Quality-Adjusted Life-Years Lack Quality in Pediatric Care: A Critical Review of Published Cost-Utility Studies in Child Health

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ABSTRACT. *Objectives.* **Cost-utility analysis in which health benefits are quantified in terms of quality-adjusted life-years (QALYs) has now become the standard type of cost-effectiveness analysis. These studies are potentially influential in determining the extent of funding for particular pediatric interventions, and so their methodologic quality is extremely important. The objective of this study was twofold: first, to critically appraise published cost-utility analyses of interventions in child and adolescent health care in terms of the methods used to derive QALYs and, second, to discuss unresolved methodologic issues that are pertinent to the measurement of QALYs in pediatric populations.**

Methods. **A comprehensive search using computerized databases (including Medline, Embase, Econlit, and databases specific to economic evaluation), Web searches, and citation tracking was undertaken to identify cost-utility studies of interventions that were aimed at those who were younger than 16 years and published before April 2004. The methods of individual studies were compared with the recognized published guidelines of the US Panel on Cost-Effectiveness in Health and Medicine and the National Institute for Clinical Excellence in England and Wales, which recommend the use of a generic health state classification system (eg, Health Utility Index, EuroQol-5D), a choice-based valuation method (eg, standard gamble or time trade-off) and preferences of the general public in estimating QALYs. Studies therefore were categorized and evaluated according to the methods used to describe the health state, the valuation technique, and source of preferences.**

Results. **Fifty-four studies were reviewed, 34 (63%) of which were published in the past 5 years. A generic health status classification instrument was used in 22 (35%) cases; the remainder developed study-specific health state descriptions or elicited preferences directly from patients or proxies. In 3 (5%) cases, sources were unclear. Preference weights were elicited using choice-based techniques in 28 (42%) cases, either as tariffs for health status classification instruments (17 cases) or by directly valuing health state descriptions or patient health (11 cases). Preferences of the general public were used in only 23 (37%) cases. Four studies aggregated QALYs for mother/child or parents/child pairs without giving any theoretical justification. Although there was an increasing tendency for studies to use generic health status classification instruments, choice-based methods, and preferences of the general public, the majority of studies still did not adhere to these standard recommendations even in the period between January 2000 and March 2004. Despite increasing standardization in the methods advocated for economic evaluation over the past 10 years, there remains extensive variation in the actual methods used by researchers to calculate QALYs for children and adolescents. It is unclear whether these results suggest poor practice or a set of positive (or reactive) choices made by analysts in a methodologically uncertain area in which specific guidance is lacking regarding how to address the complexities of pediatric outcomes within the QALY framework. Many aspects of QALY measurement in children are not yet fully developed. In particular, there is (1) a lack of appropriate health state classification instruments that take account of the dynamics of child development, (2) a lack of health state classification instruments for use in children and infants who are younger than 5 years, and (3) the need to understand fully the role of proxies for measuring and valuing child health. Additional research efforts are also required to develop methods that account for the health benefits of parents or caregivers of the child and to consider the implications of combining different forms of utility measurement in childhood and adulthood.**

Conclusions. **Although variations from standard recommendations may be attributable to poor practice among researchers who are either unaware of these recommendations or choose not to follow them, they could equally be the result of attempts to make research more rigorous and more defensible than it might be if the standard recommendations were followed. There are 4 potential approaches to conducting cost-utility analysis in pediatric populations: (1) the explicit development of a generic instrument designed to be applicable across both child and adult populations (likely to be difficult in practice), (2) insistence on use of a generic instrument developed for adults, (3) the use of generic instruments specifically developed for children without being concerned about comparability with interventions aimed at adults, and (4) abandoning attempts to use single outcome measures that combine mortality with quality weights. In the absence of a clear way forward, it is suggested that an expert panel be convened to debate and further consider these potential solutions and recommendations for best practice and future research. In the interim, comparisons of the relative cost-effectiveness reported as cost per QALY gained across interventions for different diseases and populations should be treated with extreme caution.** *Pediatrics* **2005;115:e600–e614. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2127;** ***health policy, health services research, health status measurement.***

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ABBREVIATIONS. QALY, quality-adjusted life-year; EQ-5D, EuroQol-5D; NICE, National Institute for Clinical Excellence.

Over the last 2 decades, economic evaluation has increasingly been recognized as an important tool to assist decision makers in resource-constrained health care systems in deciding which interventions and programs represent good value for money and whether to fund or reimburse particular interventions or diagnostic tests. This has resulted in an increasing number of published studies that include economic appraisals of interventions and services that are aimed at children and adolescents.[1] These studies are potentially influential in determining the extent of funding for particular pediatric interventions, and so their methodologic quality is extremely important.

Economic evaluation aims to compare interventions in terms of their costs and benefits. The main analytic techniques are cost-benefit analysis and cost-effectiveness analysis, with cost-utility analysis being one type of cost-effectiveness analysis (Table 1).[2] Whereas the measurement and valuation of costs is principally the same in all types of economic evaluations, the measurement and valuation of health benefits differs. Among all study types, cost-utility analysis, whereby health benefits are quantified in terms of quality-adjusted life-years (QALYs), has become the standard type and is now recommended in the great majority of health economics guidelines as the method of choice.[3,4]

The main reason for using QALYs as an outcome measure is that improvements in health-related quality of life and life expectancy are captured within a single index that also incorporates people's preferences for various health outcomes. Such form of analysis therefore allows the direct comparison of the relative health benefits of interventions across different disease areas and populations (eg, children, adults, older people). The use of QALYs, however, relies on a number of assumptions, including that the health of the patient is the only important outcome and that it is possible to trade directly between quality and quantity of life.[2]

To facilitate comparability between studies that are intended to inform resource allocation, the US Panel on Cost-Effectiveness in Health and Medicine defined a reference case as a standard set of methods considered to be most appropriate for cost-effectiveness analysis.[4] With regard to the estimation of QALYs, the panel recommended the use of a generic health status classification system (eg, Health Utility Index, EuroQol-5D [EQ-5D]), a choice-based valuation technique (eg, standard gamble or time trade-off method), and preferences from a representative and fully informed sample of the general population. Recently, the National Institute for Clinical Excellence (NICE) in England and Wales also adopted these specific recommendations in its reference case.[5]

However, a number of reviews have highlighted extensive variability in the methods used in economic evaluations in general[6] and cost-utility analyses in particular.[7,8] Of particular concern here, the methods used for estimating QALYs have been shown to deviate from these recommendations with little improvement over time.[9]

None of these reviews, however, has explicitly appraised cost-utility studies of child health interventions and programs within their own context. The examination of the validity of these studies is an

