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Global Assessment of Health Utilities Associated with Pneumococcal Disease in Children — Targeted Literature Reviews

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ABSTRACT

Background: Pneumococcal disease can significantly impact the quality of life (QoL) of children. Health utilities are used to measure the disease burden and calculate quality-adjusted life year (QALY) estimates. These estimates provide critical inputs in economic evaluations of pneumococcal vaccines in children.

Objectives: This study aimed to synthesize utility values used in cost-utility analyses (CUAs) of pediatric pneumococcal vaccines and to summarize published utility studies on pneumococcal disease and post-meningitis sequelae (PMS) in children on a global scale.

Methods: Two targeted literature reviews were conducted to identify CUAs of pediatric pneumococcal vaccines and original studies on health utilities of pneumococcal disease and PMS. Both literature reviews identified relevant studies using published reviews, supplemented by *de novo* searches conducted in MEDLINE in June 2024 to cover periods not included in those reviews. References from published literature reviews on QoL of pneumococcal disease and CUAs were screened to identify additional original utility studies. Health utility values applied in the CUAs were summarized and the source studies for these utilities were reviewed. For original utility studies, methods and utility estimates were summarized for each condition.

Results: The study identified 45 CUAs of pediatric pneumococcal vaccines in North America and Europe published from 2004 to 2024, and 21 original utility studies on pneumococcal disease or PMS in children published globally from 1994 to 2017. QALY decrement was the most common utility input in CUAs. Most CUAs referenced an earlier CUA for utility inputs, which were often sourced from one or two original utility studies for each health state. Most source studies were published more than two decades ago; some common source studies were conducted in adults. Utility estimates from original studies showed considerable variability, with ranges of -0.330–0.6882 for meningitis, -0.331–0.93 for non–

meningitis IPD, -0.054–0.71 for inpatient pneumonia, 0.412–0.82 for outpatient pneumonia, 0.389–0.97 for AOM/simple AOM, 0.434–0.540 for recurrent AOM, -0.33–0.89 for neurological deficits, and 0.217–0.97 for hearing loss. Variability in methods, including in the surveyed population, utility elicitation method, and use of different country-specific preference weights, substantially impacted utility values. Overall, the methods were not suitable for temporary health states. Additionally, many studies used instruments that have not been validated in children.

Conclusions: Original utility studies demonstrated that pneumococcal disease and PMS are associated with impaired QoL in children; however, there was considerable variability in utility estimates across studies, reflecting the inherent methodological challenges in estimating utilities for acute diseases in children. Most CUAs referenced previous CUAs for health utility values, which were sourced from a limited number of outdated original utility studies. Contemporary data and methods adapted for acute diseases in children are needed for future studies. Given the significance of health utilities in the economic valuations of new pneumococcal vaccines, utility values should be carefully selected in CUAs, considering alternative sources and assumptions.

KEY POINTS FOR DECISION MAKERS

- Pneumococcal disease and post-meningitis sequelae (PMS) are associated with impaired quality of life in children; however, health utility estimates for these conditions vary across published studies, likely as a result of methodological differences.
- Health utility values in published cost-utility analyses (CUAs) of pneumococcal vaccines in North America and Europe are often sourced from a limited number of outdated original utility studies.
- Utility values for pneumococcal disease and PMS estimated using contemporary data and methods adapted for acute diseases in children are needed to more accurately quantify the burden of pneumococcal disease in children and inform future CUAs.

DECLARATIONS

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Conflicts of interest: MH, EE, and SM are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc. DR is a consultant for Merck & Co., Inc and is a member of the EuroQol group. JX is an employee of XL Source, Inc., a consulting company that has provided paid consulting services to this research project. HR, YS, SL and DL are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Merck & Co., Inc. MSK is a consultant for Merck & Co., Inc. and Invivyd and provided paid consulting services to this research project.

Author contributions: MH, EE, and SM contributed to the conceptualization of the study. All authors contributed to the study design and methodology. JX, HR, SL, and DL conducted literature search and data extraction. MH and JX developed the initial summary of the results. All authors contributed to the interpretation of the findings, the development of the initial draft of the manuscript, and the revisions of the manuscript.

1 INTRODUCTION

Pneumococcal disease includes a group of infections caused by *Streptococcus pneumoniae* (*S. pneumoniae*) that leads to substantial morbidity and mortality, especially in young children [1, 2]. Pneumococcal disease has a wide range of manifestations, encompassing both non-invasive (e.g., acute otitis media [AOM]) and invasive (e.g., meningitis) infections [3]. Invasive pneumococcal disease (IPD) often requires hospitalization, resulting in substantial healthcare resource use and costs in children [4-8]. In particular, meningitis is associated with high mortality and can lead to serious long-term neurological sequelae [9-11]. Based on a review, 8.2% and 12.2% of pneumococcal meningitis cases would lead to hearing loss and neurological deficits, respectively [12]. The incidence of non-invasive pneumococcal disease is higher than the incidence of IPD, though these infections are generally less severe. For example, 60% of children in the United States (US) experience at least one episode of AOM by 3 years of age [13], making it the leading cause of pediatric outpatient visits and antibiotic prescriptions [14]. Beyond the impact on healthcare resource use and costs, pneumococcal disease can significantly impair the quality of life (QoL) of children [15]. Collectively, pneumococcal disease imposes substantial burdens on pediatric patients, their families, healthcare systems, and society at large.

Childhood immunization with pneumococcal conjugate vaccines, such as 7-valent pneumococcal conjugated vaccine (PCV), 10-valent PCV, and 13-valent PCV, has substantially reduced the global burden of pneumococcal disease over the past several decades [1]. Higher-valency vaccines have recently been approved for routine childhood vaccination, including 15-valent PCV (PCV15 or V114) and 20-valent PCV (PCV20) [16-19]. The economic value of a new pneumococcal vaccine significantly impacts its adoption into national immunization programs. Most economic evaluations of pneumococcal vaccines have applied cost-utility analysis (CUA), in which health utilities of pneumococcal disease and post-meningitis sequelae (PMS) play a critical role [20, 21]. However, existing CUAs utilize a wide range of utility values, often sourced from previous CUAs that did not provide clear rationales selection of these

utility values. These studies rarely used utility estimates that have been systematically identified from the literature, as recommended by major health technology assessment bodies, such as the National Institute for Health and Care Excellence (NICE) [22]. Thus, the first objective of this study was to conduct a targeted literature review to summarize the health utility values and sources used in published CUAs of pediatric pneumococcal vaccines in North America and Europe, through which we identify gaps in utility values in existing CUAs.

In addition, it is important to critically review the current literature on health utilities of pneumococcal disease for the purpose of economic evaluations. Valuing acute diseases in children presents multiple challenges due to the lack of patient-reported outcomes and other appropriate measures specifically developed to value temporary health states in children. Although several reviews on health utilities of pneumococcal disease have been published recently [15, 20, 23], each has overlooked important studies on health utilities of pneumococcal disease. Given the ongoing relevance of pneumococcal disease in public health and the significant impact of the cost-effectiveness of pneumococcal vaccines on policy decision making, a comprehensive and current understanding of the available literature on health utilities of pneumococcal disease is essential. Therefore, the second objective of this study was to update previous reviews of the health utilities of pneumococcal disease in children (age 0-17 years) through a comprehensive and targeted search of the global literature. Our findings provide a more detailed understanding of the QoL burden associated with pneumococcal disease and, along with the identified gaps in utility values from CUAs, can inform future economic evaluations of pneumococcal disease interventions in children.

2 METHODS

Two targeted literature reviews were conducted in this study. The first review sought to summarize utility values and their sources from relevant CUAs of pediatric pneumococcal vaccines in

North America and Europe. The second review aimed to synthesize original research studies estimating health utility values for pneumococcal disease in children globally. Both literature reviews relied on published reviews to identify the relevant studies, supplemented by *de novo* literature searches for the periods not included in the published reviews. The *de novo* literature searches were conducted on June 11, 2024, in the Medical Literature Analysis and Retrieval System Online (MEDLINE), MEDLINE Daily, MEDLINE In-Data-Review & Other Non-Index Citations, and MEDLINE In-Process using keywords. Following the guidance from the Centre for Review and Dissemination [24], we performed two levels of screening. Level 1 screened titles and abstracts and level 2 screened full-text articles identified as possibly relevant studies from the level 1 screening. Each level of screening was performed by two independent reviewers (SL and DL) and discrepancies were resolved by a third reviewer (HR). Basic publication information, including authors, publication year, country of study, and age groups, were extracted from all eligible studies. The specific methods for literature search, screening, data extraction, and evidence synthesis are described separately for each literature review below.

2.1 CUAs of pediatric pneumococcal vaccines

The keyword search used in the CUA literature review included a combination of disease terms (e.g., “pneumococcal”, “meningitis”, “bacteremia”, “pneumonia”, “otitis media”, “hearing loss”, “neurological sequelae”) and cost terms (e.g., “economic burden”, “cost”, “productivity”) (**Supplementary Table 1**). This search identified CUAs of pneumococcal vaccines and reviews on CUAs published since 2010. Relevant CUAs published before 2010 were obtained by screening the references of the published reviews. An eligible study for the current CUA literature review must have met the following inclusion criteria: 1) focused on children (0-17 years of age) in North America and Europe; 2) included a pneumococcal vaccine as an intervention arm; 3) included quality-adjusted life years (QALYs) as an outcome with utility values, disutility values, QALYs, or QALY decrements for a pneumococcal

disease or PMS reported; 4) was published in or after 1990; and 5) was published in a full-text manuscript in English. We chose to focus this review on studies conducted in North America and Europe because these are the regions where new pneumococcal vaccines have historically been first introduced.

