	row%	n	col%	row%	n	col%	row%	n	col%	row%	n	%
<b>CBA</b>	39	25.3%	19.2%	77	11.8%	37.9%	74	5.5%	36.5%	13	2.7%	6.4%	203	7.7%
<b>CEA</b>	100	64.9%	5.9%	505	77.1%	29.8%	900	67.4%	53.0%	192	39.5%	11.3%	1697	64.5%
<b>CMA</b>	11	7.1%	11.2%	42	6.4%	42.9%	43	3.2%	43.9%	2	0.4%	2.0%	98	3.7%
<b>CUA</b>	4	2.6%	0.6%	31	4.7%	4.9%	318	23.8%	50.3%	279	57.4%	44.1%	632	24.0%
<b>TOTAL</b>	154	100.0%	5.9%	655	100.0%	24.9%	1335	100.0%	50.8%	486	100.0%	18.5%	2630	100.0%

Abbreviations: CBA = cost benefit analysis; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis

Table 3. Publications in early (1980-1999) and late (2000-2013) periods by analytic technique (n=2630)

Analytic Technique	Early (1980-1999)			Late (2000-2013)			TOTAL	
	n	col%	row%	n	col%	row%	n	%
<b>CBA</b>	116	14.3%	57.1%	87	4.8%	42.9%	203	7.7%
<b>CEA</b>	605	74.8%	35.7%	1092	60.0%	64.3%	1697	64.5%
<b>CMA</b>	53	6.6%	54.1%	45	2.5%	45.9%	98	3.7%
<b>CUA</b>	35	4.3%	5.5%	597	32.8%	94.5%	632	24.0%
<b>TOTAL</b>	809	100.0%	30.8%	1821	100.0%	69.2%	2630	100.0%

Abbreviations: CBA = cost benefit analysis; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis



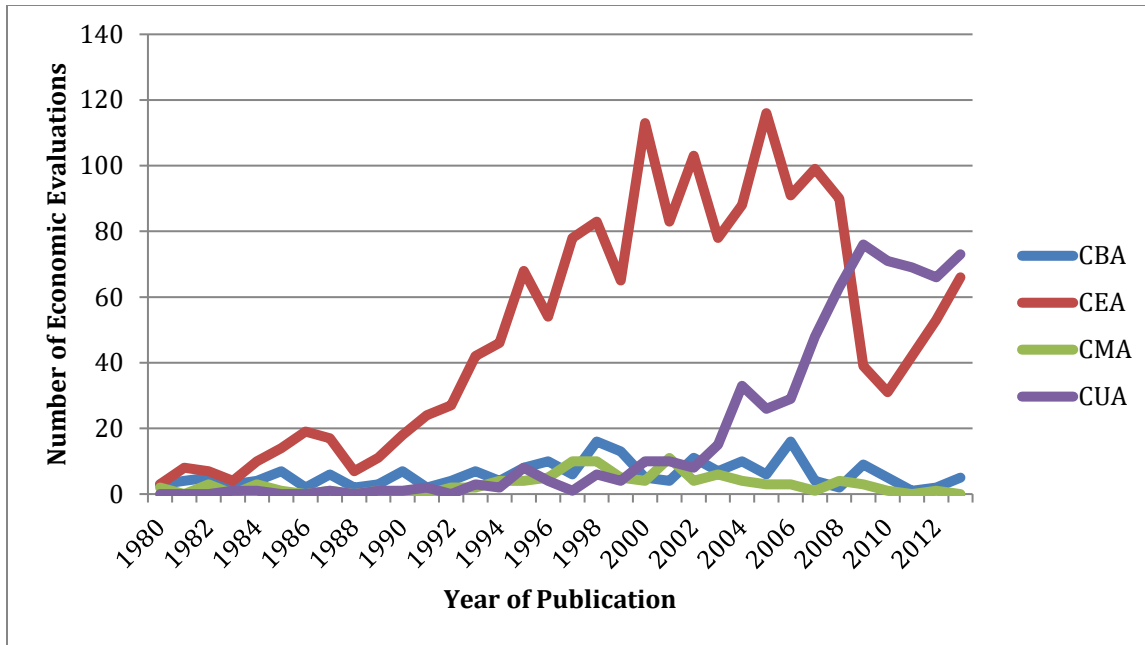


Figure 1 Distribution of economic evaluations in PEDE by year (1980-2013)

### 3.3 Journal Type

Economic evaluations may be published in a variety of journal types given the breadth of topics and analyses that are conducted. Of the eight journal categories (dentistry, general medicine, health economics/policy/methods, pediatrics/perinatal medicine, pharmacology, public health, sub-specialty medicine, other), pediatric economic evaluations were most frequently published in subspecialty medicine journals and pediatrics/perinatal medicine journals (35.3% and 26.2%, respectively). This trend was consistent across both early and late periods (Table 4). However, the overall distribution of the type of journal in which economic evaluations are published changed significantly over time ( $X^2 p < 0.0001$ ). In the late period compared with the early period, publications decreased in general medicine, pediatrics/perinatal medicine and public health journals and increased in health economics/policy/methods journals and sub-specialty medicine journals (Table 4).

Table 4. Publications in early (1980-1999) and late (2000-2013) periods by journal type (n=2630)

Journal Type	Early (1980-1999)			Late (2000-2013)			TOTAL	
	n	col%	row%	n	col%	row%	n	%
<b>Dentistry</b>	23	2.8%	43.4%	30	1.7%	56.6%	53	2.0%
<b>General medicine</b>	116	14.3%	42.5%	157	8.7%	57.5%	273	10.4%
<b>Health Economics/ policy/methods</b>	42	5.2%	16.3%	216	11.9%	83.7%	258	9.8%
<b>Pediatrics/perinatal medicine</b>	260	32.1%	37.7%	430	23.7%	62.3%	690	26.2%
<b>Pharmacology</b>	20	2.5%	40.0%	30	1.7%	60.0%	50	1.9%
<b>Public health</b>	127	15.7%	40.6%	186	10.2%	59.4%	313	11.9%
<b>Sub-specialty medicine</b>	209	25.8%	22.5%	720	39.7%	77.5%	929	35.3%
<b>Other</b>	12	1.5%	20.7%	46	2.5%	79.3%	58	2.2%
<b>TOTAL</b>	809	100.0%	30.8%	1815	100.0%	69.2%	2624	100.0%

When the analytic technique used in each of the journal types was considered (Table 5), it was observed that CEAs were most frequently published in subspecialty medicine and pediatric/perinatal journals (33.7% and 30.8%, respectively), while CUAs were most frequently published in subspecialty medicine and health economic methods/policy journals (39.6% and 18.5%, respectively). Across all journal types and periods, CEAs were the most frequently published analytic technique.

Table 5. Publications by journal type and by analytic technique (1980-2013) (n=2630 records)

Journal Type	CBA			CEA			CMA			CUA			TOTAL	
	n	row%	col%	n	row%	col%	n	row%	col%	n	row%	col%	n	%
<b>Dentistry</b>	9	17.0%	4.4%	40	75.5%	2.4%	2	3.8%	2.1%	2	3.8%	0.3%	53	2.0%
<b>General medicine</b>	23	8.4%	11.3%	190	69.6%	11.2%	8	2.9%	8.2%	52	19.0%	8.2%	273	10.4%
<b>Health economics/ policy/ methods</b>	13	5.0%	6.4%	119	46.1%	7.0%	9	3.5%	9.3%	117	45.3%	18.5%	258	9.8%
<b>Pediatrics/perinatal medicine</b>	45	6.5%	22.2%	522	75.7%	30.8%	27	3.9%	27.8%	96	13.9%	15.2%	690	26.2%
<b>Pharmacology</b>	2	3.9%	1.0%	33	64.7%	1.9%	1	2.0%	1.0%	15	29.4%	2.4%	51	1.9%
<b>Public health</b>	41	13.1%	20.2%	185	59.1%	10.9%	5	1.6%	5.2%	82	26.2%	13.0%	313	11.9%
<b>Sub-specialty medicine</b>	65	7.0%	32.0%	571	61.5%	33.7%	43	4.6%	44.3%	250	26.9%	39.6%	929	35.3%
<b>Other</b>	5	8.5%	2.5%	35	59.3%	2.1%	2	3.4%	2.1%	17	28.8%	2.7%	59	2.2%
<b>TOTAL</b>	203	7.7%	100.0%	1695	64.4%	100.0%	97	3.7%	100.0%	631	24.0%	100.0%	2630	100.0%

Abbreviations: CBA = cost benefit analysis; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis

### 3.4 Intervention Type

Economic evaluations may be conducted for a wide range of types of interventions. Of the nine categories of interventions considered in this analysis (dental, detection, diagnosis, educational, health care delivery, health program, health treatment, health prevention, surgical), economic evaluations were most frequently conducted for health prevention, health treatments and detection interventions (31.7%, 24.2% and 15.9%, respectively). This trend was observed in both early (1980-1999) and late periods (2000-2013) (Table 6). However, the overall distribution of the type of intervention on which economic evaluations are conducted changed significantly over time ( $X^2 p < 0.0001$ ). In the late period compared with the early period, an increase in the evaluation of health prevention interventions from 25.0% to 34.7% was observed, accompanied by small decreases ( $\leq 5\%$ ) that were distributed across the other interventions.