TABLE 1. Glossary

Cost-benefit analysis: A technique in which the costs are compared with benefits of an intervention, both valued in monetary terms.
Cost-effectiveness analysis: A technique in which the costs of an intervention are compared with 1 predefined health outcome (eg, cost per case detected, cost per life-year gained).
Cost-utility analysis: A special type of cost-effectiveness analysis that uses QALYs as an outcome measure.
QALYs: Quality-adjusted life-years, a measure that combines length of life and quality of life (valued on an index whereby 1 represents perfect health and 0 represents death) into a single outcome.
Health state classification instruments: Questionnaires for which a respondent's answers define his or her health state on a number of different dimensions of health such as mobility, pain, hearing, and seeing.
Tariffs for classification: A term used to describe sets of preference weights for all health states that can be described with a health state classification instrument.
Preference (or quality) weights: A numerical score associated with the value attached to a given health state. Respondents can be asked to value either their own state of health (direct elicitation) or a state of health that is described to them (indirect elicitation). Preference weights have been measured by using samples of the general population, patients who have experienced the health state or treatment outcome, or proxies of the patient (eg, parents).
Utility: A person's preference for a particular health state measured under condition of uncertainty, obtained by using the standard gamble. Preferences elicited with the time trade-off or visual analog scales are usually referred to as values.
Visual analog scale: A method of assigning preferences by which a respondent is asked to locate a given health state on a straight line with end points representing the worst imaginable and the best imaginable health state, respectively.
Standard gamble: A method of assessing preferences for a given health state. The respondent is asked to compare 2 scenarios. One is to live in a given health state with certainty, and the other is to take a treatment that offers a probability (P) of living in full health and a probability ($1 - P$) of dying immediately. The respondent is asked to indicate the value of P that would make the 2 options equally desirable. The value of the health state (to that person) then is set equal to P.
Time trade-off: A method of assessing preferences for a given health state whereby a respondent is asked to indicate a number of years (x) in full health that he or she would consider equally desirable as, for instance, 10 y in that health state. The value of that health state (to the person in question) then is defined as the ratio $x/10$.
Choice-based valuation technique: A general term used to describe methods for assessing preferences whereby respondents are asked to choose between 2 alternatives (as in the time trade-off and standard gamble exercise).
Decision analysis: A mathematical representation of the management and treatment pathways of patients or populations and the associated costs and outcomes to identify the optimal course of action among competing alternatives.
Discounting: The conversion of future costs and future health outcomes to their present value.

important research issue because of the added complexities in pediatric outcomes research[10,11] currently not addressed in standard guidelines for economic evaluation[3] and the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine[4] and NICE,[5] although there is growing recognition that the differences between children and adults have methodologic implications for the design and use of these studies.[11] One of the main obstacles to simply adapting adult measures for use in children stems from rapid developmental changes that take place in childhood and adolescence.[10,12–14] Outcome measures that not only are sensitive to changes in development and changes in health but also make allowances for different cognitive abilities of children at various ages with regard to reporting and valuing health status are required.[10] Furthermore, children's dependence on parents and family members and the resulting interdependence of quality of life between them may suggest that the impact of child health interventions on parental utility should be incorporated into economic evaluations that are conducted from a societal perspective.[11]

The study reported here examines the methods used to calculate QALYs in cost-utility studies of pediatric health interventions published before April 2004 and compares them with the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine and NICE. Additionally, it discusses some of the methodologic issues raised by these studies.

METHODS

Literature Search and Study Selection

We searched Medline, Embase, Cinahl, Econlit, York Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database, the Harvard Cost-Utility Analysis Database, and the Database of the Pediatric Economic Database Evaluation Project from the beginning of each database until April 2004 for eligible studies. Table 2 shows the search strategy used in Medline, Embase, and Cinahl. The search terms for subsequent searches in the remaining databases were based on this strategy. We also searched the Web for additional references and reviewed the reference list of papers deemed eligible for inclusion for additional papers. The search was restricted to the English language.

Study Inclusion/Exclusion

Studies were included in the review when they were original cost-effectiveness or cost-utility studies of health care interventions that were aimed at children and adolescents who were 16 years and younger and in which QALYs were used as a measure of effectiveness. The choice of a cutoff age was inevitably somewhat arbitrary given the different ages at which young people are defined as children in different countries, settings, and contexts. Sixteen years was chosen as this tends to be seen in the United Kingdom as a minimum age at which children are defined as adults (eg, 16 years is the minimum age at which a young person may marry). This also included studies in which cost and effectiveness were projected over a time horizon (eg, lifetime) beyond 16 years of age.

TABLE 2. Search Strategy Used in Medline, Embase, and Cinahl

1.	Infant, newborn/
2.	Infant/
3.	Child, preschool/
4.	Child/
5.	Adolescence/
6.	1 or 2 or 3 or 4 or 5
7.	exp quality-adjusted life-years/
8.	(cost-utility or cost utility).mp. (mp = ti, sh, ab, it, tn, ot, dm, mf, rw)
9.	(cost-effectiveness or cost effectiveness).mp. (mp = ti, sh, ab, it, tn, ot, dm, mf, rw)
10.	7 and 9
11.	8 or 10
12.	11 and 6

Data Extraction and Criteria

Data were extracted by I.G. using a specifically designed data extraction form. The reliability of data extraction was monitored. Eleven (20%) studies were selected randomly and assessed independently by 2 authors (I.G. and J.C.). Agreement on each domain was compared qualitatively to identify inconsistencies and to ensure that forms were used in a standardized way.

Background information for each study was collected, including journal name and year of publication, country of study, description of intervention under investigation, condition (according to the *International Classification of Diseases, 10th Revision* classification), and prevention stage (primary, secondary, or tertiary). Furthermore, type of study, study perspective, the age of the population under investigation, the time horizon of the analysis, and the discount rate used to adjust for future health benefits were recorded for each study. To assess the methods used to calculate QALYs, we recorded the health status classification instrument used, the measurement technique used for valuing health states, the group of individuals whose quality of life was assessed (children, parents, both, or adults generally), and the group of individuals from whom valuations were obtained. When the study was based on a primary data collection (eg, randomized clinical trial), we examined which individual completed the instrument or valued the health state. Studies were grouped according to the health status classification system as in a previous review.[9] Four groups were defined: generic (eg, instruments such as the EQ-5D, Health Utility Index, or Quality of Well-Being scale designed to be applicable across different conditions and interventions), study or disease specific (health states describing disease-specific outcomes, eg, diabetes), general disability (studies that described the health state in terms of general disability associated with the disease, eg, neurologic disability), and direct elicitation (study respondents valuing either their own health or hypothetical health states). When >1 method to derive preference weights was used or >1 group of individuals was considered, eg, in studies that modeled health benefits over a lifetime, papers were categorized in all relevant groups. Finally, we investigated whether studies performed sensitivity analyses to assess the uncertainty in the estimation of preference weights or resulting estimates of QALYs.