Health state descriptions, utility values applied in the base case and sensitivity analyses, and sources for utility values were extracted, in addition to the basic study characteristics. Because most of the CUA studies did not report utility values used in sensitivity analyses, only base-case values were summarized. The range and the most commonly used base-case utility values were summarized for each pneumococcal disease and PMS disease state. Additionally, the study design and utility elicitation methods of the source studies were described.

2.2 Original research studies estimating health utility values for pneumococcal disease

The second targeted literature review aimed to update the existing published reviews on health utilities of pneumococcal disease. The most recently published systematic literature review included literature up to January 1, 2020 [15]. Therefore, the current literature search was designed to identify original research studies and reviews of health utilities for pneumococcal diseases since 2019. The literature search method was the same as that for CUAs, except that the cost search terms were replaced with the utility search terms, such as “utility”, “quality of life”, and a list of instruments that measure health utility (**Supplemental Table 2**). In addition to the *de novo* search, we screened the references of the identified health utility reviews and the included CUAs from the first literature review for additional eligible studies published before 2019. To be included in this review, an original research study must have met the following criteria: 1) focused on the disease states frequently caused by *S. pneumoniae* in children (0-17 years of age); 2) reported an outcome of health utility, QALY estimate, disutility or QALY decrement for one episode of acute disease or long-term sequelae; and 3) published in a full-text manuscript in English. Furthermore, an original research study was excluded based on the following

criteria: 1) the study population was not representative (e.g., a population with a comorbidity that impacts QoL); 2) the symptoms, disease course or treatment of the acute disease under evaluation were different from pneumococcal disease based on input from a clinical expert (MSK); or 3) the utility estimates for acute disease included a time period after recovery. Of note, this literature review intended to capture all eligible studies, and thus no time frame or geographical restrictions were applied. Additionally, we included all measures that may represent health utility values, though some measures should not be interpreted as utility values due to lack of explicit trade-off between alternatives (e.g., visual analogue scale [VAS] scores).

Health state descriptions, population surveyed, sample size, utility estimation methods, type of utility outcomes (i.e., utility, QALY estimate, disutility, or QALY decrement) and reported utility estimates were extracted from eligible original research studies. The range of point estimates for utility outcomes was summarized for each pneumococcal disease and PMS category. Variations of point estimates, such as standard deviations, standard errors, 95% confidence intervals, and ranges were extracted from each study (if reported).

In addition, study methods were summarized, including the type of population surveyed (e.g., patients, caregivers, healthcare providers [HCPs], the general population) and the utility estimation methods used, e.g., direct methods (e.g. time trade-off [TTO] on own health), indirect methods (e.g., EuroQol-5 Dimension [EQ-5D]), and vignette-based study. Heterogeneity in methodology and results within and across studies were noted.

3 RESULTS

3.1 Literature search results

The literature review focused on CUAs of pneumococcal vaccines identified 84 studies in North America and Europe and 11 reviews of CEAs published since 2010. An additional 24 CUAs were included after review of the references of the 11 reviews (**Figure 1A**). After excluding the studies undertaken in adult populations, 45 CUAs of pneumococcal vaccines in children published between 2003 and 2024 were included (**Supplementary Table 3**). Forty of these studies applied utility inputs for IPD [25-64], 38 for pneumonia [25-27, 29-35, 38, 41-58, 60-62, 64-69], 36 for AOM [25-27, 29-35, 38, 41-43, 45-53, 55-58, 60-62, 64-69], and 40 for PMS [25-64]. These studies spanned 16 countries in North America and Europe, with the most frequent locations being the US, Canada, the United Kingdom (UK), and the Netherlands.

The literature review of original utility studies identified four *de novo* studies and three published reviews, from which 27 original utility studies were identified. An additional nine were added based on a review of the references of the included CUAs (**Figure 1B**). After excluding utility studies focused on adults only, 21 original utility studies in children published between 1994 and 2017 were included in this review [70-90] (**Supplementary Table 4**). The studies estimated utility values for pneumococcal disease and PMS (n=8), pneumococcal disease only (n=6), or PMS only (n=7). These studies were conducted in six countries — Argentina, Canada, the Netherlands, Thailand, the UK, and the US. One study was conducted in Argentina but also estimated the utility values for Chile and the UK using the country-specific preference weights from those two countries [77].

3.2 CUA studies

A summary of utility inputs applied to the pediatric CUAs of pneumococcal vaccines is presented in **Table 1**, with detailed results in the supplementary document (**Supplementary Tables 5-8**). Most

CUAs applied QALY decrements for pneumococcal disease and utilities for PMS. Overall, the ranges of base-case utility values varied substantially for each pneumococcal disease and PMS health state. For example, the base-case QALY decrements ranged from 0.006 to 0.76 for meningitis [25, 27, 29-35, 38, 41, 42, 44-58, 60-62, 64-66, 68, 69], 0.0016 to 0.21 for non-meningitis IPD [25-27, 29-35, 38, 41, 42, 44-58, 60-62, 64-66, 68, 69], 0.0060-0.59 for inpatient pneumonia [25-27, 29-35, 38, 41, 42, 44-58, 60-62, 64-69], 0.004-0.18 for outpatient pneumonia [25, 27, 29-35, 38, 41, 42, 44-58, 60-62, 64, 65, 67, 68], and 0.0016-0.011 for AOM [25-27, 29-31, 33, 34, 41, 42, 45-49, 51, 52, 55, 57, 58, 60-62, 64, 65, 67-69]. The base-case utility values ranged from 0.47-0.89 for neurologic deficits [28, 35, 36, 38-40, 43, 44, 50-56, 58-60, 62, 63] and 0.45-0.91 for hearing loss [28, 35, 36, 38-40, 43, 44, 50-56, 58-60, 62, 63].

Despite the wide ranges in the utility inputs, most CUAs referenced previous CUAs for the utility inputs, which were sourced from one CUA conducted in the UK by Melegaro et al. (2004) [45]. Specifically, Melegaro et al. derived QALY decrements for meningitis, non-meningitis IPD, as well as inpatient and outpatient pneumonia, from a utility study conducted in the US by Bennett et al. (2000) [72], which contributed to 77-81% of the included CUAs in the current review, depending on the pneumococcal disease state. Additionally, they derived the QALY decrement for AOM based on VAS responses from healthcare providers in Canada conducted by Oh et al. (1996) [86], which contributed to 81% of the CUAs including a health state related to AOM. However, Melegaro et al. did not describe the methods used to derive the QALY decrements for these health states. For PMS, the studies conducted by Oostenbrink et al. (2002) [87] and Torrance et al. (1982) [91] were the most common sources, contributing to 85% of the utility inputs for neurological deficits and 58% for hearing loss. Similar to the pneumococcal disease states, the derivations of the utility inputs for PMS were not described in the CUAs and some could not be identified from the source studies. In addition, a study conducted in the US by Erickson et al. (2001) [92] provided the utility input for hearing loss in 10 CUAs, though the utility value was estimated based on the response from a single adult.

3.3 Original health utility studies

The original studies employed various methods to estimate the utility outcomes, including health utilities, VAS outcomes, QALY estimates, disutilities, and QALY decrements, with health utilities being the most common type of outcomes overall. However, for certain conditions (e.g., recurrent AOM), VAS was the most common type of utility outcomes. The included studies surveyed parents or caregivers, experts or HCPs, the general population, and patients. While parents or caregivers were the most common respondents, expert or HCP surveys were used in five studies, two of which (Oh et al., 1996 and Oostenbrink et al., 2002) [86, 87] were widely referenced for the utility inputs for AOM and PMS, respectively, in published CUAs. The original studies employed common direct methods, including SG and TTO, as well as indirect methods, such as EQ-5D index score, HUI-3 and HUI-2. Use of vignettes was also common, applied in 10 studies. The most common source studies on children for utility inputs in CUAs (Bennett et al, 2000; Prosser et al., 2004; Oh et al, 1990; and Oostenbrink et al., 2002) all employed vignettes [72, 86, 87, 89]. In addition, a few studies applied unique methods that are different from most of the included studies. Specifically, Bennett et al. (2000) was the only study that estimated QALY per year using SG [72], and as previously described, was the most common source for the utility inputs for meningitis, non-meningitis IPD, as well as inpatient and outpatient pneumonia in CUAs. Prosser et al. (2004) [89] applied a TTO method that asked the respondents to trade their own life to prevent their child or a hypothetical child from experiencing the condition and was the only study capturing the QoL impact of the condition on both children and caregivers in a single estimate and the only study contributing to QALY decrement outcomes. This study was the source of the utility inputs for meningitis in three CUAs [32, 65, 66]. Stouthard et al. (1997) conducted a person trade-off (PTO) survey among HCPs to estimate health utility values for a number of conditions [90]. Galante et al. (2011) applied preference weights from Chile and the UK to the EQ-5D responses from an Argentinian general population to estimate the health utilities for pneumococcal disease and PMS in these two countries [77].

Finally, Gold et al. (1998) estimated the values for the Health and Limitation Index (HALex), which has been frequently used as health utility values for neurological deficits in published CUAs [78], though, strictly speaking, it is not a utility estimate. Of note, it was common for a study to apply multiple methods to estimate utility outcomes, which provided an opportunity to evaluate the impact of various methods on utilities. The utility outcomes for each pneumococcal disease and PMS condition are summarized below, with the discussion on the impact of methodology on utility estimates.