Table 6. Publications in early (1980-1999) and late (2000-2013) periods by intervention type (n=2630)

Intervention Category	Early (1980-1999)			Late (2000-2013)			TOTAL	
	n	col%	row%	n	col%	row%	n	%
Dental	31	3.8%	45.6%	37	2.0%	54.4%	68	2.6%
Detection	150	18.5%	35.9%	268	14.7%	64.1%	418	15.9%
Diagnosis	25	3.1%	32.5%	52	2.9%	67.5%	77	2.9%
Educational	15	1.9%	19.0%	64	3.5%	81.0%	79	3.0%
Health care delivery	55	6.8%	32.4%	115	6.3%	67.6%	170	6.5%
Health program	90	11.1%	42.3%	123	6.8%	57.7%	213	8.1%
Health treatment	196	24.2%	30.8%	441	24.2%	69.2%	637	24.2%
Health prevention	202	25.0%	24.2%	631	34.7%	75.8%	833	31.7%
Surgical	45	5.6%	33.8%	88	4.8%	66.2%	133	5.1%
<b>TOTAL</b>	<b>809</b>	<b>100.0%</b>	<b>30.8%</b>	<b>1819</b>	<b>100.0%</b>	<b>69.2%</b>	<b>2630</b>	<b>100.0%</b>

When the analytic technique used for each of the intervention types was considered (Table 7 and Figure 2), it was observed that CBAs were most frequently conducted for health prevention interventions (49.8%), CEAs were most frequently conducted for health treatment and health prevention interventions (25.5% and 24.2%, respectively), CUAs were most frequently conducted on health prevention interventions (50.5%) and CMAs were most frequently conducted for health treatment interventions (41.8%). Although CEAs were frequently used to analyze all intervention types, diagnostic and surgical interventions were predominantly studied using CEAs (81.8% and 80.5%, respectively).

Table 7. Publications by intervention type and by analytic technique (1980-2013) (n=2630 records)

Intervention Type	CBA			CEA			CMA			CUA			TOTAL	
	n	row%	col%	n	row%	col%	n	row%	col %	n	row%	col%	n	%
Dental	10	14.7%	4.9%	52	76.5%	3.1%	3	4.4%	3.1%	3	4.4%	0.5%	68	2.6%
Detection	53	12.7%	26.1%	289	69.1%	17.0%	8	1.9%	8.2%	68	16.3%	10.8%	418	15.9%
Diagnosis	3	3.9%	1.5%	63	81.8%	3.7%	2	2.6%	2.0%	9	11.7%	1.4%	77	2.9%
Educational	5	6.3%	2.5%	52	65.8%	3.1%	2	2.5%	2.0%	20	25.3%	3.2%	79	3.0%
Health care delivery	3	1.8%	1.5%	130	76.5%	7.7%	14	8.2%	14.3%	23	13.5%	3.6%	170	6.5%
Health program	18	8.5%	8.9%	159	74.6%	9.4%	13	6.1%	13.3%	23	10.8%	3.6%	213	8.1%
Health treatment	10	1.6%	4.9%	432	67.8%	25.5%	41	6.4%	41.8%	154	24.2%	24.4%	637	24.2%
Health prevention	101	12.1%	49.8%	411	49.3%	24.2%	2	0.2%	2.0%	319	38.3%	50.5%	833	31.7%
Surgical	0	0.0%	0.0%	107	80.5%	6.3%	13	9.8%	13.3%	13	9.8%	2.1%	133	5.1%
<b>TOTAL</b>	203	7.7%	100.0%	1697	64.5%	100.0%	98	3.7%	100.0%	632	24.0%	100.0%	2630	100.0%

Abbreviations: CBA = cost benefit analysis; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis

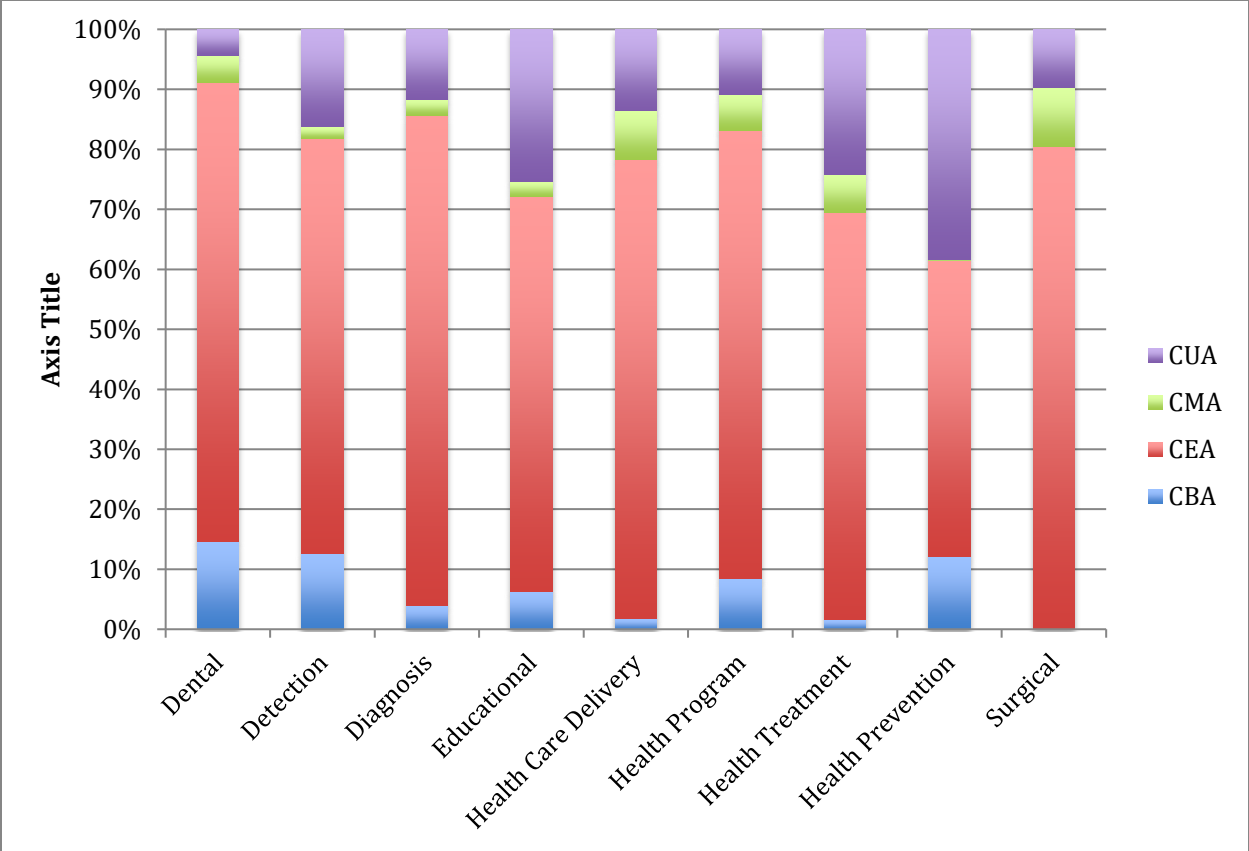


Figure 2. Analytic technique according to type of intervention studied

### 3.5 Outcome Measures

A wide variety of outcomes (n=1280) were measured across the 2630 publications in PEDE. When considering the primary outcome in each publication, the most frequent types of outcomes were QALYs or similar units, cases of non-infectious disease/condition/abnormality, cases of infectious disease/condition/abnormality and life years (22.0%, 18.6%, 13.6% and 13.2%, respectively). When comparing the early (1980-1999) and late periods (2000-2013), an increase in the use of QALYs was observed over time (4.9% versus 29.5%) paralleling the increased frequency of CUA (Table 8).

Table 8. Publications in early (1980-1999) and late (2000-2013) periods by outcome category (n=2630)

Outcome Category	Early (1980-1999)			Late (2000-2013)			TOTAL	
	n	col%	row%	n	col%	row%	n	%
Cases of complications/ adverse events	66	8.2%	44.9%	81	4.4%	55.1%	147	5.6%
Cost	0	0.0%	0.0%	26	1.4%	100.0%	26	1.0%
Cases of cures/improvements/healing	90	11.1%	49.7%	91	5.0%	50.3%	181	6.9%
Cases of infectious disease/condition/abnormality	153	18.9%	42.9%	204	11.2%	57.1%	357	13.6%
Cases of injury	9	1.1%	45.0%	11	0.6%	55.0%	20	0.8%
Life years	110	13.6%	31.6%	238	13.1%	68.4%	348	13.2%
Cases of non-infectious disease/condition/abnormality	200	24.7%	40.8%	290	15.9%	59.2%	490	18.6%
Other	6	0.7%	24.0%	34	1.9%	85.0%	40	1.5%
Changes in physiologic measure	75	9.3%	37.1%	127	7.0%	62.9%	202	7.7%
Changes in behavioural/psychosocial	21	2.6%	25.9%	60	3.3%	74.1%	81	3.1%
QALYs, or similar unit	40	4.9%	6.9%	538	29.5%	93.1%	578	22.0%
Changes in quality of life	3	0.4%	14.3%	18	1.0%	85.7%	21	0.8%
Surrogate health outcomes	5	0.6%	17.9%	23	1.3%	82.1%	28	1.1%
Time outcomes*	18	2.2%	24.3%	56	3.1%	75.7%	74	2.8%
Unspecified	0	0.0%	0.0%	6	0.3%	100.0%	6	0.2%
Cases of vaccination	13	1.6%	41.9%	18	1.0%	58.1%	31	1.2%
<b>TOTAL</b>	<b>809</b>	<b>100.0%</b>	<b>30.8%</b>	<b>1806</b>	<b>100.0%</b>	<b>68.7%</b>	<b>2630</b>	<b>100.0%</b>

\*This category refers to days in a state or days absent from a state, time to achieve an outcome or to recover

When the outcome category was grouped by analytic technique (Table 9), as expected, the outcome most frequently reported for CUAs were QALYs or similar measures (88.0%). For CEAs, the most frequently reported outcome measures were cases of non-infectious disease/condition/abnormality and life-years (23.2% and 18.1%, respectively). For CBAs, the most frequently reported clinical outcomes were cases of infectious disease/condition/abnormality and cases of non-infectious disease/condition/abnormality (35.0% and 33.5%, respectively); these outcomes were then monetized as is the standard approach in a CBA. For CMAs, cases of cures/improvements/healing were most frequently reported (28.6%).