RESULTS

Number of Papers Retrieved and Reviewed

The search identified 254 potentially eligible papers. We excluded 200 papers because they did not meet the inclusion criteria or were duplicates (working papers or reports) of papers published in peer-reviewed journals. There was a marked increase in the number of published cost-utility studies over time, with 34 of the 54 eligible papers published between 2000 and March 2004 (Fig 1). Table 3 and the Appendix show the main characteristics of included studies. Most studies were conducted in the United States (54%) and Australia (13%), and the remainder were published in Europe and Canada with the exception of 2 studies, which were undertaken from the perspective of sub-Saharan African countries[15] and developing countries in general.[16] Studies were published in 31 different journals, of which *Pediatrics* was the most common journal with 11 (20%) papers. Studies covered a wide range of conditions with a particular emphasis on infectious and parasitic diseases (n = 21; 39%) and conditions originating in the

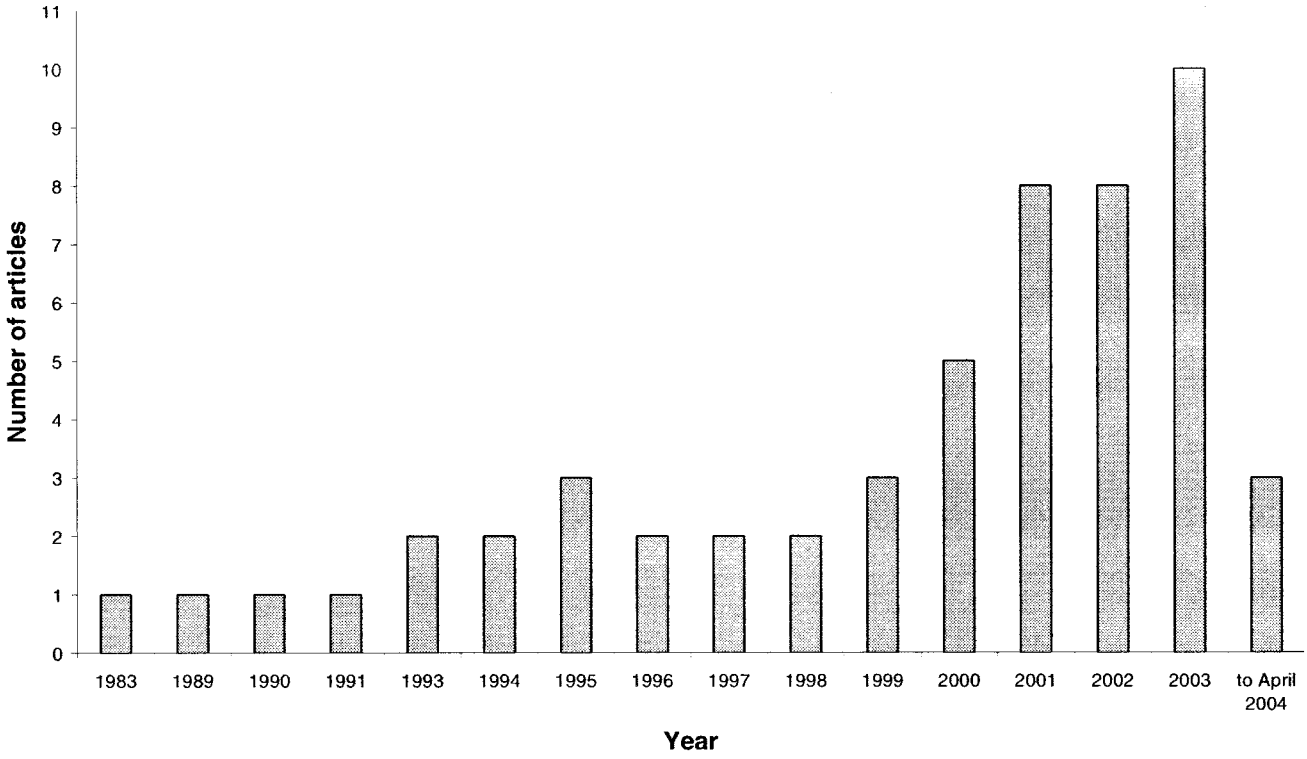

Fig 1. Number of publications per year.

perinatal period (n = 12; 22%). Vaccinations (26%), pharmaceuticals (15%), screening (13%), and medical (11%) procedures were the most frequently evaluated interventions.

Specific Study Characteristics

The great majority of studies (45 [83%]) were decision analyses (Table 4). Six studies used a before-and-after study design, and 3 studies combined a retrospective assessment of a patient cohort with modeling to extrapolate cost and benefits over a lifetime. The perspective of the study was stated explicitly in 80% of all studies, with the societal perspective being the most frequently used. The majority of studies evaluated interventions for newborn infants (54%). Costs and benefits were modeled over a lifetime in 74% of the cases. Five studies[17–21] used preference weights related to the condition under evaluation and extrapolated health benefits over a lifetime by using additional age-adjusted population utility values derived from community surveys (eg, the Beaver Dam Outcome study[22]). The majority of studies (72%) conducted sensitivity analyses to assess the impact of uncertainty surrounding health state values on final estimated cost-effectiveness ratios (Table 4).

Methods Used to Calculate QALYs

The methods that were used for calculating QALYs are detailed in Table 5. A generic health status classification instrument was used in 22 (35%) cases. Preferences were elicited directly from patients or parents as proxies in 4 (7%) cases. The remainder used study-specific descriptions (30%) or general disability states (17%) or referred to previously published studies in 4 (6%) cases as sources for the QALY gain resulting from the intervention being evaluated. In 3 (5%) cases, sources were unclear. Nine (17%) studies used >1 classification instrument or health state description, either to combine value for different ages or to present alternative sets of cost-effectiveness ratios.

In 67% of all papers, authors stated that they had explicitly considered the health-related quality of life of children. Preference weights were elicited by using choice-based techniques in 28 (42%) cases, either as tariffs for health status classification instruments (17 cases) or by directly valuing health state descriptions or patient health (11 cases). In terms of describing health status, the author's judgment was used in 35% of cases. The source of preferences was most commonly the authors' (clinicians; 40%). Preferences of the general public were used in only 23 (37%) cases.

Four studies derived incremental cost-effectiveness ratios by summing up QALYs gained and costs incurred for child/mother or child/parent pairs. These studies evaluated interventions related to child births,[23,24] antenatal care,[25] and antenatal screening.[26]

Adherence to Standards Over Time

Although there is a tendency for studies increasingly to use generic health status classification instruments, choice-based methods, and preferences of the general public, the majority of studies still did not adhere to these standard recommendations even in the period 2000 to March 2004 (Table 6).