3.3.1 Invasive pneumococcal disease

Seven studies estimated utility outcomes for meningitis. Among them, five also estimated utility outcomes for bacteremia and/or sepsis (**Table 2**).

3.3.1.1 Meningitis

The seven studies estimated different utility outcomes for a range of meningitis conditions [72, 77, 80, 82, 84, 88, 89]. Four studies estimated health utility values [77, 80, 84, 88], three estimated VAS values [77, 82, 84], one estimated QALYs [72], one provided disutilities [88], and one estimated QALY decrements [89]. Some studies estimated utility outcomes for meningitis in general, while other studies focused more on a specific treatment setting (e.g., meningitis requiring admission to the intensive care unit [ICU]). The point estimates of the utilities for meningitis ranged from -0.330 to 0.6682 [77, 80, 84, 88], with a median value of 0.265 and an interquartile range (IQR) from 0.060 to 0.377. The VAS values ranged from 0.317 to 0.535 [77, 82, 84], with a median (IQR) of 0.431 (0.415–0.475). Furthermore, QALYs per year for one episode of meningitis were estimated at 0.9768 [72]. The QALY decrement value of 0.0232 (derived from 1− 0.9768) was the most commonly cited utility input value in the CUAs. Disutility for meningitis reported by Petro et al. (2009) [88] was 0.826 compared to perfect health and 0.752 compared to the population norm. Finally, based on the results and methods described in the study by Prosser et al. (2004) [89], we estimated the QALY decrement for meningitis as 0.50 based on

interviews of parents or caregivers and 0.76 based on interviews of the general population, which was used in several CUAs [32, 65, 66].

The variability in utility estimates for meningitis reflected the variations of utility estimation methods, including health state definitions, survey populations, valuation methods, and preference weights. The way in which health states are defined had a direct impact on health utilities. For instance, the Institute of Medicine (IOM, 2000) study showed that the meningitis health states requiring ICU treatment or involving complications were associated with lower utility values [80]. The survey population also had a substantial impact on the utility estimates. For example, children with the disease gave higher valuations than their parents [84]. Parents of febrile children provided higher utility values compared to those of well children and HCPs [82]. QALY decrement estimated using the general population was higher compared to the one estimated using parent or caregiver interviews [89]. Additionally, the values also varied substantially across valuation methods. EQ-VAS led to a higher value compared to the EQ-5D index score [77, 84]. Of all the instruments applied by Kulpeng et al. (2013), the EQ-5D index score yielded the lowest values, whereas the HUI-2 resulted in highest utility estimates [84]. The selection of country-specific preference weight also had a significant impact on utility values. Galante et al. (2011) showed that the preference weights from Chile and the UK resulted in substantially lower utility values than the preference weights from Argentina [77].

3.3.1.2 Non-meningitis IPD

Five studies estimated various health states related to bacteremia and/or sepsis [72, 77, 80, 84, 89]. Three studies reported health utilities [77, 80, 84], two also estimated VAS values [77, 84], one provided a QALY estimate [72], and one estimated QALY decrement. The point estimates of health utilities for bacteremia and/or sepsis [77, 80, 84] ranged from -0.331 to 0.93, with a median of 0.469 and an IQR of 0.203 to 0.610. The VAS values ranged from 0.317 to 0.6148, with a median of 0.5746. The

QALYs per year for one episode of occult bacteremia with hospitalization were 0.9921 [72], equivalent to a QALY decrement of 0.0079. The derived QALY decrement for bacteremia based on the study by Prosser et al. (2004) [89] was 0.10 based on interviews of parents or caregivers and 0.21 based on interviews of the general population. Health states, survey populations, utility valuation methods, and the choice of preference weights had similar impacts on health utilities of non-meningitis IPD compared to meningitis, except that the comparison of health utility estimates between parents/caregivers and children showed mixed findings, depending on the instruments [84].

3.3.2 Pneumonia

Seven studies estimated utility outcomes for pneumonia [72, 77, 80, 82, 84, 89, 90] (**Table 3**). Of these studies, three estimated the outcomes for inpatient and outpatient pneumonia separately [77, 80, 89], one estimated the utility for inpatient pneumonia only [72], while the remaining studies reported the utility values for pneumonia with unspecified setting [82, 84, 90].

3.3.2.1 Inpatient and outpatient pneumonia

The four studies estimated various pneumonia health states defined by treatment setting, severity, and complications [72, 77, 80, 89]. Of the four studies, two estimated health utilities [77, 80], with one also providing EQ-VAS [77], one estimated QALYs per year [72], and one estimated QALY decrements [89]. The range of point estimates for the utility of inpatient pneumonia was -0.054 to 0.71, with a median value of 0.309 and an IQR from 0.035 to 0.64 [77, 80]. The EQ-VAS reported by Galante et al. (2011) was 0.464 [77]. Bennett et al. (2000) estimated QALYs per year of 0.9941 for one episode of occult bacteremia with local infection [72], which was considered to be representative of inpatient pneumonia based on input from the clinical expert. The derived QALY decrement of 0.0059 (1−0.9941) was the most common utility input value for inpatient pneumonia in CUAs. Furthermore, the QALY decrement per episode of “severe pneumonia” was estimated at 0.27 based on interviews of parents or caregivers and

0.59 based on interviews of the general population [89]. The range of point estimates for the utility of outpatient pneumonia was 0.412 to 0.82, with a median of 0.719 and an IQR of 0.538 to 0.818 [77, 80]. The EQ-VAS for outpatient pneumonia was 0.584 reported by Galante et al. (2011) [77]. The QALY decrements for "moderate pneumonia" based on the study by Prosser et al. (2004) were 0.00 and 0.18, based on the interviews of parents/caregivers and the general population, respectively [89]. Consistent with the findings in IPD, health states, survey populations, and the choice of preference weights had substantial impacts on the utility outcomes for inpatient and outpatient pneumonia.

3.3.2.2 Pneumonia, unspecified setting

Three studies estimated utility outcomes for pneumonia without specifying care setting: one estimated both health utility and VAS values [84], one estimated health utility only [90], and one estimated VAS only [82]. The point estimates for utilities ranged from 0.4610 to 0.90 (median: 0.587; IQR: 0.509 to 0.708) [84, 90]. The VAS values ranged from 0.669 to 0.831 (median: 0.7261; IQR: 0.6795–0.749) [82, 84]. While the utility estimates for pneumonia varied across different survey populations, we observed somewhat different trends here compared to those observed for IPD. For example, in the study by Kramer et al. (1994) [82], the responses from HCPs yielded the highest utility values, while the ones from parents of febrile children resulted in the lowest utility values. The utility values based on the same valuation methods were similar between parent-proxy report and patient self-report in the study by Kulpeng et al. (2013) [84], and with some instruments, patients gave slightly lower valuations than parents or caregivers.

3.3.3 Acute otitis media

Ten studies were included in the utility estimation of AOM [73, 74, 76, 77, 79, 80, 83, 84, 86, 89] (**Table 4**). Seven studies estimated utility outcomes for AOM/simple AOM [74, 76, 77, 80, 84, 86, 89]; four for recurrent AOM [73, 79, 83, 89]; one for AOM with myringotomy [77].

3.3.3.1 AOM/simple AOM

Among the studies estimating utility outcomes for AOM/simple AOM, four reported health utility values [74, 77, 80, 84], four estimated VAS outcomes [76, 77, 84, 86], and one study estimated QALY decrements [89]. The point estimates of utilities for AOM ranged from 0.389 to 0.97 (median: 0.647; IQR: 0.554 to 0.749) [74, 77, 80, 84]. The VAS values ranged from 0.634 to 0.79 (median: 0.667; IQR: 0.666 to 0.699) [76, 77, 84, 86]. The QALY decrements per episode of "simple AOM" were 0.00 based on the interviews of parents or caregivers and 0.01 based on the interviews of the general population in the study by Prosser et al. (2004) [89]. The values estimated using the EQ-VAS were consistently higher than those from the EQ-5D index score in the two studies that included these measurements [77, 84]. However, there was no consistent trends in the comparisons between proxy-reported and self-reported utility estimates and among different instruments [84].

3.3.3.2 Recurrent AOM

Of the four studies that estimated utility outcomes for recurrent AOM [73, 79, 83, 89], three surveyed parents or caregivers of children with the disease using the VAS from the OM-6 questionnaire [73, 79, 83]. The point estimates for VAS values ranged from 0.434 to 0.540, with a median value of 0.534. The QALY decrements per episode based on the study by Prosser et al. (2004) [89] were 0.25 using interviews of parents or caregivers and 0.36 using interviews of the general population. None of the studies estimated health utility for recurrent AOM.

3.3.3.3 AOM with myringotomy

In addition to AOM, Galante J et al. (2011) [77] estimated the utility value for AOM with myringotomy, which ranged from 0.064 to 0.339 based on the EQ-5D index score. Consistent with previous results, the utility estimates based on the Chile and UK preference weights yielded lower utility estimates in comparison to estimates that used the Argentinian preference weights.

3.3.4 Post-meningitis sequelae

A total of 15 studies estimated utility outcomes for various PMS health states [70-72, 74, 75, 77, 78, 80-82, 84, 85, 87, 88, 90] (**Table 5**). These studies covered a wide range of conditions, varying in severity, some of which may not be directly related to pneumococcal disease.