Table 9. Number of publications by outcome category and by analytic technique (n=2630 records)

Outcome Category	CBA			CEA			CMA			CUA			TOTAL	
	n	row%	col%	n	row%	col%	n	row%	col%	n	row%	col%	n	%
Cases of complications/adverse events	5	3.4%	2.5%	127	86.4%	7.5%	14	9.5%	14.3%	1	0.7%	0.2%	147	5.6%
Cost	6	23.1%	3.0%	15	57.7%	0.9%	4	15.4%	4.1%	1	3.8%	0.2%	26	1.0%
Cases of cures/improvements	7	3.9%	3.4%	144	79.6%	8.5%	28	15.5%	28.6%	2	1.1%	0.3%	181	6.9%
Cases of infectious disease/condition/abnormality	71	19.9%	35.0%	261	73.1%	15.4%	3	0.8%	3.1%	22	6.2%	3.5%	357	13.6%
Cases of injury	3	15.0%	1.5%	16	80.0%	0.9%	1	5.0%	1.0%	0	0.0%	0.0%	20	0.8%
Life Years	11	3.2%	5.4%	308	88.5%	18.1%	7	2.0%	7.1%	22	6.3%	3.5%	348	13.2%
Cases of non-infectious disease/condition/abnormality	68	13.9%	33.5%	393	80.2%	23.2%	14	2.9%	14.3%	15	3.1%	2.4%	490	18.6%
Other	2	5.0%	1.0%	34	85.0%	2.0%	3	7.5%	3.1%	1	2.5%	0.2%	40	1.5%
Changes in physiologic measure	5	2.5%	2.5%	183	90.6%	10.8%	11	5.4%	11.2%	3	1.5%	0.5%	202	7.7%
Changes in behavioral/ psychosocial	14	17.3%	6.9%	61	75.3%	3.6%	4	4.9%	4.1%	2	2.5%	0.3%	81	3.1%
QALYs, or similar unit	4	0.7%	2.0%	18	3.1%	1.1%	0	0.0%	0.0%	556	96.2%	88.0%	578	22.0%
Changes in QOL	0	0.0%	0.0%	17	81.0%	1.0%	0	0.0%	0.0%	4	19.0%	0.6%	21	0.8%
Surrogate Health Outcomes	1	3.6%	0.5%	23	82.1%	1.4%	3	10.7%	3.1%	1	3.6%	0.2%	28	1.1%
Time Outcomes	0	0.0%	0.0%	70	94.6%	4.1%	2	2.7%	2.0%	2	2.7%	0.3%	74	2.8%
Unspecified	2	33.3%	1.0%	2	33.3%	0.1%	2	33.3%	2.0%	0	0.0%	0.0%	6	0.2%
Cases of vaccination	4	12.9%	2.0%	25	80.6%	1.5%	2	6.5%	2.0%	0	0.0%	0.0%	31	1.2%
<b>TOTAL</b>	<b>203</b>	<b>7.7%</b>	<b>100.0%</b>	<b>1697</b>	<b>64.5%</b>	<b>100.0%</b>	<b>98</b>	<b>3.7%</b>	<b>100.0</b>	<b>632</b>	<b>24.0%</b>	<b>100.0</b>	<b>2630</b>	<b>100.0%</b>

Abbreviations: CBA = cost benefit analysis; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis



### 3.6 Age Group

The pediatric population is a heterogeneous group that is often classified and studied according to standard age groups related to periods of maturation and development. These age groups are typically perinate (antenatal period), neonate (newborn to < 1 month), infant (1 month to < 1 year), child (> 1 year to 12 years), adolescent (13 to 18 years), and adult (19 and older). The inclusion of adults age groups occurred i) in studies where interventions were targeted at pregnant or breastfeeding women and where outcomes were measured in offspring, or ii) in studies with lifetime time horizons. The most frequently studied age group was the child at 40.6% of publications, which was consistent across both early (1980-1999) and late periods (2000-2013) (Table 10). However, the overall distribution of the age groups studied changed significantly over time ( $X^2 p < 0.0001$ ). In the late period compared with the early period, economic evaluations of children increased from 35.7% to 42.9% while they decreased in perinates from 13.1% to 5.1% with small fluctuations (<5%) observed in other age groups.

Table 10. Publications in early (1980-1999) and late (2000-2013) periods by age category (n=2630 records)

Age	Early (1980-1999)			Late (2000-2013)			TOTAL	
	n	col%	row%	n	col%	row%	n	%
<b>Perinate</b>	162	13.1%	54.9%	133	5.1%	45.1%	295	7.6%
<b>Neonate</b>	171	13.8%	27.1%	460	17.5%	72.9%	631	16.3%
<b>Infant</b>	240	19.4%	34.6%	454	17.3%	65.4%	694	18.0%
<b>Child</b>	442	35.7%	28.2%	1126	42.9%	71.8%	1568	40.6%
<b>Adolescent</b>	190	15.3%	31.8%	408	15.5%	68.2%	598	15.5%
<b>Adult</b>	34	2.7%	44.2%	43	1.6%	55.8%	77	2.0%
<b>TOTAL</b>	1239	100.0%	32.1%	2624	100.0%	67.9%	3863	100.0%

Each record may contain multiple age groups; a total of 3863 age groups were studied

When the type of intervention studied was categorized by age group (Table 11), diagnostic interventions were most frequently evaluated in perinates (41.4%), health prevention and detection interventions were most frequently studied in neonates (29.3% and 26.9%), health prevention interventions were most frequently studied in infants (43.6%), health prevention and health treatment interventions were most frequently studied in both children (33.0 and 29.8%) and adolescents (26.9% and 29.15). For adults included in these publications, health prevention interventions were most frequently studied (48.1%).

Table 11. Publications by intervention type and by age group (n=2630 records)  
**(A = Perinate, Neonate, Infant; B = Child, Adolescent, Adult, Total)**

**A**

INTERVENTION	Perinate (antenatal period)			Neonate (newborn to ≤ 1 month)			Infant (1 month to ≤ 1 year)		
	n	row%	col%	n	row%	col%	n	row%	col%
Dental	0	0.0%	0.0%	1	1.0%	0.2%	7	7.3%	1.0%
Detection	122	23.6%	41.4%	170	32.9%	26.9%	52	10.1%	7.5%
Diagnosis	5	3.9%	1.7%	20	15.7%	3.2%	28	22.0%	4.0%
Educational	0	0.0%	0.0%	7	6.4%	1.1%	13	11.9%	1.9%
Health Care Delivery	24	8.8%	8.1%	52	19.0%	8.2%	53	19.3%	7.6%
Health Program	32	10.6%	10.8%	70	23.2%	11.1%	55	18.2%	7.9%
Health Treatment	38	4.1%	12.9%	104	11.1%	16.5%	140	15.0%	20.1%
Health Prevention	71	5.6%	24.1%	185	14.6%	29.3%	304	24.1%	43.6%
Surgical	3	1.4%	1.0%	20	9.2%	3.2%	44	20.2%	6.3%
<b>TOTAL</b>	295	7.7%	100.0%	631	16.4%	100.0%	697	18.1%	100.0%

**B**

Intervention Type	Child (> 1 year to 12 years)			Adolescent (13 to 18 years)			Adult (19 and older)		TOTAL		
	n	row%	col%	n	row%	col%	n	row%	col%	n	%
Dental	64	66.7%	4.1%	24	25.0%	4.0%	0	0.0%	0.0%	96	2.5%
Detection	113	21.9%	7.2%	52	10.1%	8.7%	7	1.4%	13.0%	516	13.4%
Diagnosis	52	40.9%	3.3%	20	15.7%	3.3%	2	1.6%	3.7%	127	3.3%
Educational	58	53.2%	3.7%	30	27.5%	5.0%	1	0.9%	1.9%	109	2.8%
Health Care Delivery	97	35.4%	6.2%	46	16.8%	7.7%	2	0.7%	3.7%	274	7.1%
Health Program	100	33.1%	6.4%	42	13.9%	7.0%	3	1.0%	5.6%	302	7.9%
Health Treatment	468	50.1%	29.8%	174	18.6%	29.1%	10	1.1%	18.5%	934	24.3%
Health Prevention	517	40.9%	33.0%	161	12.7%	26.9%	26	2.1%	48.1%	1264	32.9%
Surgical	99	45.4%	6.3%	49	22.5%	8.2%	3	1.4%	5.6%	218	5.7%
<b>TOTAL</b>	1569	40.8%	100.0%	598	15.6%	100.0%	54	1.4%	1.0%	3844	100.0%

Each record may contain multiple age groups; a total of 3863 age groups were studied)

When outcome measures were categorized by age group (Table 12), cases of non-infectious disease/condition/abnormality were most frequently reported for perinates (39.0%). For neonates, life-years, QALYs or similar measures and cases of non-infectious disease/condition/abnormality were the most frequently reported outcomes (22.5%, 22.3% and 21.2%, respectively). For infants, QALYs or similar measures and cases of infectious disease/condition/abnormality were the most frequently reported outcomes (20.7% and 18.0%, respectively). Among both children and adolescents, the most frequently reported outcomes were QALYs or similar measures (23.2% and 19.1%). For adults included in these publications, cases of infectious disease/condition/abnormality was the most frequently reported outcome (24.1%).