TABLE 3. General Study Characteristics

Characteristic	Articles (n = 54), n (%)
By country	
United States	29 (54)
Australia	7 (13)
United Kingdom	4 (7)
Canada	3 (6)
Netherlands	5 (9)
France	1 (2)
Switzerland	2 (4)
Germany	1 (2)
Other	2 (4)
Journal	
Pediatrics	11 (20)
Vaccine	5 (9)
Emerging Infectious Diseases	2 (4)
Journal of Paediatrics and Child Health	2 (4)
Medical Decision Making	2 (4)
Pediatric Infectious Disease Journal	2 (4)
Journal of Pediatric Surgery	2 (4)
Clinical Therapeutics	2 (4)
Journal of the American Medical Association	2 (4)
International Journal of Health Technology Assessment	2 (4)
Journal of Acquired Immune Deficiency Syndromes	2 (4)
Other	20 (37)
Condition	
Conditions originating in the perinatal period	12 (22)
Infectious and parasitic diseases	21 (39)
Blood and blood-forming organs	2 (4)
Injury and poisonings	2 (4)
Nervous system	1 (2)
Diseases of the eye	3 (6)
Diseases of the ear	3 (6)
Neoplasm	1 (2)
Congenital malformations, deformations, and chromosomal abnormalities	4 (7)
Endocrine, nutritional, and metabolic diseases	4 (7)
Various	1 (2)
Prevention Stage	
Primary	18 (33)
Secondary	15 (28)
Tertiary	21 (39)
Type of intervention	
Screening	7 (13)
Diagnostic	4 (7)
Care delivery	5 (9)
Pharmaceutical	8 (15)
Medical procedure	6 (11)
Immunization	14 (26)
Health education	3 (6)
Medical device	4 (7)
Surgical	2 (4)
Other	1 (2)

TABLE 4. Specific Study Characteristics

Item	Articles, n (%)
Type of study	
Decision analysis	45 (83)
Before and after study	6 (11)
Retrospective study with modeling	3 (6)
Study perspective	
Society	30 (56)
Health service	4 (7)
Third-party payer	9 (17)
Not stated	11 (20)
Age of population*	
Newborns/infants <1 y	32 (54)
1–5 y	11 (19)
6–16 y	16 (27)
Study time horizon†	
<1 y	1 (2)
1–10 y	6 (11)
10–20 y	6 (11)
21–40 y	2 (4)
Lifetime	42 (74)
Discount rate used for health benefits	
3%	26 (48)
4%	3 (6)
5%	11 (20)
6%	2 (4)
Not performed/not stated	12 (22)
Uncertainty assessed for health benefits‡	
Preference weights	
Univariable	27 (47)
Multivariable	11 (19)
Probabilistic sensitivity analysis	3 (5)
Not performed/not stated	16 (28)

* In this category, n = 59 because studies reported cost-effectiveness for different age groups in their analysis.
† In this category, n = 57 because studies reported cost-effectiveness for different time horizons.
‡ In this category, n = 57 because studies used different forms of sensitivity analyses.

DISCUSSION

Despite increasing standardization in the methods advocated for economic evaluation over the past 10 years, there is extensive variation in the actual methods used by researchers to calculate QALYs for children and adolescents. In this respect, this review of the use of cost-utility analysis in a pediatric population mirrors similar reviews outside this specific population, which also suggest variable quality and little improvement over time.[6,9] It could have been expected, however, that, compared with previous studies, the review reported here would have been more likely to identify improvements in practice given that the standard recommendations of the US Panel on Cost-Effectiveness in Health and Medicine have now been available for ~8 years. Because this is not the case, it is important to examine the reasons. Does this review suggest poor practice, with analysts ignoring sound and expert advice from internationally respected bodies? Or does it suggest a set of positive (or reactive) choices by analysts in a methodologically uncertain area in which the general advice for estimating QALYs seems, at best, limited and, at worst, impossible to apply in any rigorous manner? The remainder of the discussion focuses on this issue, considering the nature of QALY measurement and valuation for children and the issue of combining QALY measures. First, however, some limitations of the review are noted.

Limitations

This review selected only papers that were published in peer-reviewed journals, which may have led to a smaller overall number of retrieved studies than might have been the case if the gray literature had also been searched. A more comprehensive search, however, would have been unlikely to alter the findings reported here; indeed, if anything, it could be expected that incorporating research that is available only through nonpublished sources would

TABLE 5. Methods Used for Calculating QALYs

Item	Articles, *n* (%)
Health status classification instrument*	
Generic	22 (35)
Health Utility Index	12
EuroQol-5D	5
Quality of Well-Being scale	2
Other	3
Classified by	
Child	1 (4)
Parent	6 (26)
Author/clinician	12 (52)
Other	1 (4)
Not stated	3 (13)
Study or disease specific	19 (30)
General disability only	11 (17)
Direct elicitation	4 (6)
Cited study	4 (6)
Not stated	3 (5)
Application of >1 method	
Yes	9 (17)
No	45 (83)
Whose quality of life was considered†	
Child	39 (67)
Both (child/parent)	3 (5)
Adults generally	14 (24)
Not stated	2 (3)
Measurement techniques used for valuing health state‡	
Author/clinician judgment	23 (35)
Tariffs for classification (choice based)	17 (26)
Tariffs for classification (non–choice based)	5 (8)
Visual analog scale or other rating techniques	2 (3)
Time trade-off	9 (14)
Standard gamble	2 (3)
Transformation of visual analog scale	1 (2)
Not stated	7 (11)
Sources of preferences§	
Child	1 (2)
Parents	3 (5)
Author/clinician	25 (40)
Community	23 (37)
Adult patients	6 (10)
Not stated	5 (8)

* In this category, $n = 63$ because 9 studies used >1 health status classification instrument.
† In this category, $n = 59$ because quality of life of >1 group was considered.
‡ In this category, $n = 66$ because studies used >1 technique to value health states.
§ In this category, $n = 63$ because studies used >1 source of preference.

have reduced further the reported quality of studies, given that such research has not been subject to the peer-review process.

The review was also limited in scope, focusing as it does only on the methods used for estimating QALYs. Undoubtedly, there are other important aspects of economic evaluation in the pediatric population that also merit review,[11] but the focus here was limited deliberately so as to enable detailed examination of this particular topic.

An additional limitation concerns the assessment of reliability. Within the resources available, it was possible for only a small proportion of studies to be assessed by 2 reviewers. There thus was believed to be little value in providing a quantitative assessment of reliability; rather the process of 2 people's assessing each study was used to ensure a more reliable process throughout, through clarification of issues of contention. Nevertheless, a quantitative assessment of reliability would have been helpful in assessing the extent to which there may have been bias in the assessment of the studies by the main reviewer.