3.3.4.1 Neurological deficit

Ten studies estimated utility outcomes for various conditions that represented neurological deficits [72, 74, 77, 78, 80, 82, 84, 87, 88, 90], which were classified into five categories: cerebral palsy, epilepsy/seizures, mental retardation, other neurological sequelae (primarily locomotor impairment), and multiple neurological sequelae (which included two or more of the previous categories). Eight studies estimated health utilities [72, 74, 77, 80, 84, 87, 88, 90], three estimated VAS outcomes [77, 82, 84], one provided disutility values [88], and one estimated other utility outcomes (specifically the HALex score) [78]. The point estimates for health utilities across all neurological conditions ranged from -0.33 for severe mental retardation and tetraplegia to 0.89 for epilepsy [72, 74, 77, 78, 80, 82, 84, 87, 88, 90]. The ranges were narrower within each of the five categories of neurological deficits but still demonstrated substantial variations in utility values. Specifically, the range of utility estimates was 0.276–0.88 for cerebral palsy [74, 78, 88], 0.334–0.89 for epilepsy/seizures [74, 84, 87, 88, 90], 0.24–0.84 for mental retardation [74, 84, 87, 90], 0.51–0.83 for other neurological sequelae [87, 90], and -0.33–0.7393 for multiple neurological sequelae [72, 74, 80, 84, 87, 88, 90]. The “multiple neurological sequelae” category included mixed neurological conditions and thus exhibited the widest range among the five categories. While disease severity contributed to the variations within each category, it was not the only factor, as considerable differences in utility estimates were observed for the same severity within and across studies. For instance, utility point estimates for mild mental retardation ranged from 0.24 to 0.84 [74, 84, 87], reflecting the same range observed across all mental retardation conditions. However, the median (IQR) utility values were consistent with the relative disease severity for each category, with 0.760

(0.575–0.815) for cerebral palsy, 0.7904 (0.6682–0.84) for epilepsy, 0.652 (0.591–0.722) for mild mental retardation, 0.389 (0.227–0.53) for severe mental retardation, and 0.735 (0.630–0.808) for other neurological sequelae. Other utility outcomes, including VAS and disutility, were also reported but uncommon. Two studies estimated health utilities for unspecified neurological sequelae [77, 80], ranging from 0.217 to 0.6, with a median value of 0.413 and an IQR from 0.294 to 0.531.

There was more variability in health utility estimates based on indirect methods compared to direct methods. For example, the studies by Kulpeng et al. (2013) and Oostenbrink et al. (2002) showed considerable within-study variations in utility estimates across different instruments [84, 87]. In contrast, Carroll et al. (2009) showed that utility values were comparable between the two direct methods (SG and TTO) [74]. Preference weights had a considerable impact on utility estimates, similar to the observations in pneumococcal disease states; while the health utility values were similar across different survey populations when the same valuation method was used.

3.3.4.2 Hearing loss

Eleven studies estimated utility outcomes for hearing loss [71, 72, 74, 75, 77, 82, 84, 85, 87, 88, 90], among which eight were also included in the summary for neurological deficit [72, 74, 77, 82, 84, 87, 88, 90]. These studies encompassed a wide spectrum of hearing loss, ranging from mild to profoundly deaf. Nine studies estimated utility values [71, 72, 74, 75, 77, 84, 87, 88, 90], while VAS values were estimated in three studies [77, 82, 84]. Additionally, two studies reported disutility values [85, 88].

Overall, utility point estimates for hearing loss ranged from 0.25 for pre-cochlear implant among profoundly deaf children [75] to 0.97 for post-cochlear implant in the same population [75]. The median value was 0.680, with an IQR of 0.580 to 0.860 [71, 72, 74, 75, 77, 84, 87, 88, 90]. The range of utility point estimates for mild-to-moderate hearing loss (including mild and moderate hearing loss, unilateral hearing loss, and post-cochlear implant) was 0.64–0.97 (median: 0.890; IQR: 0.667 to 0.920) [71, 74, 75,

87, 90], while that for severe hearing loss (including severe/profound hearing loss, bilateral hearing loss, deafness, and pre-cochlear transplant) was 0.25–0.8611 (median: 0.683; IQR: 0.439 to 0.805) [71, 72, 74, 75, 87, 88, 90]. The VAS values for hearing loss ranged from 0.368 to 0.8330, with a median of 0.516 and an IQR of 0.451 to 0.652 [77, 82, 84]. The disutility estimates for hearing loss reported by two studies varied from 0.117 for hearing impairment to 0.583 for deafness, compared to perfect health [85, 88]. Consistent with previous findings, substantial variability in utility estimates was observed within and across studies, even for similar levels of disease severity. Within the same study, direct methods of SG and TTO generated more consistent utility estimates [74]. More variability was observed across indirect methods, with the HUI-3 consistently producing the lowest utility estimates and the EQ-5D index score generating the highest utility estimates [84, 87]. Cross-study comparisons revealed similar trends, with SG and TTO resulting in the highest utility estimates and the HUI-3 instrument generally yielding the lowest utility estimates.

3.3.4.3 Unspecified PMS states

Three studies estimated the utility for a PMS health state in general without differentiating specific sequelae, two of which focused on meningitis survivors who may or may not have sequelae [81, 85] and one included all sequelae in the observed cohort [70]. The utility estimates from these studies ranged from 0.774 to 0.92. In addition, the study by Al-Janabi et al. (2016) also reported the spillover effect on family members, with a utility estimate of 0.87 [70].

4 DISCUSSION

Health utilities are an important measure of disease burden of pneumococcal disease and play a major role in the economic evaluations of pneumococcal vaccines. These evaluations are often used to inform policy decisions regarding public funding for immunizations. The current study provides a comprehensive and up-to-date review of utility estimates from original utility studies focused on

pneumococcal disease and PMS in children and is, to our knowledge, the first study to summarize utility inputs in published CUAs of pneumococcal vaccines in children.

While the published CUAs in North America and Europe applied wide ranges of utility inputs from the literature, most studies referred to one CUA conducted in the UK [45], which sourced utility inputs from one or two original studies for each pneumococcal disease or PMS health state [72, 86, 87, 93, 94]. Importantly, the rationales for utility study selection and input derivations were not described in this study. The CUAs frequently applied the same utility estimate to different pneumococcal disease states, despite the fact that the symptoms and disease courses of these conditions vary considerably. In addition, the original utility studies most frequently referenced by the CUAs were published more than two decades ago.

The current literature review identified a significantly larger number of original utility studies for pneumococcal disease and PMS in children relative to the number of studies referenced by published CUAs. However, the overall body of literature is rather limited, with most studies published more than a decade ago. In particular, there are considerable gaps in health utility estimates for inpatient and outpatient pneumonia and AOM with tympanostomy tube placement. Nonetheless, existing studies suggest that pneumococcal disease and PMS are associated with reduced QoL, particularly meningitis, non-meningitis IPD, inpatient pneumonia and various PMS conditions.

Consistent with the findings of previous literature reviews [15, 20, 23], we found a wide range of utility estimates for most disease states in pneumococcal disease and PMS, spanning values worse than death to nearly perfect health. Differences in geographic region, survey population, health state description, utility elicitation method, and preference weights may have contributed to the substantial variability in utility estimates across studies. In general, direct methods, such as SG and TTO, tended to result in higher utility estimates and thus smaller QALY decrements compared to indirect methods, with

an exception of the TTO study conducted by Prosser et al. (2004) [89], which generated substantially larger QALY decrements across all pneumococcal disease states than other studies. Notably, the study was the only one capturing the QoL impact on both children and parents in a single estimate while other utility studies focused solely on the QoL impact on children. The study asked the respondents to trade their own life to prevent their child or a hypothetical child from experiencing the condition, which deviates from the wider preference elicitation literature. In addition, the formula that the study provided to estimate QALY decrements implied that the respondents would forgo a certain number of days each year in the remaining years of their lives to avoid the condition. These factors likely resulted in larger QALY decrements for pneumococcal disease states [95]. An alternative approach to using discounted life expectancy as the denominator to estimate QALY decrements may be preferred if such data is available. VAS is commonly used in the literature on health utilities of pneumococcal disease, and in some earlier studies, it was the only method used for valuation [82, 86]. However, strictly speaking, VAS is not a measure of utility [93, 96]. Among the studies employing indirect methods, EQ-5D, HUI-2, and HUI-3 were the common preference-based instruments. The results varied substantially across different instruments, with no consistent associations between specific instruments and utility values.

The substantial variations in methodologies and utility estimates in the existing literature underscore the inherent challenges in estimating utilities for acute diseases in children, which may explain the general lack of recent high-quality utility studies in pneumococcal disease. There is no universally accepted standards for valuing acute diseases [97]. Generic instruments were typically developed for chronic health states and may not fully capture the impact of acute diseases [98]. Furthermore, validated methods for valuing children's health, especially in a very young age group (0-4 years) are lacking. While EQ-5D was commonly used in the identified studies, it was originally developed for adults. The EQ-5D-Youth (EQ-5D-Y) version is intended for use in children and adolescents [99], but not for very young children less than 5 years. While adapted versions for younger age groups, including infants, have been

developed, with some demonstrating improved psychometric performance compared to the original versions [100], these are not yet widely available for use in research. Other generic instruments, such as HUI-2 and HUI-3 are appropriate for children 5 years or older [101]. Other issues in the valuation of children's health included impact of responses from the use proxy responses (e.g., parents or caregivers) rather than the responses from the children themselves (particularly for children at younger ages) and the challenges of appropriate value sets to generate utilities [101]. Currently, there are no specific recommendations from Health Technology agencies regarding the methodology for valuing children's health in economic evaluations [101, 102]. Vignette-based studies offer an alternative approach that can include disease-specific experience and may provide more accurate estimates of health utilities for acute diseases in children. However, the valuation of vignettes using SG and TTO, for example, may result in "ceiling effects" if respondents do not perceive the temporary health state worthy of trading time or risking death to avoid [97]. Variations of these methods have been developed for temporary health states, such as TTO with specific disease duration and chained approaches for TTO or SG, each with its strengths and limitations [97, 103].