Table 12 Publications by summary outcome and by age group (n=2630 records)  
**(A = Perinate, Neonate, Infant; B = Child, Adolescent, Adult, Total)**

**A**

OUTCOMES	Perinate (antenatal period)			Neonate (newborn to ≤ 1 month)			Infant (1 month to ≤ 1 year)		
	n	row%	col%	n	row%	col%	n	row%	col%
Cases of complications/adverse events	9	3.8%	3.1%	23	9.6%	3.6%	48	20.1%	6.9%
Cost	2	5.3%	0.7%	4	10.5%	0.6%	9	23.7%	1.3%
Cases of cures/improvements/healing	4	1.4%	1.4%	24	8.5%	3.8%	51	18.1%	7.3%
Cases of infectious disease/condition/abnormality	45	8.1%	15.3%	82	14.8%	13.0%	125	22.6%	18.0%
Cases of injury	1	3.0%	0.3%	3	9.1%	0.5%	5	15.2%	0.7%
Life Years	45	8.9%	15.3%	142	28.0%	22.5%	104	20.5%	15.0%
Cases of non-infectious disease/condition/abnormality	115	17.0%	39.0%	134	19.8%	21.2%	101	14.9%	14.6%
Other	2	3.6%	0.7%	8	14.3%	1.3%	7	12.5%	1.0%
Changes in physiologic measure	36	12.9%	12.2%	41	14.7%	6.5%	35	12.6%	5.0%
Changes in behavioural/psychosocial	1	0.9%	0.3%	12	10.3%	1.9%	10	8.6%	1.4%
QALYs, or similar unit	31	3.9%	10.5%	141	17.6%	22.3%	144	17.9%	20.7%
Changes in QOL	0	0.0%	0.0%	0	0.0%	0.0%	7	17.9%	1.0%
Surrogate Health Outcomes	2	4.7%	0.7%	7	16.3%	1.1%	6	14.0%	0.9%
Time Outcomes	0	0.0%	0.0%	8	6.4%	1.3%	29	23.2%	4.2%
Unspecified	0	0.0%	0.0%	1	11.1%	0.2%	2	22.2%	0.3%
Cases of vaccination	2	4.9%	0.7%	1	2.4%	0.2%	11	26.8%	1.6%
<b>TOTAL</b>	<b>295</b>	<b>7.7%</b>	<b>100.0%</b>	<b>631</b>	<b>16.4%</b>	<b>100.0%</b>	<b>694</b>	<b>18.1%</b>	<b>100.0%</b>

Table 12, continued

**B**

OUTCOMES	Child (> 1 year to 12 years)			Adolescent (13 to 18 years)			Adult (19 and older)			TOTAL	
	n	row%	col%	n	row%	col%	n	row%	col%	n	%
Cases of complications/adverse events	107	44.8%	6.8%	48	20.1%	8.0%	4	1.7%	7.4%	239	6.2%
Cost	18	47.4%	1.1%	5	13.2%	0.8%	0	0.0%	0.0%	38	1.0%
Cases of cures/improvements/healing	147	52.1%	9.4%	51	18.1%	8.5%	5	1.8%	9.3%	282	7.3%
Cases of infectious disease/condition/abnormality	204	36.9%	13.0%	84	15.2%	14.0%	13	2.4%	24.1%	553	14.4%
Cases of injury	17	51.5%	1.1%	7	21.2%	1.2%	0	0.0%	0.0%	33	0.9%
Life Years	155	30.5%	9.9%	56	11.0%	9.4%	6	1.2%	11.1%	508	13.2%
Cases of non-infectious disease/condition/abnormality	231	34.1%	14.7%	88	13.0%	14.7%	8	1.2%	14.8%	677	17.6%
Other	29	51.8%	1.8%	10	17.9%	1.7%	0	0.0%	0.0%	56	1.5%
Changes in physiologic measure	113	40.6%	7.2%	50	18.0%	8.4%	3	1.1%	5.6%	278	7.2%
Changes in behavioural/psychosocial	56	48.3%	3.6%	37	31.9%	6.2%	0	0.0%	0.0%	116	3.0%
QALYs, or similar unit	364	45.3%	23.2%	114	14.2%	19.1%	9	1.1%	16.7%	803	20.9%
Changes in QOL	19	48.7%	1.2%	11	28.2%	1.8%	2	5.1%	3.7%	39	1.0%
Surrogate health outcomes	20	46.5%	1.3%	8	18.6%	1.3%	0	0.0%	0.0%	43	1.1%
Time outcomes	61	48.8%	3.9%	24	19.2%	4.0%	3	2.4%	5.6%	125	3.3%
Unspecified	4	44.4%	0.3%	2	22.2%	0.3%	0	0.0%	0.0%	9	0.2%
Cases of vaccination	23	56.1%	1.5%	3	7.3%	0.5%	1	2.4%	1.9%	41	1.1%
<b>TOTAL</b>	1568	40.8%	100.0%	598	15.6%	100.0%	54	1.4%	100.0%	3844	100.0%

### 3.7 Disease category

Established disease classifications schema were applied to the publications in PEDE. Over the period covered by the database (1980-2013), both ICD-9-CM and ICD-10 schema (18, 19) were used and are merged in this analysis. Overall, infective and parasitic diseases were most frequently studied in pediatric populations (29.2%), a trend which was consistent in both early and late periods (Table 13).

Table 13. Publications in early (1980-1999) and late (2000-2013) periods by ICD9/10 disease category (n=2630)

ICD 9/10 DISEASE CLASSIFICATION	Early (1980-1999)			Late (2000-2013)			TOTAL	
	n	col%	row%	n	col%	row%	n	%
Accidents, poisonings, and violence	36	4.5%	52.2%	33	1.8%	47.8%	69	2.6%
Blood and blood-forming organs	29	3.6%	22.1%	102	5.6%	77.9%	131	5.0%
Certain conditions originating in the perinatal period	70	8.7%	70.0%	30	1.7%	30.0%	100	3.8%
Infective and parasitic	191	23.7%	24.9%	576	31.7%	75.1%	329	29.2%
Pregnancy, childbirth and the puerperium	84	10.4%	44.4%	105	5.8%	55.6%	189	7.2%
Circulatory system	14	1.7%	26.9%	38	2.1%	73.1%	52	2.0%
Congenital anomalies	88	10.9%	46.8%	100	5.5%	53.2%	188	7.1%
Dental	32	4.0%	97.0%	1	0.1%	3.0%	33	1.3%
Digestive system	22	2.7%	30.1%	51	2.8%	69.9%	73	2.8%
Nervous system and sensory organs	34	4.2%	22.1%	120	6.6%	77.9%	154	5.9%
Genitourinary system	20	2.5%	24.7%	61	3.4%	75.3%	81	3.1%
Musculoskeletal system	4	0.5%	16.0%	21	1.2%	84.0%	25	1.0%
Skin and sub-cutaneous tissue	3	0.4%	11.5%	23	1.3%	88.5%	26	1.0%
Respiratory system	31	3.8%	17.4%	147	8.1%	82.6%	178	6.8%
Endocrine, nutrition and metabolism, and immunity disorders	47	5.8%	30.3%	108	5.9%	69.7%	155	5.9%
External causes of morbidity and mortality	0	0.0%	0.0%	28	1.5%	100.0%	28	1.1%
Factors influencing health status and contact with health services	3	0.4%	3.2%	92	5.1%	96.8%	95	3.6%
General health	43	5.3%	62.3%	26	1.4%	37.7%	69	2.6%
Mental disorders	12	1.5%	14.1%	73	4.0%	85.9%	85	3.2%
Neoplasms	26	3.2%	36.1%	46	2.5%	63.9%	72	2.7%
Symptoms, Signs and Ill-defined Conditions	18	2.2%	33.3%	36	2.0%	81.8%	54	2.1%
Other	2	0.2%	66.7%	1	0.1%	33.3%	3	0.1%
<b>TOTAL</b>	<b>807</b>	<b>100.0%</b>	<b>30.7%</b>	<b>1817</b>	<b>100.0%</b>	<b>69.1%</b>	<b>2630</b>	<b>100.0%</b>

When the ICD-9/10 disease classification was categorized by analytic technique (Table 14), CEAs and CUAs were most frequently conducted on infectious and parasitic diseases (24.6% and 40.6%, respectively). No CUAs were conducted in the area of dental diseases or general health conditions. In all disease categories, CEAs were most frequently conducted with the lowest proportion of CEAs being 39.3% for external causes of morbidity and mortality.