QALY Measurement and Valuation for Children

QALY measurement and valuation for children is intrinsically more difficult than that for adults for a number of reasons. First, because children undergo dramatic changes in growth and function (eg, mobility, self-care) at different rates, difficulties may arise to attribute improvements to health care interventions rather than to normal development. There is no methodologic guidance about how this confounding should or even might be dealt with. One solution that researchers in the studies reviewed here may have chosen to use is the development of their own health status scenarios that allow for changes from the age-related norm as a means of adjusting for this problem rather relying on instruments that have been developed for adults.[27] This goes against the standard recommendations but may be perceived by researchers as a methodologic improvement.

Second, all current generic measures are derived from adult populations with the exception of the Health Utility Index Mark 2,[28] and additional attributes that are particularly relevant to child health, including, for example, autonomy, body image, cognitive skills, and family relationships,[29] may not be captured by these measures. Furthermore, no generic instrument for children and infants younger than 5 years is available. Although attempts have been made to establish feasibility and validity of the EQ-5D[30] and the Quality of Well-Being Scale[31] and there have been attempts to adapt the EQ-5D linguistically to produce a child-friendly version,[32] the applicability of these instruments to pediatric populations is questionable. The result may be an implicit reluctance on the part of researchers to use these measures (note that only one third of studies here chose to use generic measures), instead choosing other routes toward utility measurement, such as the use of study of disease-specific states or general estimates of disability.

Third, children, particularly young children (note that >70% of the studies reported here were conducted for children who initially were aged 5 years and under) do not have the cognitive ability to comprehend and complete valuation or even measurement tasks. The implication is that, for very young children, some form of proxy inevitably will be used for measurement tasks, whether this be the clinician or the parent. Although parents may be perceived by economists as the more appropriate source of measurement and/or valuation,[33] the potential for interaction between the utility function of the parent and the proxy (their child) for whom he or she is making the measurement/valuation may lead researchers to choose to use clinician judgment to avoid this problem.

TABLE 6. Improvement Over Time

Item	Articles	
	1980–1999 (n = 20), % of Articles	2000 to March 2004 (n = 34), % of Articles
Generic health status classification instrument	30	37
Choice-based valuation technique	33	46
Community preferences	35	37

Combining QALY Measures

The estimation of pediatric QALYs inevitably leads to questions about how to combine utility values both across various periods of a lifetime and between various individuals. The first problem may arise if it is acknowledged that different measures or sources of values are required for childhood than in adulthood. If different measures are used to determine quality of life weights in childhood and in adulthood as in some of the studies reviewed here, then can the utility values that are applied to different years be combined to produce 1 overall QALY? If not, then must the same measure be used across both periods of life, despite the inadequacy of such an approach?

The second problem may arise when QALYs are developed for both mother (and/or father) and child. In studies that evaluate interventions related to antenatal screening and child birth, for which there are impacts on both mother and child and both are, essentially, the patient, there is an inevitable question about how to combine the 2 sets of utility values. Furthermore, these questions are not restricted to this period; for health interventions that are provided to older children, the outcomes of treatment may clearly affect parents' health (eg, in terms of anxiety, ability to carry out usual activities). Simple aggregation of QALYs is unlikely to be a valid solution because of interdependence between the utility function of the child and the parent,[34] but it is difficult to see an alternative within the cost-effectiveness framework with its desire for a single outcome measure (unless, of course, 1 source of utility gain is ignored).

CONCLUSIONS

These difficulties suggest that although the variations from standard recommendations may be attributable to poor practice among researchers who are either unaware of these recommendations or choose not to follow them, they could equally be the result of attempts to make research more rigorous and more defensible than it might be if the standard recommendations were followed. In practice, it is likely that they are a combination of the 2, with the methodologic problems undoubtedly influencing the choices of researchers in some situations.

There seem to be a number of potential approaches to solving these problems. The choice of approach, however, is likely to be affected by beliefs about the best way forward in health care decision making.

The first set of solutions assumes that the use of comparable generic instruments across all research studies is an absolute requirement. Within this requirement, there are 2 broad approaches. The first is to develop measures that are applicable across both child and adult populations; this is likely to be difficult, particularly when taking into account children under 5 years. The second is to use current measures developed for adult populations with an (implicit or explicit) acceptance that their use could seriously under- or overestimate the utility associated with particular options and thus result in incorrect decisions. This option would effectively maintain the current status quo, in which generic adult measures are recommended but, because of problems with their use, analysts may choose "alternative" forms of QALY measurement.

The second set of solutions relaxes the absolute requirement for comparability across all research studies. One approach here would be to develop generic measures for use specifically in pediatric populations, without requiring comparability with adult populations. This would allow comparison across childhood interventions but if the benefits of an intervention were expected to last beyond the age of 16 years would result in the problem of how to combine with adult measures. An alternative solution would be to use cost-consequences analysis[34] rather than aiming to obtain a single outcome variable. This makes comparison across different studies more difficult but has the benefit of allowing information about outcomes to different people to be explicitly included in the decision-making process.

It has to be accepted than none of these approaches, apart perhaps from the first, is ideal. The problem with the first approach is that it could prove difficult, time consuming, and ultimately unfeasible. Although the number of published pediatric cost-utility studies continues to grow exponentially[1] (and can be expected to do so into the future as new, high-cost diagnostic tests and medical procedures emerge), it is vital to improve on the current situation in which comparability is lost and what replaces it is ideal from no one's point of view.

As shown in this article, the estimation of QALYs in pediatric studies should not yet be regarded as standardized. Comparisons of the relative cost-effectiveness reported as cost per QALY gained across interventions for different diseases and populations should be treated with extreme caution. There is a pressing need for additional methodologic research to resolve the issues identified in this article before the QALY framework can be applied confidently in this population. In the absence of a clear way forward, it is suggested here that an expert panel, along

the lines of the US Panel on Cost-Effectiveness in Health and Medicine, should be convened to debate and consider further the potential solutions outlined above and to make clear recommendations for best practice and future research. In the absence of such clear recommendations, future research using outcomes in the form of QALYs (or, indeed, choosing not to use the QALY as an outcome measure) should clearly justify their choice of methods for measurement and valuation.