Based on the discussion above, the identified utilities have significant limitations when used in economic evaluations of pneumococcal vaccines in children. All studies applying indirect methods used instruments that are only validated in adults, with the exception of the study by Kulpeng et al. (2013) [84]. While this study used the EQ-5D-Y, a version of the EQ-5D measuring health in children and adolescents, to estimate self-reported utilities, it included only children aged 7-14 years as EQ-5D-Y is not applicable to younger children. Additionally, this study had small sample sizes (7 to 16), which may affect the reliability of the point estimates. Overall, there are few generic measures available to generate utilities for young children. As a result, other methods, such as vignettes, are frequently used approaches to generating health state utility values for this population. The studies applying direct methods based on vignettes also have limitations. As previously discussed, Prosser et al. (2004) and Stouthard et al. (1997)

used TTO methods that are uncommon in the utility literature [89, 90]. Because these methods were not validated, they may introduce bias into the utility estimates [90, 95]. The utilities reported by the studies conducted by Bennett et al. (2000) and Carroll et al. (2009) may be suitable for economic evaluations [72, 74], as they used the most robust utility estimation methods among all the studies; however, the time periods in which these studies were conducted raises questions regarding their applicability to contemporary research. Overall, there is a substantial gap in the current literature regarding utility inputs for pneumococcal disease in children.

The current study also identified three recently published literature reviews on health utility associated with pneumococcal disease and PMS. The review and pooled analysis conducted by Tang et al. (2022) [23] identified 15 studies published up to 2019. Compared to that review, the current one included 11 additional studies published between 1994 and 2017 [71, 73, 75, 76, 78-80, 82, 83, 88, 90]. Conversely, the current review excluded two studies [104, 105] included in the pooled analysis conducted by Tang et al. (2022), because the disease states were deemed to be not representative of acute pneumococcal disease. In addition, the study by Carroll et al. (2009) [74] was included in the pooled analysis for meningitis by Tang et al. (2022) but excluded from the current review of meningitis as it was not directly related to IPD. On the other hand, the study by Bennett et al. (2000) [72], which described the utilities for outcomes of occult bacteremia, was excluded from the pooled analysis for bacteremia by Tang et al., but was included in both meningitis and bacteremia summaries in the current review. Another review by O'Reilly et al. (2022) [15] conducted a systematic literature review up to January 2020. It is the most recent and comprehensive published review on the health utility of pneumococcal disease. Similar to the current review, the authors highlighted marked variations in utility values and utility estimation methods across identified studies. However, that review did not include a summary of utility inputs reported in the CUAs and omitted the study conducted by Prosser et al. (2004) [89]. With a focus on acute pneumococcal disease states, the review neglected PMS, which is essential in CUAs. Finally, a review by

Shiri et al. (2019) [20] included nine utility studies up to 2016 and did not discuss methodological differences between these studies.

Several limitations should be noted in the current review. First, this review focused on the pneumococcal disease and PMS conditions that are commonly included in economic models evaluating pneumococcal vaccines, and it does not provide a comprehensive review of all pneumococcal disease states. In particular, to balance the inclusiveness and relevance of the studies identified from the initial literature search, the search strategies did not include all PMS conditions, potentially resulting in the exclusion of studies of certain PMS conditions. Furthermore, other than for PMS, the review primarily focused on utility estimates during the acute phases of pneumococcal disease states. The impact of these disease states on QoL is likely to extend beyond these acute time periods, as evidenced by several studies demonstrating long-term utility decrements following pneumonia and AOM [106-108], including two CUAs conducted in Europe that considered hearing loss after AOM [30, 49]. While this consideration is infrequent in CUAs of pneumococcal vaccines, future economic models may benefit from incorporating the long-term sequelae following non-meningitis IPD, pneumonia, and AOM to fully capture the impact of pneumococcal disease on QoL among children.

Notwithstanding these limitations, the current literature review provides an important update on the literature regarding the health utilities of pneumococcal disease and PMS. Whilst there remain considerable challenges in identifying optimal methods to evaluate health utilities of acute diseases in children, future utility studies on pediatric pneumococcal disease should strive for methodological rigor. It is important to ensure that disease states or vignettes align with pneumococcal disease states. While both direct and indirect methods can be utilized, direct methods may be preferred due to lack of validated instruments in the very young age group. VAS should be discouraged as it is not a utility measure, so are other non preference-based measures, e.g., HALex. TTO surveys should avoid asking respondents to

trade their own lives to avoid children having to experience the disease, as this may introduce confounding factors such as guilt or altruism. Moreover, patients and parents, rather than HCPs, may be preferred as their perspectives are likely to offer more accurate insights into the impact of pneumococcal disease on the QoL of their children. By adhering to these principles, future utility studies can enhance the validity and reliability of their findings, contributing to a better understanding of the QoL burden of pneumococcal disease and informing rigorous cost-effectiveness analyses of interventions. Regarding the latter, future CUAs should select utility studies with robust methodology based on critical assessment and synthesis of the literature. The rationale for selecting a specific utility estimate should be detailed. Ideally, the disease population and duration should match with the ones in CUAs to reduce potential bias. QALY decrements per acute episode and QALY decrements per year for PMS should be reported to facilitate comparisons across studies. Explicit assumptions and derivation methods used to estimate utility inputs in CUAs from original utility studies should be provided. When converting utility values to QALY decrements, the background utilities in the CUAs should align with those in the original utility studies. If the background utilities were not discussed in the original utility studies, assumptions and potential limitations of QALY decrement derivation should be noted. Additionally, given the expected variations in utility estimates, sensitivity analyses testing a range of values should be conducted to improve the credibility of the results.

The current review focuses on a qualitative synthesis of the original utility studies of pneumococcal disease and PMS in children. For economic evaluations with a lifetime horizon, health utilities for these conditions in adults are needed. Moreover, given the variability of individual studies, a quantitative synthesis of health utilities accounting for the heterogeneity could better inform future economic evaluations.

5 CONCLUSIONS

The current literature review suggests that pneumococcal disease and PMS are associated with impaired QoL in children. However, considerable variability in utility estimates is evident across studies, which may be largely attributable to differences in the methodology, geographical region, and quality of these studies. Such variability reflects the inherent methodological challenges in estimating utilities for acute diseases in children. The health utility inputs used in CUAs of pediatric pneumococcal vaccines were sourced from a limited number of original utility studies that are likely to be outdated. Utility studies for pneumococcal disease and PMS based on contemporary data and methods adapted for acute diseases in children are needed. Given the significance of health utilities in the economic values of new pneumococcal vaccines, utility values should be carefully selected in CUAs, and alternative values and assumptions should be evaluated in sensitivity analyses.

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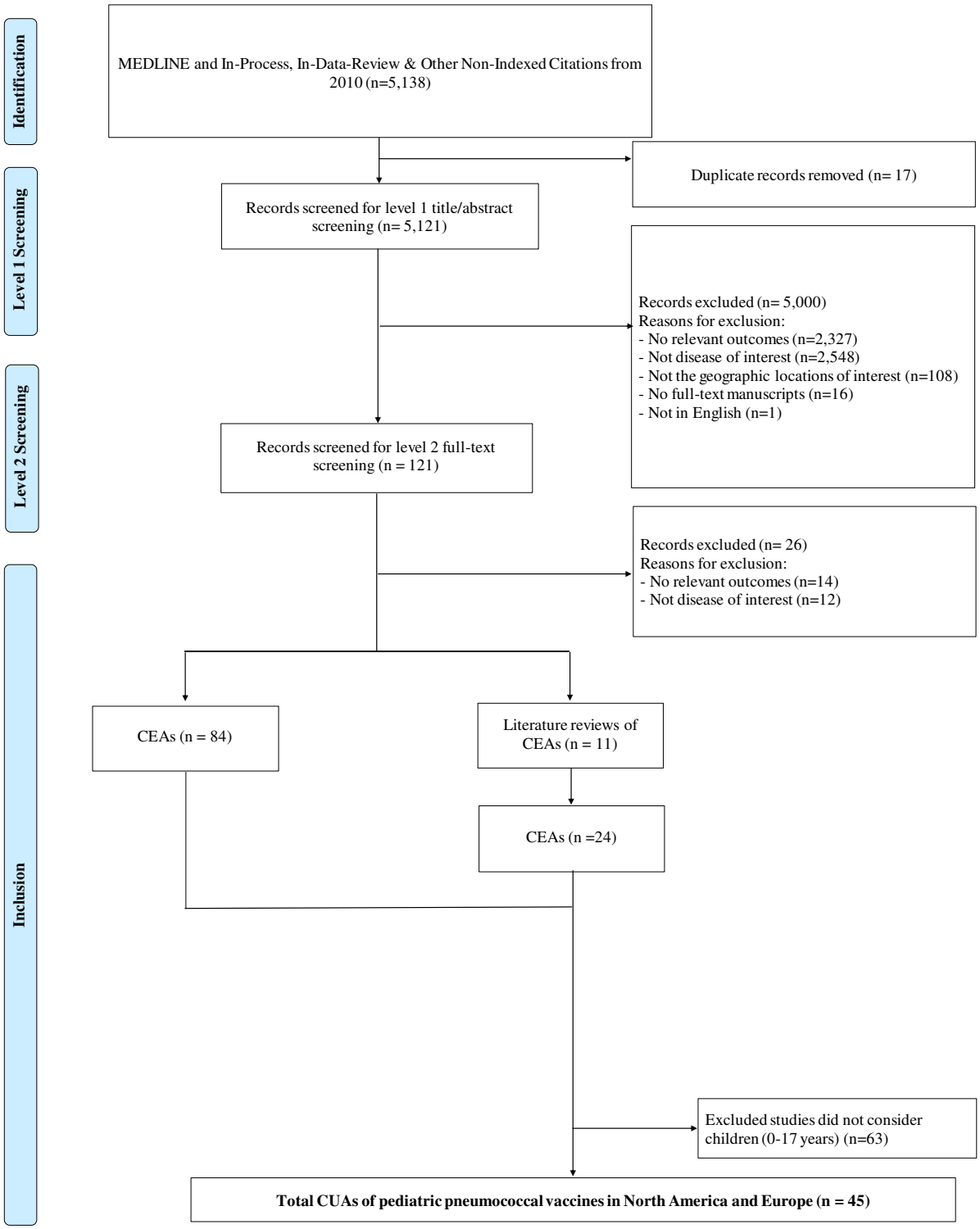
FIGURES AND TABLES