Table 14. Publications by ICD-9/10 disease classification and by analytic technique (n=2630 records)

ICD 9/10 DISEASE CLASSIFICATION	CBA			CEA			CMA			CUA			TOTAL	
	n	row%	col%	n	row%	col%	n	row%	col%	n	row%	col%	n	%
Accidents, poisonings, and violence	6	8.7%	3.0%	51	73.9%	3.0%	7	10.1%	7.2%	5	7.2%	0.8%	69	2.6%
Blood and blood-forming organs	4	3.1%	2.0%	85	64.9%	5.0%	5	3.8%	5.2%	37	28.2%	5.9%	131	5.0%
Certain conditions originating in the perinatal period	4	4.0%	2.0%	76	76.0%	4.5%	5	5.0%	5.2%	15	15.0%	2.4%	100	3.8%
Infective and parasitic	83	10.8%	40.9%	418	54.5%	24.6%	10	1.3%	10.3%	256	33.4%	40.6%	767	29.2%
Pregnancy, childbirth and the puerperium	12	6.3%	5.9%	152	80.4%	9.0%	8	4.2%	8.2%	17	9.0%	2.7%	189	7.2%
Circulatory system	3	5.8%	1.5%	37	71.2%	2.2%	3	5.8%	3.1%	9	17.3%	1.4%	52	2.0%
Congenital anomalies	27	14.4%	13.3%	137	72.9%	8.1%	6	3.2%	6.2%	18	9.6%	2.9%	188	7.1%
Dental	4	12.1%	2.0%	27	81.8%	1.6%	2	6.1%	2.1%	0	0.0%	0.0%	33	1.3%
Digestive system	1	1.4%	0.5%	59	80.8%	3.5%	4	5.5%	4.1%	9	12.3%	1.4%	73	2.8%
Nervous system and sensory organs	4	2.6%	2.0%	87	56.5%	5.1%	7	4.5%	7.2%	56	36.4%	8.9%	154	5.9%
Genitourinary system	3	3.7%	1.5%	43	53.1%	2.5%	6	7.4%	6.2%	29	35.8%	4.6%	81	3.1%
Musculoskeletal system	0	0.0%	0.0%	19	76.0%	1.1%	2	8.0%	2.1%	4	16.0%	0.6%	25	1.0%
Skin and sub-cutaneous tissue	0	0.0%	0.0%	17	65.4%	1.0%	1	3.8%	1.0%	8	30.8%	1.3%	26	1.0%
Respiratory system	2	1.1%	1.0%	124	69.7%	7.3%	3	1.7%	3.1%	49	27.5%	7.8%	178	6.8%
Endocrine, nutrition and metabolism, and immunity disorders	16	10.3%	7.9%	103	66.5%	6.1%	4	2.6%	4.1%	32	20.6%	5.1%	155	5.9%
External causes of morbidity and mortality	5	17.9%	2.5%	11	39.3%	0.6%	1	3.6%	1.0%	11	39.3%	1.7%	28	1.1%
Factors influencing health status and contact with health services	11	11.6%	5.4%	52	54.7%	3.1%	3	3.2%	3.1%	29	30.5%	4.6%	95	3.6%
General health	10	14.5%	4.9%	54	78.3%	3.2%	5	7.2%	5.2%	0	0.0%	0.0%	69	2.6%
Mental disorders	5	5.9%	2.5%	50	58.8%	2.9%	3	3.5%	3.1%	27	31.8%	4.3%	85	3.2%
Neoplasms	1	1.4%	0.5%	45	62.5%	2.7%	10	13.9%	10.3%	16	22.2%	2.5%	72	2.7%
Symptoms, Signs and Ill-defined Conditions	2	3.7%	1.0%	46	85.2%	2.7%	2	3.7%	2.1%	4	7.4%	0.6%	54	2.1%
Other	0	0.0%	0.0%	3	100.0%	0.2%	0	0.0%	0.0%	0	0.0%	0.0%	3	0.1%
<b>TOTAL</b>	<b>203</b>	<b>7.7%</b>	<b>100.0%</b>	<b>1696</b>	<b>64.5%</b>	<b>100.0%</b>	<b>97</b>	<b>3.7%</b>	<b>100.0%</b>	<b>631</b>	<b>24.0%</b>	<b>100.0%</b>	<b>2630</b>	<b>100.0%</b>

Abbreviations: CBA = cost benefit analysis; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis



When the ICD-9/10 disease classification was categorized by intervention type (Table 15), some associations were observed. For example, detection interventions were most frequently studied in congenital abnormalities (24.9%) while health prevention interventions were most frequently studied in infective and parasitic diseases (66.0%).

Table 15. Publications by ICD-9/10 disease classification and by intervention type (n=2630 records)

(**A** = Detection, Diagnosis, Educational; **B** = Health Care Delivery, Health Care Program, Health Treatment; **C** = Surgical, Dental, Total)

**A**

ICD 9/10 DISEASE CLASSIFICATION	Detection			Diagnosis			Educational		
	n	row%	col%	n	row%	col%	n	row%	col%
Accidents, poisonings, and violence	6	8.7%	1.4%	1	1.4%	1.3%	2	2.9%	2.5%
Blood and blood-forming organs	34	26.0%	8.1%	4	3.1%	5.2%	0	0.0%	0.0%
Certain conditions originating in the perinatal period	13	13.0%	3.1%	3	3.0%	3.9%	0	0.0%	0.0%
Infective and parasitic	67	8.7%	16.0%	14	1.8%	18.2%	7	0.9%	8.9%
Pregnancy, childbirth and the puerperium	42	22.2%	10.0%	1	0.5%	1.3%	1	0.5%	1.3%
Circulatory system	14	26.9%	3.3%	4	7.7%	5.2%	2	3.8%	2.5%
Congenital anomalies	104	55.3%	24.9%	14	7.4%	18.2%	1	0.5%	1.3%
Dental	2	6.1%	0.5%	0	0.0%	0.0%	0	0.0%	0.0%
Digestive system	6	8.2%	1.4%	6	8.2%	7.8%	1	1.4%	1.3%
Nervous system and sensory organs	49	31.8%	11.7%	6	3.9%	7.8%	0	0.0%	0.0%
Genitourinary system	4	4.9%	1.0%	7	8.6%	9.1%	0	0.0%	0.0%
Musculoskeletal system	3	12.0%	0.7%	1	4.0%	1.3%	0	0.0%	0.0%
Skin and sub-cutaneous tissue	0	0.0%	0.0%	1	3.8%	1.3%	2	7.7%	2.5%
Respiratory system	7	3.9%	1.7%	4	2.2%	5.2%	10	5.6%	12.7%
Endocrine, nutrition and metabolism, and immunity disorders	44	28.4%	10.5%	4	2.6%	5.2%	11	7.1%	13.9%
External causes of morbidity and mortality	2	7.1%	0.5%	0	0.0%	0.0%	4	14.3%	5.1%
Factors influencing health status and contact with health services	3	3.2%	0.7%	0	0.0%	0.0%	20	21.1%	25.3%
General health	1	1.4%	0.2%	0	0.0%	0.0%	3	4.3%	3.8%
Mental disorders	7	8.2%	1.7%	1	1.2%	1.3%	11	12.9%	13.9%
Neoplasms	9	12.5%	2.2%	2	2.8%	2.6%	1	1.4%	1.3%
Symptoms, signs and ill-defined conditions	1	1.9%	0.2%	4	7.4%	5.2%	3	5.6%	3.8%
Other	0	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%
<b>TOTAL</b>	<b>418</b>	<b>15.9%</b>	<b>100.0%</b>	<b>77</b>	<b>2.9%</b>	<b>100.0%</b>	<b>79</b>	<b>3.0%</b>	<b>100.0%</b>

Table 15, continued

**B**

ICD 9/10 DISEASE CLASSIFICATION	Health Care Delivery			Health Program			Health Treatment		
	n	row%	col%	n	row%	col%	n	row%	col%
Accidents, poisonings, and violence	7	10.1%	4.1%	7	10.1%	3.3%	27	39.1%	4.3%
Blood and blood-forming organs	4	3.1%	2.4%	0	0.0%	0.0%	64	48.9%	10.1%
Certain conditions originating in the perinatal period	8	8.0%	4.7%	22	22.0%	10.4%	37	37.0%	5.8%
Infective and parasitic	16	2.1%	9.4%	36	4.7%	17.0%	72	9.4%	11.3%
Pregnancy, childbirth and the puerperium	28	14.8%	16.5%	36	19.0%	17.0%	31	16.4%	4.9%
Circulatory system	4	7.7%	2.4%	1	1.9%	0.5%	19	36.5%	3.0%
Congenital anomalies	10	5.3%	5.9%	2	1.1%	0.9%	18	9.6%	2.8%
Dental	0	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%
Digestive system	5	6.8%	2.9%	1	1.4%	0.5%	18	24.7%	2.8%
Nervous system and sensory organs	4	2.6%	2.4%	3	1.9%	1.4%	70	45.5%	11.0%
Genitourinary system	5	6.2%	2.9%	0	0.0%	0.0%	19	23.5%	3.0%
Musculoskeletal system	0	0.0%	0.0%	0	0.0%	0.0%	11	44.0%	1.7%
Skin and sub-cutaneous tissue	1	3.8%	0.6%	0	0.0%	0.0%	15	57.7%	2.4%
Respiratory system	17	9.6%	10.0%	13	7.3%	6.1%	78	43.8%	12.3%
Endocrine, nutrition and metabolism, and immunity disorders	13	8.4%	7.6%	18	11.6%	8.5%	44	28.4%	6.9%
External causes of morbidity and mortality	4	14.3%	2.4%	2	7.1%	0.9%	3	10.7%	0.5%
Factors influencing health status and contact with health services	8	8.4%	4.7%	12	12.6%	5.7%	10	10.5%	1.6%
General health	13	18.8%	7.6%	29	42.0%	13.7%	5	7.2%	0.8%
Mental disorders	5	5.9%	2.9%	18	21.2%	8.5%	34	40.0%	5.4%
Neoplasms	5	6.9%	2.9%	3	4.2%	1.4%	41	56.9%	6.5%
Symptoms, Signs and Ill-defined Conditions	11	20.4%	6.5%	8	14.8%	3.8%	19	35.2%	3.0%
Other	2	66.7%	1.2%	1	33.3%	0.5%	0	0.0%	0.0%
<b>TOTAL</b>	<b>170</b>	<b>6.5%</b>	<b>100.0%</b>	<b>212</b>	<b>8.1%</b>	<b>100.0%</b>	<b>635</b>	<b>24.1%</b>	<b>100.0%</b>