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APPENDIX. Summary of Published Cost-Utility Studies of Pediatric Interventions Included in the Review

Study/Country	Intervention (Comparators)	Study Type	Age of Study Population/Time Horizon of Analysis	Perspective	Health State Classification System	Valuation Technique	Source of Preferences	Discount Rate*	Sensitivity Analysis*	Comments
Boyle et al,[35] 1983/ Canada	Neonatal intensive care for low birth weight infants (vs no intensive care)	Before and after study using different cohorts	Newborns/15 y and lifetime	Society	Generic (HUI I–classified by children and pediatricians)	Tariffs for classification	Community (Canada)	5%	Univariable	Pediatricians made forecasts for outcomes past age 15 y
Binkin et al,[25] 1989/ US	Recurrent herpes screening in pregnancy (vs no screening)	Decision analysis	Newborns/lifetime	Not stated	General disability	Authors' judgment	Authors	5%	No	QALYs gained reported both as aggregated sum (mother-child pair) and separately (child, mother)
Tubman et al,[36] 1990/ UK	Surfactant therapy for severe neonatal respiratory distress syndrome (vs no intervention)	Retrospective survey	Newborns/lifetime	Health service	NS	NS	NS	NS	NS	No details on QALY calculations given
Lawler et al,[37] 1991/ US	Routine neonatal circumcision (vs no circumcision)	Decision analysis	Newborns/lifetime	Not stated	Study specific	Authors' judgment	Authors	No	Univariable	
Javitt et al,[38] 1993/US	Weekly screening and cryotherapy for threshold retinopathy of prematurity (vs biweekly or monthly screening)	Decision analysis	Newborns/lifetime	Society	Cited study (which used the HUI on adults)	Tariffs for classification	Society (Canada)	3%	No	
Kitchen et al,[39] 1993/ Australia	Neonatal intensive care in 1985–1987 (vs neonatal intensive care in 1979–1980)	Before and after study using 2 different cohorts	Newborns/lifetime	NS (but only direct cost was included)	General disability	Authors' judgment	Authors	5%	Multivariable	
Harris et al,[40] 1994/ Australia	Childhood immunization at 2, 4, and 12 mo against *H influenzae* type b (vs vaccination at 18 mo only)	Decision analysis	Newborns/lifetime	Society	General disability	Authors' judgment	Authors	5%	Multivariable	
McIntyre et al,[41] 1994/Australia	Childhood immunization against *H influenzae* type b (vs no vaccination)	Decision analysis	Newborns/lifetime	Society	Generic (HUI I–classified by clinician)	Tariffs for classification	Community (Canada) and authors	5%	Univariable	
Adams et al,[42] 1995/ Canada	Screening for hemachromatosis (vs no screening)	Decision analysis	10 y old/lifetime	Third-party payer (health insurance)	Disease specific (eg, cirrhosis, diabetes)	Authors' judgment	Author	NS	No	Preference weights for treatment process were estimated and incorporated (eg, blood testing, physician visits)
Glotzer et al,[43] 1995/ US	Four different interventions for childhood lead poisoning	Decision analysis	2 y old/lifetime	Third-party payer (hospital)	General disability	VAS	Clinicians	5%	Univariable	
Shepard et al,[16] 1995/ US (analysis performed for developing countries)	Different childhood vaccinations (vs no vaccinations)	Decision analysis	Newborns/lifetime	NS (but only direct cost was included)	NS	NS	NS	3%	NS	Preference weights only used for 1 vaccine (polio); no additional details given
Livartowski et al,[44] 1996/France	Vaccination against *H influenzae* type B (vs no vaccination)	Decision analysis	Newborns/10 y	Third-party payer (health insurance)	Generic (Rosser index classified by clinical experts)	Tariffs for classification	Community (UK)	6%	Univariable	

APPENDIX. Continued

Study/Country	Intervention (Comparators)	Study Type	Age of Study Population/Time Horizon of Analysis	Perspective	Health State Classification System	Valuation Technique	Source of Preferences	Discount Rate*	Sensitivity Analysis*	Comments
Oh et al,[45] 1996/Canada	Second-line antibiotics for acute otitis media (cefaclor vs amoxicillin-clavunate vs erythromycin-sulfisoxazole)	Decision analysis	2 y old/30 d	NS	Study specific	VAS	Clinicians	No	Univariable (QALDs were varied) and probabilistic	Results are reported as cost per QALD
Graham et al,[18] 1997/US	Driver-side and front passenger's airbags (vs no airbags)	Decision analysis	All ages/lifetime	Society	Cited study (which directly elicited values from adults) and authors' judgment	Cited study (TTO) and authors' judgment	Cited study (adults) and authors	3%	Univariable (different sets of preference weights applied [see comments])	Age-specific preference weights based on Beaver Dam Health Outcome Study were used in base case; YHL system tested in sensitivity analysis; no baseline adjustment tested in sensitivity analysis
Victorian Infant Collaborative Study Group,[46] 1997/Australia	Neonatal intensive care in 1991–1992 (vs neonatal intensive care in 1979–1980; 1985–1987)	Before and after study using 3 different cohorts	Newborns/lifetime	NS (but only direct cost was included)	General disability	Authors' judgment	Authors' judgment	5%	Multivariable	
Rowley et al,[26] 1998/US	Prenatal screening for cystic fibrosis (vs no screening)	Decision analysis	Parents and newborns/lifetime	NS	Direct elicitation (using parents as proxies) and caregiver's health status (Caregiver Quality of Life Instrument)	TTO	Parents	NS	No	Health benefits (QALYs) are reported as the sum of QALYs accrued by the family (child plus father plus mother)
Tao and Remafedi,[47] 1998/US	HIV prevention intervention for gay and bisexual male adolescents (vs no prevention)	Decision analysis	13–21 y old/10 y	Society	Cited study (which reported QALYs lost as a result of HIV infection)	NS	NS	3%	No	
Bovier et al,[15] 1999/Sub-Saharan Africa	Vaccination against *N meningitis* (vs no vaccination)	Decision analysis	5 y old/30 y	Society	Generic (HUI 1 classified by authors)	Tariffs for classification	Community (Canada)	3%	Univariable	Results also presented as cost per life gained
Brown et al,[48] 1999/US	Laser photocoagulation in the treatment of threshold retinopathy of prematurity (vs cryotherapy)	Decision analysis	Infants (3 mo old)/lifetime	NS (but only direct cost was included)	Cited study (which directly elicited values from adult patients with several visual impairments)	Cited study (TTO)	Cited study (adult patients)	3%	No	Different discount rates for health outcomes were tested in sensitivity analyses
Carter and Hailey,[49] 1999/Australia	Cochlear implant for childhood deafness (vs no implant)	Decision analysis	NS (children, and adults)/10, 15, and 20 y	Third-party payer	Generic (15-D classified by authors)	Tariffs for classification	Community (Finland)	5%	Univariable	Classification into the 15D was done for adults and children
Cheng et al,[50] 2000/US	Cochlear implant for childhood deafness (preintervention vs postintervention)	Before and after study	7–10 y old/lifetime	Society	Direct elicitation (patient health states) and generic (HUI III classified by parents)	VAS, TTO, and tariffs for classification	Parents and community (Canada)	3%	Univariable (QALYs gained were varied)	VAS scores were also transformed into TTO scores using a power function cost per QALY gained using VAS, TTO, and HUI scores separately