Figure 1A. PRISMA diagram based on the literature review of CUAs pneumococcal vaccines[1]

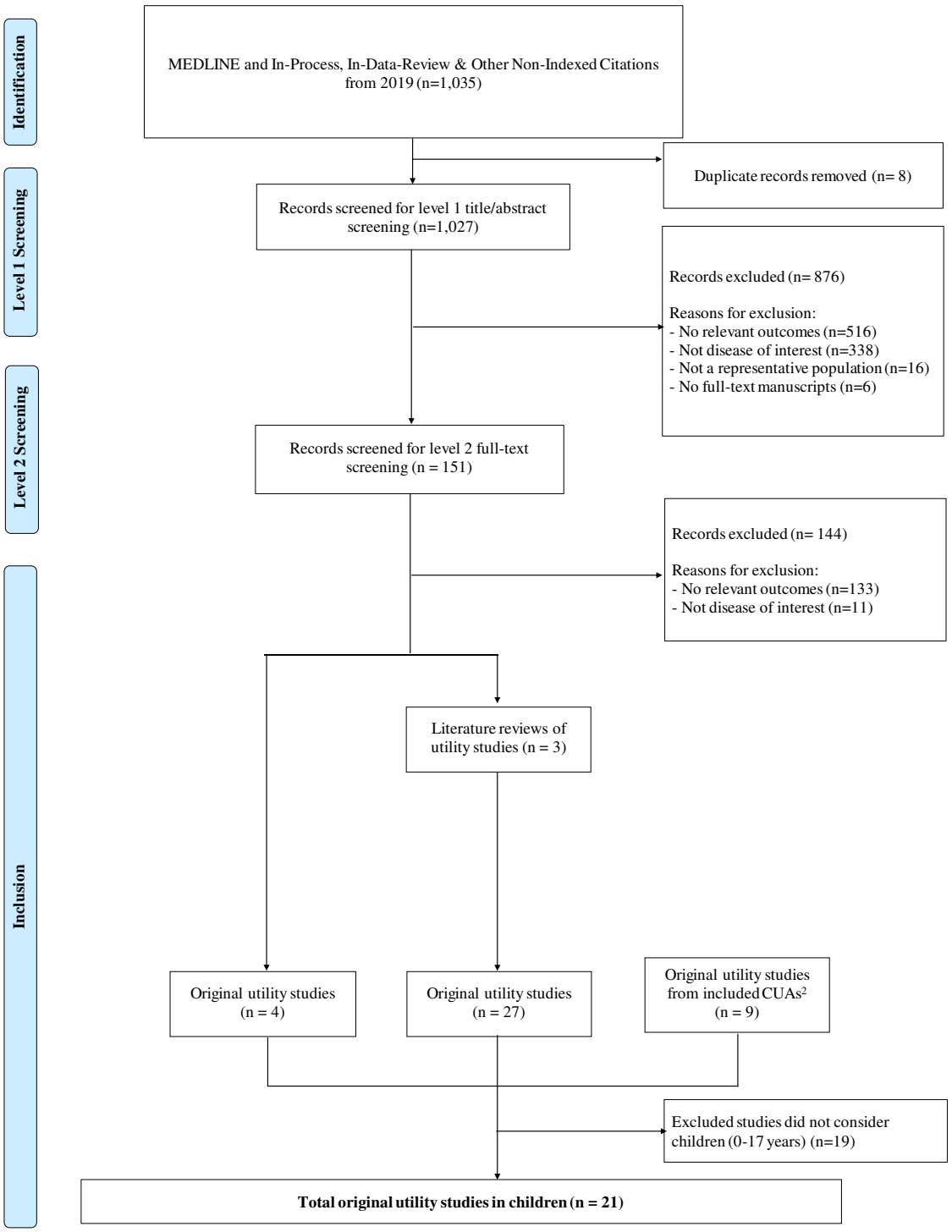


Abbreviations: PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CUA=Cost-utility analysis; CEA=Cost-effectiveness analysis.

Notes:

1. The literature search was conducted in MEDLINE on June 11, 2024.

Figure 1B. PRISMA diagram based on the literature review of original research studies on health utilities of pneumococcal disease[1]



Abbreviations: PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CUA=Cost-utility analysis; CEA=Cost-effectiveness analysis.

Notes:

1. The literature search was conducted in MEDLINE on June 11, 2024.

2. CUAs of pneumococcal vaccines in North America and Europe were identified through a separate literature review (see Figure 1A). These nine original studies were identified from the references of the included CUAs.

Table 1: Summary of utility inputs in the pediatric CUAs of pneumococcal vaccines in the US, Canada, and Europe

Health state	Type of utility input	Number of studies	Range of base-case values	Number of studies referencing previous CUAs	Most common source studies
IPD					
Meningitis	QALY decrement [25, 27, 29-35, 38, 41, 42, 44-58, 60-62, 64-66, 68, 69]	35	0.006–0.76	16	Bennett JE 2000 [72]
	QALY multiplier [43]	1	0.997	0	
Non-meningitis IPD	QALY decrement [25-27, 29-35, 38, 41, 42, 44-58, 60-62, 64-66, 68, 69]	36	0.0016–0.21	16	Bennett JE 2000 [72]
	Utility [28, 39]	2	0.90–0.90	0	
	QALY multiplier [43]	1	0.996	0	
Unspecified IPD	QALY decrement [42, 66, 67]	3	0.007–0.009	1	Bennett JE 2000 [72]
Pneumonia					
Inpatient pneumonia	QALY decrement [25-27, 29-35, 38, 41, 42, 44-58, 60-62, 64-69]	37	0.0060–0.59	23	Bennett JE 2000 [72]
	QALY multiplier [43]	1	0.984	0	
Outpatient pneumonia	QALY decrement [25, 27, 29-35, 38, 41, 42, 44-58, 60-62, 64, 65, 67, 68]	34	0.004–0.18	24	Bennett JE 2000 [72]; Vold Pepper P 2000 [94]

	QALY multiplier [43]	1	0.9980	0	
Pneumonia, unspecified setting	QALY decrement [66]	1	0.19	0	Prosser LA 2004 [89]
AOM					
AOM	QALY decrement [25-27, 29-31, 33, 34, 41, 42, 45-49, 51, 52, 55, 57, 58, 60-62, 64, 65, 67-69]	28	0.0016–0.011	18	Oh PI 1996 [86]
Simple AOM	QALY decrement [32, 35, 38, 50, 53, 56, 66]	7	0.005–0.01	4	Oh PI 1996 [86]
	QALY multiplier [43]	1	0.998	0	
Complex/recurrent AOM	QALY decrement [32, 35, 38, 50, 53, 56, 66]	7	0.005–0.36	4	Oh PI 1996 [86]
	QALY multiplier [43]	1	0.998	0	
AOM tympanostomy tube placement	QALY December [29, 30, 34, 38, 46, 47, 58, 65]	8	0.0016–0.11	4	Oh PI 1996 [86]
AOM myringotomy	QALY decrement [41, 49, 50, 53, 57]	5	0.005–0.005	3	Oh PI 1996 [86]
Other AOM states	QALY December [29, 30, 32, 49]	4	0.005–0.090	1	Oh PI 1996 [86]; Oostenbrink R 2002 [87]
PMS					
Neurological deficits	Utility [28, 35, 36, 38-40, 43, 44, 50-56, 58-60, 62, 63]	20	0.47–0.89	6	Oostenbrink R 2002 [87]; Torrance GW 1982 [91]

	QALY decrement [25, 29-32, 34, 41, 47-49, 61, 64]	12	0.10–0.400	10	
	Quality adjustment factor [27]	1	0.6	1	
Hearing loss	Utility [28, 35, 36, 38-40, 43, 44, 50-56, 58-60, 62, 63]	20	0.45–0.91	6	
	QALY decrement [25, 26, 29-34, 41, 42, 45, 47-49, 57, 61, 64]	17	0.054–0.460	14	Oostenbrink R 2002 [87]; Torrance GW 1982 [91]
	Quality adjustment factor [27]	1	0.8	1	
PMS overall	QALY decrement [42, 46]	2	0.200–0.5300	2	Cheng AK 1999 [93]; Oostenbrink R 2002 [87]; Torrance GW 1982 [91]
	Quality adjustment factor [37]	1	0.6	1	
Unspecified PMS states	Utility [35]	1	0.40	0	Oostenbrink R 2002 [87]; Erickson LJ 2001 [92]

Abbreviations: CUA=Cost-utility analysis; US=United States; IPD=Invasive pneumococcal disease; QALY=Quality-adjusted life year; AOM=Acute otitis media; PMS=Post-meningitis sequelae.