Table 15, continued

C

ICD 9/10 DISEASE CLASSIFICATION	Surgical			Dental			TOTAL	
	n	row%	col%	n	row%	col%	n	%
Accidents, poisonings, and violence	2	2.9%	1.5%	0	0.0%	0.0%	69	2.6%
Blood and blood-forming organs	8	6.1%	6.0%	0	0.0%	0.0%	131	5.0%
Certain conditions originating in the perinatal period	3	3.0%	2.3%	0	0.0%	0.0%	100	3.8%
Infective and parasitic	5	0.7%	3.8%	0	0.0%	0.0%	767	29.2%
Pregnancy, childbirth and the puerperium	3	1.6%	2.3%	0	0.0%	0.0%	189	7.2%
Circulatory system	5	9.6%	3.8%	0	0.0%	0.0%	52	2.0%
Congenital anomalies	33	17.6%	24.8%	0	0.0%	0.0%	188	7.1%
Dental	0	0.0%	0.0%	31	93.9%	45.6%	33	1.3%
Digestive system	23	31.5%	17.3%	1	1.4%	1.5%	73	2.8%
Nervous system and sensory organs	10	6.5%	7.5%	1	0.6%	1.5%	154	5.9%
Genitourinary system	17	21.0%	12.8%	0	0.0%	0.0%	81	3.1%
Musculoskeletal system	9	36.0%	6.8%	0	0.0%	0.0%	25	1.0%
Skin and sub-cutaneous tissue	1	3.8%	0.8%	0	0.0%	0.0%	26	1.0%
Respiratory system	1	0.6%	0.8%	0	0.0%	0.0%	178	6.8%
Endocrine, nutrition and metabolism, and immunity disorders	5	3.2%	3.8%	0	0.0%	0.0%	155	5.9%
External causes of morbidity and mortality	1	3.6%	0.8%	0	0.0%	0.0%	28	1.1%
Factors influencing health status and contact with health services	3	3.2%	2.3%	22	23.2%	32.4%	95	3.6%
General health	0	0.0%	0.0%	11	15.9%	16.2%	69	2.6%
Mental disorders	0	0.0%	0.0%	2	2.4%	2.9%	85	3.2%
Neoplasms	3	4.2%	2.3%	0	0.0%	0.0%	72	2.7%
Symptoms, Signs and Ill-defined Conditions	1	1.9%	0.8%	0	0.0%	0.0%	54	2.1%
Other	0	0.0%	0.0%	0	0.0%	0.0%	3	0.1%
<b>TOTAL</b>	<b>133</b>	<b>5.1%</b>	<b>100.0%</b>	<b>68</b>	<b>2.6%</b>	<b>100.0%</b>	<b>2630</b>	<b>100.0%</b>

When ICD-9/10 disease classification was categorized by age group (Table 16), diseases of pregnancy, childbirth and the puerperium and congenital anomalies were the most frequently studied conditions in perinates (37.6% and 24.4%, respectively). Among the remaining age groups - neonates, infants, children, adolescents and adults - infective and parasitic diseases were the most frequently studied conditions (25.9%, 44.6%, 34.6%, 28.9% and 51.9%, respectively).

Table 16. Publications by ICD-9/10 disease classification and by age group (n=2630 records)  
**(A = Perinate, Neonate, Infant; B = Child, Adolescent, Adult, Total)**

**A**

ICD 9/10 DISEASE CLASSIFICATION	Perinate (antenatal period)			Neonate (newborn to ≤ 1 month)			Infant (1 month to ≤ 1 year)		
	n	row%	col%	n	row%	col%	n	row%	col%
Accidents, poisonings, and violence	0	0.0%	0.0%	5	7.2%	0.8%	22	31.9%	3.4%
Blood and blood-forming organs	15	11.5%	5.1%	39	29.8%	5.9%	23	17.6%	3.5%
Certain conditions originating in the perinatal period	16	16.0%	5.4%	74	74.0%	11.3%	18	18.0%	2.8%
Infective and parasitic	22	2.9%	7.5%	170	22.2%	25.9%	291	37.9%	44.6%
Pregnancy, childbirth and the puerperium	111	58.7%	37.6%	80	42.3%	12.2%	6	3.2%	0.9%
Circulatory system	2	3.8%	0.7%	11	21.2%	1.7%	10	19.2%	1.5%
Congenital anomalies	72	38.3%	24.4%	80	42.6%	12.2%	6	3.2%	0.9%
Dental	0	0.0%	0.0%	0	0.0%	0.0%	3	9.1%	0.5%
Digestive system	0	0.0%	0.0%	11	15.1%	1.7%	25	34.2%	3.8%
Nervous system and sensory organs	3	1.9%	1.0%	35	22.7%	5.3%	44	28.6%	6.7%
Genitourinary system	2	2.5%	0.7%	12	14.8%	1.8%	18	22.2%	2.8%
Musculoskeletal system	1	4.0%	0.3%	2	8.0%	0.3%	3	12.0%	0.5%
Skin and sub-cutaneous tissue	0	0.0%	0.0%	4	15.4%	0.6%	11	42.3%	1.7%
Respiratory system	9	5.1%	3.1%	33	18.5%	5.0%	53	29.8%	8.1%
Endocrine, nutrition and metabolism, and immunity disorders	10	6.5%	3.4%	37	23.9%	5.6%	29	18.7%	4.4%
External causes of morbidity and mortality	2	7.1%	0.7%	5	17.9%	0.8%	5	17.9%	0.8%
Factors influencing health status and contact with health services	2	2.1%	0.7%	23	24.2%	3.5%	22	23.2%	3.4%
General health	27	39.1%	9.2%	19	27.5%	2.9%	12	17.4%	1.8%
Mental disorders	1	1.2%	0.3%	2	2.4%	0.3%	5	5.9%	0.8%
Neoplasms	0	0.0%	0.0%	3	4.2%	0.5%	21	29.2%	3.2%
Symptoms, Signs and Ill-defined Conditions	0	0.0%	0.0%	10	18.5%	1.5%	23	42.6%	3.5%
Other	0	0.0%	0.0%	1	33.3%	0.2%	3	100.0%	0.5%
<b>TOTAL</b>	<b>295</b>	<b>11.2%</b>	<b>100.0%</b>	<b>656</b>	<b>24.9%</b>	<b>100.0%</b>	<b>653</b>	<b>24.8%</b>	<b>100.0%</b>

Table 16, continued

**B**

ICD 9/10 DISEASE CLASSIFICATION	Child (> 1 year to 12 years)			Adolescent (13 to 18 years)			Adult (19 and older)			Total	
	n	row%	col%	n	row%	col%	n	row%	col%	n	%
Accidents, poisonings, and violence	64	92.8%	4.2%	26	37.7%	4.4%	2	2.9%	3.7%	69	4.6%
Blood and blood-forming organs	79	60.3%	5.2%	41	31.3%	6.9%	3	2.3%	5.6%	131	8.7%
Certain conditions originating in the perinatal period	11	11.0%	0.7%	1	1.0%	0.2%	0	0.0%	0.0%	100	6.6%
Infective and parasitic	523	68.2%	34.6%	171	22.3%	28.9%	28	3.7%	51.9%	767	50.7%
Pregnancy, childbirth and the puerperium	2	1.1%	0.1%	8	4.2%	1.4%	1	0.5%	1.9%	189	12.5%
Circulatory system	32	61.5%	2.1%	23	44.2%	3.9%	2	3.8%	3.7%	52	3.4%
Congenital anomalies	2	1.1%	0.1%	8	4.3%	1.4%	1	0.5%	1.9%	188	12.4%
Dental	31	93.9%	2.1%	15	45.5%	2.5%	0	0.0%	0.0%	33	2.2%
Digestive system	64	87.7%	4.2%	21	28.8%	3.5%	0	0.0%	0.0%	73	4.8%
Nervous system and sensory organs	109	70.8%	7.2%	25	16.2%	4.2%	1	0.6%	1.9%	154	10.2%
Genitourinary system	61	75.3%	4.0%	26	32.1%	4.4%	1	1.2%	1.9%	81	5.4%
Musculoskeletal system	13	52.0%	0.9%	15	60.0%	2.5%	2	8.0%	3.7%	25	1.7%
Skin and sub-cutaneous tissue	21	80.8%	1.4%	7	26.9%	1.2%	0	0.0%	0.0%	26	1.7%
Respiratory system	126	70.8%	8.3%	44	24.7%	7.4%	5	2.8%	9.3%	178	11.8%
Endocrine, nutrition and metabolism, and immunity disorders	100	64.5%	6.6%	32	20.6%	5.4%	4	2.6%	7.4%	155	10.3%
External causes of morbidity and mortality	19	67.9%	1.3%	9	32.1%	1.5%	0	0.0%	0.0%	28	1.9%
Factors influencing health status and contact with health services	65	68.4%	4.3%	23	24.2%	3.9%	1	1.1%	1.9%	95	6.3%
General health	22	31.9%	1.5%	7	10.1%	1.2%	1	1.4%	1.9%	69	4.6%
Mental disorders	60	70.6%	4.0%	47	55.3%	7.9%	0	0.0%	0.0%	85	5.6%
Neoplasms	65	90.3%	4.3%	26	36.1%	4.4%	2	2.8%	3.7%	72	4.8%
Symptoms, signs and ill-defined conditions	40	74.1%	2.6%	15	27.8%	2.5%	0	0.0%	0.0%	54	3.6%
Other	3	100.0%	0.2%	2	66.7%	0.3%	0	0.0%	0.0%	3	0.2%
<b>TOTAL</b>	<b>1512</b>	<b>57.5%</b>	<b>100.0%</b>	<b>592</b>	<b>22.5%</b>	<b>100.0%</b>	<b>54</b>	<b>2.1%</b>	<b>100.0%</b>	<b>2630</b>	<b>100.0%</b>

### 3.8 Target Population

Among the 2630 publications included in PEDE between 1980 and 2013, there were 2878 separate populations that were studied as some publications included multiple population types. While some studies targeted children strictly by age group, others targeted patients with a specific condition or health risk. To reduce heterogeneity in the analysis, these were grouped together when possible, resulting in 410 target populations.