APPENDIX. Continued

Study/Country	Intervention (Comparators)	Study Type	Age of Study Population/Time Horizon of Analysis	Perspective	Health State Classification System	Valuation Technique	Source of Preferences	Discount Rate*	Sensitivity Analysis*	Comments
Mrus et al,[23] 2000/US	Elective cesarean delivery for HIV-infected women (vs vaginal delivery)	Decision analysis	25-y-old women and newborns/lifetime	Societal	Mothers: cited study (which used adult patients); children: authors' judgment	TTO, SG, and authors' judgment	Patients, authors	3%	Univariable and multivariable	QALYs gained reported both as aggregated sum (mother-child pair) and separately (child, mother), age-adjusted values used for unaffected individuals (assumed 1.0 for individuals aged <45 y)
O'Neill et al,[51] 2000/UK	Cochlear implant for childhood deafness (vs no implant)	Decision analysis	4 y old/lifetime	Society	Cited study (which reported QALYs gained from adult population)	NA	NA	6%	No	Source of QALY increment not stated
Pinkerton et al,[52] 2000/US	HIV risk reduction intervention in black male adolescents (vs no intervention)	Decision analysis	15 y old/lifetime	Society	Cited study (which reported QALY lost as a result of HIV infection)	NA	NA	3%	NS	
Sinha and Das,[53] 2000/US	Treatment of chronic hepatitis C infection with interferon-based therapies (vs no treatment)	Decision analysis	10 y old/lifetime	Third-party payer	Study specific (authors' judgment based on adult studies)	Authors' judgment	Authors	3%	Multivariable and first-order Monte Carlo simulation	
Barnato et al,[20] 2001/US	Vaccination against *C immitis* (vs no and selective vaccination)	Decision analysis	Children with mean age of 8.85 y and adults/lifetime	Society	Study specific and general disability	Authors' judgment	Authors	3%	Univariable	Preference weights assumed to be the same for children and adults; authors also used age-specific QALY weights based on national study (years of healthy life measure)
Chung et al,[24] 2001/US	Elective repeat cesarean delivery after previous cesarean (vs vaginal delivery)	Decision analysis	30-y-old mother and newborns/lifetime	Society	Mothers: generic-QWB, classified by authors; children: authors' judgment	Tariffs for classification and authors' judgment	Society and authors	3%	Univariable	QALYs gained reported both as aggregated sum (mother-child pair) and separately (child, mother)
Ekert et al,[54] 2001/Australia	Recombinant factor VIIa for children with inhibitors to factors VIII or IX (vs no intervention)	Before and after study	14 y old/1.5 y	NS	Generic (EQ-5D classification by ?)	Tariffs for classification	Community (UK)	NS	No	Not clear who classified the health scenarios obtained from study diaries onto the EQ-5D
Gilmore and Milne,[55] 2001/UK	Methylphenidate for children with hyperactivity (vs no intervention)	Decision analysis	9 y old/1 y	Health service	Generic (IHRQL classified by authors)	Tariffs for classification	?	NS	Different classifications were tested	Limitations of IHRQL discussed
Medina et al,[56] 2001/US	MRI for children with suspected brain tumor (vs MRI-CT or no imaging)	Decision analysis	5 y old/20 y	Society	Generic (HUI II based on cited study)	Tariffs for classification and authors' judgment	Community (Canada)	3%	Univariable	Time horizon was changed in sensitivity analyses

APPENDIX. Continued

Study/Country	Intervention (Comparators)	Study Type	Age of Study Population/Time Horizon of Analysis	Perspective	Health State Classification System	Valuation Technique	Source of Preferences	Discount Rate*	Sensitivity Analysis*	Comments
Medina et al,[57] 2001/US	MRI for newborns with suspected occult spinal dysraphism (vs ultrasound or plain radiographs or no imaging)	Decision analysis	Newborns/lifetime	Society	Study specific	Clinician's judgment	Clinician	3%	Univariable (results also presented as cost per life gained)	
Poley et al,[58] 2001/Netherlands	Neonatal surgery for congenital anorectal malformations (vs no surgery)	Retrospective study using patient sample and modeling exercise	Mean age: 15.1 y (range: 1–51 y)/lifetime	Society	Generic (EQ-5D classified by parents for patients younger than 16 y) and disease specific	Tariffs for classification and authors' judgment	Community (UK) and authors	5%	Univariable	Preference weight for comparator "no treatment" (hypothetical health state) was estimated by the authors to be 0.5 (range 0.4–0.6), examined in the sensitivity analysis
Tengs et al,[19] 2001/US	Intensive school-based antitobacco education (vs no intervention)	Decision analysis	Newborns/lifetime	Society	Cited studies (generic: HUI for children aged 0–5 y and 6–8 y, extrapolation for age 9–17 y based on national statistics; QWB for adults)	Tariffs for classification	Community (US and Canada)	3%	Multivariable and probabilistic	Analysis conducted using the Tobacco Policy Model
Bos et al,[59] 2002/Netherlands	Vaccination with a hexagonal meningococcal outer-membrane vesicle vaccine (vs no vaccination)	Decision analysis	Newborns/lifetime	Society	Generic (EQ-5D classified by authors)	Tariffs for classification	Community (Netherlands)	4%	Univariable (results also presented as cost per life gained)	Authors acknowledged that short-term events (eg, sepsis, meningococcal disease) were not valued
Insinga et al,[60] 2002/US	Newborn screening for inborn errors of metabolism MCADD (vs no screening)	Decision analysis	Newborns/lifetime	Society	Cited study (which directly elicited values from extremely low birth weight survivors with mild neurologic impairment) and generic (HUI III classified by authors)	SG and tariffs for classification	Patients and community (Canada)	3%	NS	Authors also used age-specific preference weights based on national study (years of healthy life measure)
Medina et al,[61] 2002/US	Diagnostic strategies for suspected children with craniosynostosis (no imaging vs conventional radiography vs 3D CT)	Decision analysis	Newborns/20 y	Society	Study specific	Authors' judgment	Authors	NS	Univariable	
Membreno et al,[62] 2002/US	Surgical treatment strategies for amblyopia (vs nonsurgical strategies)	Decision analysis	4 y old/lifetime	Third-party payer	Cited study (which directly elicited values from adult patients with several visual impairments)	Cited study (TTO)	Cited study (adult patients)	3%	Multivariable	
Moya and Goldberg et al,[63] 2002/US	Prophylactic indomethacin in very low birth weight infants (vs no indomethacin)	Decision analysis	Newborns/15 y	Society	Study specific	Clinician's judgment	Clinicians	Yes (rate not given)	Univariable and multivariable	