Table 2: Summary of health state utility values for IPD based on original utility studies

Author and year	Country	Age group	Health state	Population Surveyed	Sample size	Utility estimation methods	Outcome Estimates		
							Preference Measure/Outcome	Mean [SD/SE] (95% CI)	Median [IQR] (Range)
Meningitis									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	Meningitis	Parents/caregivers of children with the condition	19	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.0200 (0.0000,0.2265)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.3390 (0.1541,0.5208)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.5208 (0.3945,0.6456)	
		7-14		Patients with the condition	7	Self-reported EQ-5D-Y with Thai weights	Utility while experiencing the disease	0.2606 (0.0000,0.6370)	
						Self-reported HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.4967 (0.1381,0.8508)	
						Self-reported HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.6682 (0.4788,0.8575)	
Galante J 2011 [77]	Argentina	Unspecified	Meningitis	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	-0.049 (-0.118,-0.019)	-0.179 [-0.206,0.083]
	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	-0.330 (-0.383,-0.276)	-0.437 [-0.487,-0.238]
	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	-0.330 (-0.394,-0.265)	-0.429 [-0.484,-0.221]

Petrou S 2009 [88]	UK	5-16 (mean: 13)	Meningitis	Parents/caregivers of children with the condition	44	Proxy report of HUI-3 with Canadian scoring function	Utility	0.181	0.181 [-0.120,0.371]
IOM 2000 [80]	US	0-5 and ≥5	Meningitis ICU	Experts	14	Indirect methods based on vignettes and HUI-2 with Canadian scoring function	Utility	0.24	
			Meningitis inpatient after ICU				Utility	0.28	
			Meningitis inpatient no ICU				Utility	0.39	
			Meningitis inpatient acute complications				Utility	0.27	
VAS outcomes									
Kulpeng W 2013 [84]	Thailand	5-14	Meningitis	Parents/caregivers of children with the condition	19	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.4607 (0.3205,0.6009)	
		7-14		Patients with the condition	7	Self-reported EQ-VAS	VAS value while experiencing the disease	0.4989 (0.3029,0.6927)	
Galante J 2011 [77]	Argentina	Unspecified	Meningitis	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.342 (0.305,0.379)	0.300 [0.255,0.500]
Kramer MS 1994 [82]	Canada	3-24 months	Bacterial meningitis	Parents of well children	100	Direct methods based on vignettes rated using VAS	VAS value	0.475	
				Parents of febrile children	61		VAS value	0.535	
				HCPs (Attending staff physicians in ED)	56		VAS value	0.415	
			Bacterial meningitis with delayed diagnosis	Parents of well children	100		VAS value	0.426	
				Parents of febrile children	61		VAS value	0.431	
				HCPs (Attending staff physicians in ED)	56		VAS value	0.317	
QALY estimate									
Bennett JE 2000 [72][1]	US	3-36 months	Meningitis with recovery	Parents with children presented in an urban hospital ED	94	Direct methods based on SG	QALY average over a year with one episode of disease	0.9768 [0.08]	0.9997 [0.9931,1.0000]
Disutility									

Petrou S 2009 [88]	UK	5-16 (mean: 13)	Meningitis	Parents/caregivers of children with the condition	44	Proxy report of HUI-3 with Canadian scoring function	Disutility (vs perfect health)	0.826 (0.677,0.975)	
							Disutility (vs norm)	0.751 (0.606,0.904)	
QALY decrement									
Prosser LA 2004 [89]	US	1	Meningitis	Parents/caregivers of children with the condition	101	Direct methods based on TTO capturing the impact on both children and parents	QALY decrement per episode		0.50 [0.02,1.35]
				General population	109		QALY decrement per episode		0.76 [0.13,3.40]
Non-meningitis IPD									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	Bacteremia	Parents/caregivers of children with the condition	16	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.3790 (0.1741,0.5855)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.5501 (0.3898,0.7088)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.6163 (0.4792,0.7519)	
		7-14		Patients with the condition	9	Self-reported EQ-5D-Y with Thai weights	Utility while experiencing the disease	0.3318 (0.0111,0.6548)	
						Self-reported HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.4788 (0.1269,0.8307)	
						Self-reported HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.6882 (0.4699,0.9087)	
Galante J 2011 [77]	Argentina	Unspecified	Sepsis	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	-0.034 (-0.103,0.035)	-0.179 [-0.206,0.164]

	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	-0.331 (-0.381,-0.282)	-0.437 [-0.487,-0.222]
	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	-0.295 (-0.359,-0.231)	-0.331 [-0.484,-0.166]
IOM 2000 [80]	US	0-5 and ≥5	Bacteremia/sepsis outpatient care only	Experts	14	Indirect methods based on vignettes and HUI-2 with Canadian scoring function	Utility	0.93	
			Bacteremia/sepsis ICU				Utility	0.16	
			Bacteremia/sepsis inpatient after ICU				Utility	0.46	
			Bacteremia/sepsis inpatient no ICU				Utility	0.71	
			Bacteremia/sepsis inpatient; complications				Utility	0.59	
VAS outcomes									
Kulpeng W 2013 [84]	Thailand	5-14	Bacteremia	Parents/caregivers of children with the condition	19	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.6148 (0.4900,0.7396)	
		7-14		Patients with the condition	9	Self-reported EQ-VAS	VAS value while experiencing the disease	0.5746 (0.4165,0.7305)	
Galante J 2011 [77]	Argentina	Unspecified	Sepsis	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.317 (0.278,0.356)	0.300 [0.200,0.400]
QALY estimate									
Bennett JE 2000 [72][1]	US	3-36 months	Occult bacteremia with hospitalization	Parents with children presented in an urban hospital ED	94	Direct methods based on SG	QALY average over a year with one episode of disease	0.9921 [0.03]	1.0000 [0.9998,1.0000]
QALY decrement									

Prosser LA 2004 [89]	US	1	Bacteremia	Parents/caregivers of children with PD	101	Direct methods based on TTO	QALY decrement per episode	0.10 [0.00,0.61]
				General population	109		QALY decrement per episode	0.21 [0.00,1.89]

Abbreviations: IPD=Invasive pneumococcal disease; SD=Standard deviation; SE=Standard error; CI=Confidence interval; IQR=Interquartile range; IOM=Institute of Medicine; UK=United Kingdom; US=United States; ICU=Intensive care unit; PD=Pneumococcal disease; HCP=Health care provider; ED=Emergency department; SG=Standard gamble; TTO=Time trade-off; EQ-5D=EuroQoL 5-dimensions; HUI=Health utilities index; EQ-VAS=EuroQoL visual analogue scale; VAS=Visual analogue scale; QALY=Quality-adjusted life year.

Notes:

1. Although the study by Bennet et al., 2000, described the outcomes as “utility”, these values were interpreted as QALYs per year based on the description of the methods and how the results were applied in the CUAs. Mathematically, it is equivalent to 1-QALY decrement.

Table 3: Summary of health state utility values for pneumonia based on original utility studies

Author and year	Country	Age group	Health state	Population Surveyed	Sample size	Utility estimation methods	Outcome Estimates		
							Preference Measure/Outcome	Mean [SD/SE] (95% CI)	Median [IQR] (Range)
Inpatient pneumonia									
Health utility									
Galante J 2011 [77]	Argentina	Unspecified	Hospitalized pneumonia	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	0.309 (0.239,0.380)	0.330 [0.059,0.612]
	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	-0.054 (-0.130,0.023)	-0.286 [-0.286,0.196]
	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	0.035 (-0.048,0.118)	-0.056 [-0.239,0.258]
IOM 2000 [80]	US	0-5 and ≥5	Pneumonia inpatient	Experts	14	Indirect methods based on vignettes and HUI-2 with Canadian scoring function	Utility	0.71	
			Pneumonia with emphysema inpatient				Utility	0.64	
VAS outcomes									
Galante J 2011 [77]	Argentina	Unspecified	Hospitalized pneumonia	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.464 (0.426,0.501)	0.450 [0.395,0.600]
QALY estimate									
Bennett JE 2000 [72][1]	US	3-36 months	Occult bacteremia with local infection	Parents with children presented in an urban hospital ED	94		QALY average over a year with one episode of disease	0.9941 [0.03]	1.0000 [0.9998,1.0000]
QALY decrement									

Prosser LA 2004 [89]	US	1	Severe pneumonia	Parents/caregivers of children with the condition	101	Direct methods based on TTO capturing the impact on both children and parents	QALY decrement per episode		0.27 [0.01,1.03]
				General population	109		QALY decrement per episode		0.59 [0.03,2.39]
Outpatient pneumonia									
Health utility									
Galante J 2011 [77]	Argentina	Unspecified	Ambulatory pneumonia	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	0.628 (0.584,0.673)	0.662 [0.532,0.770]
	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	0.412 (0.348,0.476)	0.564 [0.296,0.590]
	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	0.508 (0.442,0.575)	0.673 [0.346,0.708]
IOM 2000 [80]	US	0-5 and ≥5	Pneumonia outpatient care only	Experts	14	Indirect methods based on vignettes and HUI-2 with Canadian scoring function	Utility	0.82	
			Pneumonia outpatient after inpatient				Utility	0.81	
			Pneumonia with emphysema outpatient after inpatient				Utility	0.82	
VAS outcomes									
Galante J 2011 [77]	Argentina	Unspecified	Ambulatory pneumonia	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.584 (0.551,0.617)	0.600 [0.500,0.700]
QALY decrement									