The top ten target populations covered 42% of the studied populations and were: universal, defined as all individuals (10.1%), pregnant women (9.8%), children (5.6%), neonates (3.9%), vaccinated persons (2.9%), cancer patients or individuals at risk of cancer (2.5%), patients with asthma (2.4%), patients with or at risk of HIV (2.2%), patients with cardiac abnormalities (1.8%) and patients with or at risk of rotavirus (1.4%). When each of the 10-year periods covered by the database were considered, some changes were observed reflecting changes in disease patterns and health priorities, however cancer patients and pregnant women were consistently in the top ten (Tables 17 to 21).

Table 17. Publications by the ten most frequent target populations (1980-2013)

Target population	n	%
Universal	290	10.1%
Pregnant	281	9.8%
Children	160	5.6%
Neonates	111	3.9%
Vaccinated	84	2.9%
Cancer	72	2.5%
Asthma	70	2.4%
HIV	62	2.2%
Cardiac abnormality	53	1.8%
Rotavirus	40	1.4%
<b>TOTAL</b>	<b>1223</b>	<b>42%</b>

Total number of categorized target populations reported in 1980-2013 = 410

Abbreviation: HIV = human immunodeficiency virus



Table 18. Publications by the most frequent target populations (1980-1989)

Target population	n	%
Universal	62	35.4%
Pregnant	40	22.9%
Premature	6	3.4%
Low birth weight	4	2.3%
Low income	4	2.3%
Underserviced	4	2.3%
Diarrhea	3	1.7%
Cancer	3	1.7%
<b>TOTAL</b>	126	69.7%

Total number of categorized target populations reported in 1980-89 = 175. Data were sparse for the many remaining populations (n = 1 or 2) so only the top eight target populations are provided for this decade.

Table 19. Publications by the ten most frequent target populations (1990-1999)

Target population	n	%
Universal	199	26.7%
Pregnant	122	16.4%
Underserviced	26	3.5%
Cardiac abnormality	24	3.2%
Premature	19	2.5%
Cancer	17	2.3%
Neonates	16	2.1%
Intensive care	15	2.0%
Low birth weight	15	2.0%
Asthma	13	1.7%
<b>TOTAL</b>	466	62.5%

Total number of categorized target populations reported in 1990-1999 = 746

Table 20. Publications by the ten most frequent target populations (2000-2009)

Target population	n	%
Children	138	9.6%
Pregnant	105	7.3%
Vaccinated	72	5.0%
Neonates	68	4.7%
HIV	43	3.0%
Asthma	40	2.8%
Cancer	32	2.2%
Respiratory syncytial virus	26	1.8%
Adolescents	25	1.7%
Cardiac abnormality	22	1.5%
<b>TOTAL</b>	<b>571</b>	<b>39.8%</b>

Total number of categorized target populations reported in 2000-2009 = 1436  
 Abbreviation: HIV = human immunodeficiency virus

Table 21. Publications by the ten most frequent target populations (2010-2013)

Target population	n	%
Neonates	26	5.0%
Children	22	4.2%
Rotavirus	21	4.0%
Cancer	20	3.8%
Pneumonia	17	3.3%
HPV	16	3.1%
Asthma	15	2.9%
Pregnant	14	2.7%
Influenza	13	2.5%
HIV	11	2.1%
Vaccinated	11	2.1%
<b>TOTAL</b>	<b>186</b>	<b>35.7%</b>

Note: Total number of categorized target populations reported in 2010-2013 = 521. HIV and vaccinated populations were tied for tenth place.

Abbreviations: HIV = human immunodeficiency virus; HPV = human papilloma virus

The most frequent target populations were considered for four key disease classifications, including infectious disease, pregnancy and childbirth, conditions originating in the perinatal period, and congenital anomalies (Table 22 to 25). Among studies of infective and parasitic diseases, the most frequent target populations were universal, children and vaccinated persons (18.2%, 9.6% and 9.0%, respectively). Among conditions of pregnancy, childbirth and puerperium, the top target populations were pregnant women, children with or at risk of HIV and neonates (60.3%, 5.6% and 4.7%, respectively). Among certain conditions originating in the

perinatal period, the top target populations were low birth weight, prematurity and neonates (15.7%, 14.9% and 14.2%, respectively). Among congenital anomalies, the top target populations were pregnant women, patients with cardiac abnormalities and patients with congenital anomalies (29.1%, 12.8% and 7.4%, respectively).

Table 22. Most frequent target populations within infective and parasitic class (1980-2013) (n=329 records)

Target Population	n	%
Universal	154	18.2%
Children	81	9.6%
Vaccinated	76	9.0%
Human immunodeficiency virus	40	4.7%
Rotavirus	37	4.4%
Malaria	24	2.8%
Influenza	23	2.7%
Respiratory syncytial virus infection	22	2.6%
Neonates	22	2.6%
Underserved	21	2.5%
Pregnant	21	2.5%

Underserved and pregnant populations were tied for tenth place.

Table 23. Most frequent target populations within pregnancy, childbirth and puerperium class (1980-2013) (n=189 records)

Target Population	n	%
Pregnant	140	60.3%
Human immunodeficiency virus	13	5.6%
Neonates	11	4.7%
Premature	9	3.9%
Infertile	8	3.4%
Diabetes	6	2.6%
Adolescents	4	1.7%
Herpes	4	1.7%
Without adequate prenatal care	4	1.7%
Placenta previa	3	1.3%
Universal	3	1.3%

Placenta previa and universal populations were tied for tenth place.

Table 24. Most frequent target populations within certain conditions originating in the perinatal period (1980-2013) (n=100 records)

Target Population	n	%
Low birth weight	21	15.7%
Premature	20	14.9%
Neonates	19	14.2%
ICU	12	9.0%
Respiratory distress syndrome	8	6.0%
Underserviced	5	3.7%
Universal	4	3.0%
Respiratory	3	2.2%

Data were sparse for the many remaining populations (n = 1 or 2) so only the top eight target populations are provided.

Table 25. Most frequent target populations within congenital anomalies class (1980-2013) (n=188 records)

Target Population	n	%
Pregnant	59	29.1%
Cardiac abnormality	26	12.8%
Congenital anomalies	15	7.4%
Universal	13	6.4%
Down syndrome	9	4.4%
Hirschsprung's disease	7	3.4%
Neonates	6	3.0%
Children	5	2.5%
Hypertrophic pyloric stenosis	5	2.5%
Chromosomal abnormalities	5	2.5%

The most frequent target populations were also considered for three key intervention types, including health prevention, health treatments and detection interventions (Table 26 to 28). Among studies of health prevention interventions, the most frequent target populations were universal, children and vaccinated persons (17.4%, 9.8% and 7.9%, respectively). Among studies of health treatment interventions, the top target populations were patients with cancer, asthma and pregnant women (5.5%, 4.7% and 4.1%, respectively). Among studies of detection interventions, the most frequent target populations were pregnant women, universal and neonates (25.7%, 14.8% and 7.4%, respectively).

Table 26. Most frequent target populations within health prevention (1980-2013), (n=833 records)

Target Population	n	%
Universal	160	17.4%
Children	90	9.8%
Vaccinated	73	7.9%
Pregnant	60	6.5%
Rotavirus	35	3.8%
HPV	33	3.6%
HIV	33	3.6%
RSV	28	3.0%
Hepatitis B	23	2.5%
Neonates	22	2.4%

Table 27. Most frequent target populations within health treatment (1980-2013), (n=637 records)

Target Population	n	%
Cancer	37	5.5%
Asthma	32	4.7%
Pregnant	28	4.1%
Children	21	3.1%
Cardiac abnormalities	17	2.5%
Otitis media	17	2.5%
Fractures	14	2.1%
Neonates	13	1.9%
Premature	13	1.9%
ADHD	12	1.8%

Table 28. Most frequent target populations within detection (1980-2013), (n=418 records)

Target Population	n	%
Pregnant	108	25.7%
Universal	62	14.8%
Neonates	31	7.4%
Children	17	4.0%
HIV	11	2.6%
Down syndrome	11	2.6%
Hearing disability	8	1.9%
Cardiac abnormality	7	1.7%
Cystic fibrosis	7	1.7%
Chromosomal abnormality	7	1.7%

## **4 DISCUSSION**

### **4.1 Key Findings**

A total of 2630 published pediatric health economic evaluations were identified through PEDE between 1980 and 2013, indicating that the field of pediatric economic evaluation continues to grow. Substantially more CEAs and CUAs are being published compared with CBAs and CMAs (64.5% and 24.0% versus 7.7% and 3.7%, respectively) and this trend appears consistent regardless of the type of intervention, disease or age group being studied. Since 2009 CUA has dominated as the most frequent type of analytic technique despite the significant challenges in valuing health states in children. Statistically significant changes in the distribution of analysis types, journal types, intervention types and age groups were observed when comparing early (1980-1999) and late (2000-2013) periods ( $\chi^2$   $p < 0.0001$  for each test). The change in distribution of analysis types likely reflects the increase in CEAs and CUAs over time. The main focus of pediatric health economic evaluations has consistently remained infectious diseases at 29.2% with the next most frequently studied conditions being those of pregnancy, childbirth and the puerperium at 7.2%.