APPENDIX. Continued

Study/Country	Intervention (Comparators)	Study Type	Age of Study Population/Time Horizon of Analysis	Perspective	Health State Classification System	Valuation Technique	Source of Preferences	Discount Rate*	Sensitivity Analysis*	Comments
Oostenbrink et al,[64] 2002/Netherlands	Diagnostic and treatment strategies for children with meningeal signs (comparing different management strategies)	Decision analysis	Infants (age range: 1 mo to 15 y)/15 y	Society	Generic (HUI III vignettes describing different health states classified by clinicians)	Tariffs for classification	Community (Canada)	4%	Univariable	Alternative set of preference weights from published study was applied
Poley et al,[65] 2002/Netherlands	Neonatal surgery for congenital diaphragmatic hernia (vs no surgery)	Retrospective study using patient sample and modeling exercise	Mean age: 14.8 y old (range: 1–42 y)/lifetime	Society	Generic (EQ-5D classified by parents for patients <16 y old)	Tariffs for classification	Community (UK)	5%	NS	Authors' assumed that patients not treated would die shortly after birth (QALYs = 0)
Schoen et al,[66] 2002/US	Newborn screening for inborn errors of metabolism (vs no screening)	Decision analysis	Newborns/lifetime	Third-party payer (health insurance)	General disability	NS	Authors	3%	Univariable	
Angus et al,[67] 2003/US	Inhaled nitric oxide for neonatal respiratory failure (vs no inhaled nitric oxide)	Decision analysis	Newborns/1 y	Society	General disability	Authors' judgment	Authors	NO	Univariable	Authors refer to adult studies and studies of extremely low birth weight survivors; preference weight of 0.49 for survivors with chronic neurologic and chronic respiratory disability was assumed to be the product of preference weights for survivors with either disability (both 0.70)
Bos et al,[68] 2003/Netherlands	Vaccination with a 7-valent conjugated pneumococcal vaccine (vs no vaccination)	Decision analysis	Newborns/lifetime	Society	Generic (EQ-5D classified by authors)	Tariffs for classification	Community (Netherlands)	4%	NS	Authors acknowledged that short-term events (eg, sepsis, meningitis) were not considered
Brisson et al,[69] 2003/UK	Varicella vaccination (infants strategy vs catch-up and adolescent strategy)	Decision analysis	Infants, 2–11 y old and 11 y old/lifetime	Health service and society	Generic (HUI II classified by parents of children with history of chickenpox)	Tariffs for classification	Community (Canada)	3%	Univariable and probabilistic	Adult's preference weight for chickenpox was assumed to be the same to that of mild zoster
Ess et al,[70] 2003/Switzerland	Vaccination with 7-valent conjugated pneumococcal vaccine (vs no vaccination)	Decision analysis	Newborns/5 y	Society	General disability	Authors' judgment	Authors	NS	NS	
Eastman et al,[71] 2003/US	Use of the Glucowatch biographer for type 1 diabetes (vs no use)	Decision analysis using patient sample and existing model	Age range 7–17 y/lifetime	Third-party payer	NS	NS	NS	3%	NS	No details given of how preference weights were generated
Jacobs et al,[72] 2003/US	Universal childhood hepatitis A vaccination (vs selective vaccination)	Decision analysis	2 y old/lifetime	Health service and society	Study specific	TTO	Adults	3%	Univariable (95% CI of TTO)	

APPENDIX. Continued

Study/Country	Intervention (Comparators)	Study Type	Age of Study Population/Time Horizon of Analysis	Perspective	Health State Classification System	Valuation Technique	Source of Preferences	Discount Rate*	Sensitivity Analysis*	Comments
Ruedin et al,[73] 2003/ Switzerland	General vaccination regimen against meningococcal and pneumococcal diseases (vs selective regimen)	Decision analysis	Newborns/lifetime	Third-party payer (health insurance)	General disability	Clinician's judgment	Clinicians	No	Multivariable	Discount rates of 2% and 5% for effects tested in sensitivity analyses
Sanders and Taira,[17] 2003/US	Vaccination against human papillomavirus (vs no vaccination)	Decision analysis	12 y old/lifetime	Society	Cited study (HUI and study specific)	Tariffs for classification and authors' judgment	Community (Canada) and authors	3%	Univariable	Age-specific preference weights based on Beaver Dam Health Outcome Study were used in a Markov model
Venditti et al,[74] 2003/ US	Newborn screening for inborn errors of metabolism (MCADD) (vs no screening)	Decision analysis	Newborns/20 and 70 y	Society	Study specific	Authors' judgment	Authors	3%	Univariable	The value of a false-positive screening result was assumed to be 0 over a period of 3 mo
Zupanic et al,[75] 2003/ US	Predischarge monitoring for apnea of prematurity (different durations of monitoring vs no monitoring)	Decision analysis	Newborns/lifetime	Society	Cited study (which asks parents of prematurely born children to classify them on the HUI) and study specific (temporary health states)	Tariffs for classification and authors' judgment	Community and authors	3%	Univariable	No additional details given for the calculation of preference weights except for temporary health states
Doyle et al,[76] 2004/ Australia	Neonatal intensive care in 1997 (vs neonatal intensive care in 1979–1980; 1985–1987; 1991–1992)	Before and after study using different 4 different cohorts	Newborns/lifetime	NS (but only direct cost was included)	General disability	Authors' judgment	Authors' judgment	3%	Multivariable	
Konig et al,[77] 2004/ Germany	Childhood screening for amblyopia (vs no screening)	Decision analysis	3 y/lifetime	Third-party payer (health insurance)	Cited study (which elicited values from adult patients with several visual impairments)	Cited study (TTO)	Cited study (adult patients)	5%	Univariable and probabilistic	Preference weights for unilateral visual impairment based on authors' judgment
Prosser et al,[27] 2004/ US	Vaccination with pneumococcal conjugate vaccine (vs no vaccination)	Decision analysis	Newborns/lifetime	Society	Study specific	TTO	Parents of patients and community sample	TTO values were discounted at 3%	Univariable (25th and 75th percentiles of TTO values, responses from both samples were tested)	Parents were ask to trade their own life to avoid condition-related temporary health state of their child and were asked explicitly to consider their HRQoL as well

NS indicates not stated; NA, not applicable; HRQoL, health-related quality of life; QWB, Quality of Well-Being scale; HUI, Health Utility Index; IHRQL, Index of Health-Related Quality of Life; QALD, quality-adjusted life day; 15D, 15-dimensional measure of health-related quality of life; VAS, visual analog scale; SG, standard gamble; TTO, time trade-off.
* Discount rate and sensitivity analysis refer only to health outcomes (QALYs).

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