### **4.2 Comparison with Literature**

A substantial increase in the volume of publications was observed when compared with the initial analysis of PEDE which covered the period from 1980 to 1999 and resulted in 787 full pediatric economic evaluations (7, 9). This growth has paralleled the increasing acceptance and capacity for conducting health economic evaluations in adult health (20). In the initial analysis of PEDE, the most common health outcome category was cases of disease/condition/abnormality. Because of the large number of studies reporting cases of disease/condition/abnormality in the current analysis, this category was split into infectious and non-infectious disease outcomes, resulting in QALYs or similar measures as the most commonly reported outcome overall. This rise in QALYs as a frequently reported outcome is consistent with the rise in CUAs that has been observed. This suggests that there has been increased attention to guidelines stipulating the use of CUA (1, 2) but there is evidence that measuring and reporting child health utilities continue to be a challenge (6, 21, 22). In recent years there have been advancements in the development of pediatric-specific health state classification schemes and underlying preference weights which may help to improve the frequency and quality of pediatric CUAs (23-25).

Other databases of economic evaluations exist such as the Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry (26) and the National Health Service Economic

Evaluation Database (NHS EED) (27), however, there are key features that differ from PEDE. In both databases, although pediatric economic evaluations are included, they also include economic evaluations in general adult populations. Also, the CEA registry only includes CUAs. The NHS EED differs in that it includes critical commentaries of economic evaluations and is primarily targeted at decision-makers; few quantitative analyses of the NHS EED exist. Due to lack of funding, updating of NHS EED ceased in 2014. Variables included in each of the databases also differ; for example the CEA registry includes information on sponsorship. Neither the CEA Registry nor NHS EED search as many citations databases or grey literature sources as PEDE and are therefore considered less comprehensive as sources for pediatric economic evaluations.

An analysis of the CEA registry compared adult and pediatric CUAs from 1986 to 2001 (28), a period similar to the early time period (1980 -1999) covered in this analysis of the PEDE database. That analysis found that while economic evaluations in pediatric populations focused on respiratory and infectious diseases, evaluations in adults focused on cardiovascular, neurologic, cancer and infectious conditions. This is consistent with our current analysis, which found that the most frequent diseases studied in pediatric economic evaluations are infectious and parasitic, as classified in ICD-9 and ICD-10. Lapado et al., found that the most frequent interventions studied in pediatric CUAs were pharmaceuticals and immunizations (17% each) while the most frequent intervention in adults was pharmaceuticals (36%). Education and behavioural interventions were studied more frequently in pediatric populations compared with adult populations (14% versus 3%, respectively).(28) In contrast, the analysis of PEDE over 1980-2013 found that health prevention interventions (which includes immunizations) were most frequently studied in pediatric CUAs (51%), followed by health treatment (which includes pharmaceuticals) at 24%. Only 1.4% of pediatric CUAs were educational interventions in the PEDE analysis. Detection interventions were studied in 10.8% of pediatric CUAs the PEDE analysis compared with 3% in pediatric CUAs in the CEA registry. These variations may be a result of the small number of pediatric economic evaluations included in the CEA registry, which was 35 at the time of the analysis compared with the 632 CUAs currently in PEDE.

An analysis of the CEA registry from 1990-2012 does not analyze pediatric economic evaluations separately (29). However, that analysis found that when regional disease burden as assessed by the World Health Organization (WHO) was compared with diseases studied in economic evaluations, there was some divergence. For example, that study found that the proportion of musculoskeletal CUAs was high in Europe compared with its relative disease

burden and that for the Western Pacific region, the number of CUAs focused on cancer and infectious disease is large relative to their corresponding disease burdens. In all regions, few CUAs focused on injuries relative to the corresponding disease burden. The current analysis of PEDE found that the leading conditions studied were infectious and parasitic diseases at 29.2%, with the next most frequent condition being diseases of pregnancy, childbirth and the puerperium at 7.2%. While this may reflect a historical focus on infectious disease in child health, a recent analysis of data from the WHO's Global Health Observatory suggests that the contribution of infectious diseases to child mortality is likely to decline while congenital anomalies, non-communicable diseases and injuries are likely to increase (30).

Publication of economic evaluations in journals of pediatrics/perinatal medicine and subspecialty medicine were frequent in both the early analysis of PEDE (1980-1999) and the later years (2000-2013) suggesting that most studies are directed to a clinical decision-making audience. When CUAs in adults and children were considered, an analysis of the CEA registry (29) noted that of the top ten journals publishing cost utility analyses in 2012, many were health economic journals (e.g. *Journal of Medical Economics*, *Value in Health*, *Pharmacoeconomics*), which is consistent with the current finding that 45.3% of CUAs are published in health economic/policy/methods journals. However, other top ten journals from the CEA registry analysis included *Clinical Therapeutics* and *BMJ Open*, indicating that CUAs are still disseminated to clinical audiences. Educational initiatives for clinical and decision-making audiences regarding the more complex CUAs will be important to ensure their appropriate interpretation and application.

### **4.3 Strengths and Limitations**

Some of the limitations associated with the development of the PEDE database have previously been described (7, 17) but include those related to development of a search strategy, data extraction approaches and completeness of the database. In building the full PEDE database, a complex search strategy is used in order to include all relevant, publicly available studies. It is possible that the database missed economic evaluations conducted in the adolescent age group, when adolescents were studied together with adults or when adolescents were not identified with a "pediatric" keyword in the title or abstract. While every attempt was made to obtain relevant grey literature through perusal of websites, newsletters and textbooks, it is possible that some pertinent papers were missed. Foreign language articles were included in the PEDE database as long as an English abstract was available. Despite this relatively small potential for missing citations, the multi-stage exhaustive search strategy employed in the



building of the PEDE database, has resulted in a database that is vastly more comprehensive and inclusive than existing ones with respect to pediatric economic evaluations. The extent of the literature searched and the tests of inter-rater reliability among abstract reviewers support the comprehensiveness and accuracy of the PEDE database.

A particular challenge in identifying pediatric economic evaluations of health care interventions relates to the way 'health' is defined. In the pediatric population, health is intricately connected to behaviour and development (6). Many health problems in children are manifested as behavioural changes for which social services and educational interventions are advocated. Scanning only the medical literature may have excluded relevant economic evaluations of psychological or social service interventions. A greater understanding of child health that integrates psychological, educational and social service interventions will necessitate a broader approach to assessing health outcomes in children.

Another challenge in building the PEDE database was categorizing highly heterogeneous data fields such as outcome measures and target populations and therefore misclassifications may have occurred. Challenges in classifying the analytical technique were also encountered given a lack of standardized health economic nomenclature in early publications and frequent mislabeling of CBAs by authors. Our reviewers therefore independently assigned the analytic technique based on a careful review of the paper's methodology. The addition of other variables to the PEDE database such as sponsorship and additional methodological characteristics will allow more in-depth future analyses of pediatric health economic evaluations.

#### ***4.4 Policy Implications and Future Research***

The increasing rate of publication in pediatric and sub-specialty journals suggests that there is a growing appreciation of the importance of economic evaluation in pediatric medicine. However, publication in a medical journal alone may be inadequate. As an applied form of research, the results of health economic evaluation must be disseminated in a manner that will best aid policy decision-making. Further consideration on the best approaches to the dissemination and knowledge translation of economic evaluations for clinicians and policymakers in the field of child health would be of value.

Pediatric health economic evaluations are frequently conducted in the field of infectious diseases but expanding pediatric health economic evaluations to focus on other disease areas and target populations to support emerging child health priorities such as non-infectious

diseases, chronic conditions, mental health initiatives and advances in personalized medicine should be considered (30). The new Global Strategy for Women's, Children's and Adolescents' Health that is being developed in collaboration with the United Nations has identified adolescent health needs as an emerging priority(11). Realizing and meeting adolescent health needs will require focusing on prevention of injuries, violence, and self-harm; good sexual and reproductive health outcomes; and prevention of non-communicable disease (31). The current innovations in the field of pharmacogenomics and personalized medicine also promise to impact future child health prevention strategies and treatments (14). Yet, there are concerns surrounding sustainability and affordability in the development and delivery of healthcare to small, individualized patient populations (15). Ensuring health economic evaluations accompany the development and implementation of these initiatives will contribute to robust and evidence-informed policy decision-making in the field of child health.

The field of pediatric health economic evaluations continues to grow, supporting the need for the ongoing maintenance and updating of PEDE for pediatric researchers, health practitioners and those engaged in health technology assessment and systematic reviews. While CUAs have increased, there is still room for further growth in the development of methods to support pediatric health economic evaluations. Ongoing analyses of the PEDE database will contribute to greater understanding of current approaches in pediatric health economic evaluation and an awareness of the need for more robust methodologies. This analysis of trends in pediatric health economic evaluations between 1980 and 2013 will further allow researchers and policymakers to identify areas of research needed to support informed decision-making in the field of child health.

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