Prosser LA 2004	US	1	Moderate pneumonia	Parents/caregivers of children with the condition	101	Direct methods based on TTO capturing the impact on both children and parents	QALY decrement per episode		0.00 [0.00,0.30]
				General population	109		QALY decrement per episode		0.18 [0.00,1.28]
Pneumonia, unspecified setting									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	Pneumonia	Parents/caregivers of children with the condition	24	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.4792 (0.3374,0.6210)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.5871 (0.4284,0.7427)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.6949 (0.5778,0.8089)	
		7-14		Patients with the condition	8	Self-reported EQ-5D-Y with Thai weights	Utility while experiencing the disease	0.4610 (0.1314,0.7884)	
						Self-reported HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.5390 (0.1693,0.9109)	
						Self-reported HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.7216 (0.4766,0.9666)	
Stouthard ME 1997 [90]	Netherlands	Unspecified	Pneumonia (duration 2 weeks)	HCPs (physician panels)	38	Direct methods based on PTO	Utility, disability weight	0.90 (0.809,0.984)	
VAS outcomes									
Kulpeng W 2013 [84]	Thailand	5-14	Pneumonia	Parents/caregivers of children with the condition	24	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.6795 (0.5917,0.7643)	
		7-14		Patients with the condition	8	Self-reported EQ-VAS	VAS value while experiencing the disease	0.7261 (0.5189,0.9354)	

Kramer MS 1994 [82]	Canada	3-24 months	Pneumonia with delayed diagnosis	Parents of well children	100	Direct methods based on vignettes rated using VAS	VAS value	0.749
				Parents of febrile children	61		VAS value	0.669
				HCPs (Attending staff physicians in ED)	56		VAS value	0.831

Abbreviations: SD=Standard deviation; SE=Standard error; CI=Confidence interval; IQR=Interquartile range; IOM=Institute of Medicine; UK=United Kingdom; US=United States; PD=Pneumococcal disease; HCP=Health care provider; ED=Emergency department; SG=Standard gamble; TTO=Time trade-off; EQ-5D=EuroQoL 5-dimensions; HUI=Health utilities index; EQ-VAS=EuroQoL visual analogue scale; VAS=Visual analogue scale; PTO=Person trade-off; QALY=Quality-adjusted life year.

Notes:

1. Although the study by Bennet et al., 2000, described the outcomes as “utility”, these values were interpreted as QALYs per year based on the description of the methods and how the results were applied in the CUAs. Mathematically, it is equivalent to 1-QALY decrement.

Table 4: Summary of health state utility values for AOM based on original utility studies

Author and year	Country	Age group	Health state	Population Surveyed	Sample size	Utility estimation methods	Outcome Estimates		
							Preference Measure/Outcome	Mean [SD/SE] (95% CI)	Median [IQR] (Range)
AOM/Simple AOM									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	AOM	Parents/caregivers of children with the condition	18	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.6086 (0.5285,0.6918)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.7119 (0.5855,0.8382)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.7750 (0.6687,0.8814)	
		7-14		Patients with the condition	7	Self-reported EQ-5D-Y with Thai weights	Utility while experiencing the disease	0.6236 (0.4633,0.7817)	
						Self-reported HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.5212 (0.2829,0.7595)	
						Self-reported HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.6704 (0.4833,0.8575)	
Galante J 2011 [77]	Argentina	Unspecified	AOM	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	0.565 (0.508,0.621)	0.612 [0.390,0.770]
	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	0.389 (0.323,0.455)	0.411 [0.178,0.572]

	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	0.391 (0.310,0.473)	0.516 [0.088,0.691]
Carroll A 2009 [74]	US	0-18	OM with pain	Parents of children from the general population	255	Direct methods based on SG	Utility	0.96 [0.11/0.01]	1.00; 5th-95th percentile range (0.82,1.00)
					255	Direct methods based on TTO	Utility	0.97 [0.12/0.01]	1.00; 5th-95th percentile range (0.74,1.00)
IOM 2000 [80]	US	0-5	OM	Experts	14	Indirect methods based on vignettes and HUI-2 with Canadian scoring function	Utility	0.74	
VAS outcomes									
Crawford B 2017 [76]	Malaysia	0-5	AOM	Parents/caregivers of children with the condition	110	Proxy report of VAS from OM-6	VAS value while experiencing the disease	0.6655 [0.2025]	0.7000
Kulpeng W 2013 [84]	Thailand	5-14	AOM	Parents/caregivers of children with the condition	18	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.6672 (0.5901,0.7411)	
		7-14		Patients with the condition	7	Self-reported EQ-VAS	VAS value while experiencing the disease	0.6993 (0.5323,0.8708)	
Galante J 2011 [77]	Argentina	Unspecified	AOM	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.634 (0.601,0.668)	0.620 [0.575,0.700]
Oh PI 1996 [86]	Canada	2	AOM	HCPs (physicians)	10	Direct methods based on vignettes rated using VAS	VAS value	0.79	
QALY decrement									
Prosser LA 2004 [89]	US	1	Simple OM	Parents/caregivers of children with the condition	101	Direct methods based on TTO capturing the impact on both children and parents	QALY decrement per episode		0.00 [0.00,0.01]
				General population	109		QALY decrement per episode		0.01 [0.00,0.66]

Recurrent AOM									
VAS outcomes									
Kujala T 2014 [83]	Finland	10 months-2 years	Recurrent AOM	Parents/caregivers of children with the condition	123	Proxy report of VAS from OM-6	VAS value while experiencing the disease	0.534 [0.194]	
Heidemann CH 2013 [79]	Denmark	0-6	Recurrent AOM with or without OME	Parents/caregivers of children with the condition	226	Proxy report of VAS from OM-6	VAS value while experiencing the disease	0.434 [0.205]	
Brouwer CN 2005 [73]	Netherlands	0-7	Recurrent AOM	Parents/caregivers of children with the condition	383	Proxy report of VAS from OM-6	VAS value while experiencing the disease	0.540	
QALY decrement									
Prosser LA 2004 [89]	US	1	Complex OM	Parents/caregivers of children with the condition	101	Direct methods based on TTO capturing the impact on both children and parents	QALY decrement per episode		0.25 [0.00,1.14]
				General population	109		QALY decrement per episode		0.36 [0.03,1.75]
AOM with myringotomy									
Health utility									
Galante J 2011 [77]	Argentina	Unspecified	AOM with myringotomy	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	0.339 (0.258,0.420)	0.356 [0.088,0.651]
	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	0.064 (-0.026,0.154)	0.036 [-0.223,0.454]

	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	0.073 (-0.029,0.174)	-0.008 [-0.261,0.585]
VAS outcomes									
Galante J 2011 [77]	Argentina	Unspecified	AOM with myringotomy	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.506 (0.467,0.546)	0.500 [0.400,0.600]

Abbreviations: AOM=Acute otitis media; SD=Standard deviation; SE=Standard error; CI=Confidence interval; IQR=Interquartile range; IOM=Institute of Medicine; UK=United Kingdom; US=United States; OM=Otitis media; OME=Otitis media with effusion; PD=Pneumococcal disease; HCP=Health care provider; ED=Emergency department; SG=Standard gamble; TTO=Time trade-off; EQ-5D=EuroQoL 5-dimensions; HUI=Health utilities index; EQ-VAS=EuroQoL visual analogue scale; VAS=Visual analogue scale; QALY=Quality-adjusted life year.

Table 5: Summary of health state utility values for PMS based on original utility studies

Author and year	Country	Age group	Health state	Population Surveyed	Sample size	Utility estimation methods	Outcome Estimate		
							Preference Measure/Outcome	Mean [SD/SE] (95% CI)	Median [IQR] (Range)
Neurological deficits									
Cerebral palsy									
Health utility									
Carroll A 2009 [74]	US	0-18	Mild cerebral palsy	Parents of children from the general population	463	Direct methods based on SG	Utility	0.87 [0.20/0.01]	0.96; 5th-95th percentile range (0.50,1.00)
						Direct methods based on TTO	Utility	0.88 [0.19/0.01]	0.96; 5th-95th percentile range (0.50,1.00)
			Moderate cerebral palsy		413	Direct methods based on SG	Utility	0.76 [0.23/0.01]	0.80; 5th-95th percentile range (0.25,1.00)
						Direct methods based on TTO	Utility	0.76 [0.26/0.01]	0.86; 5th-95th percentile range (0.11,1.00)
			Severe cerebral palsy		411	Direct methods based on SG	Utility	0.60 [0.28/0.01]	0.50; 5th-95th percentile range (0.02,1.00)
						Direct methods based on TTO	Utility	0.55 [0.33/0.02]	0.50; 5th-95th percentile range (0.01,1.00)
Petrou S 2009 [88]	UK	5-16 (mean: 11.6; median: 11)	Cerebral palsy	Parents/caregivers of children with the condition	178	Proxy report of HUI-3 with Canadian scoring function	Utility	0.276	0.269 [0.050,0.520]
Disutility									
Petrou S 2009 [88]	UK	5-16 (mean: 11.6; median: 11)	Cerebral palsy	Parents/caregivers of children with the condition	178	Proxy report of HUI-3 with Canadian scoring function	Disutility (vs perfect health)	-0.726 (-0.607,-0.846)	
							Disutility (vs norm)	-0.652 (-0.536,-0.775)	
Other utility outcomes									

Gold MR 1998 [78]	US	All ages (mean: 54)[1]	Cerebral palsy	Individuals or proxy respondents from the NHIS 1987-1992	100	Indirect methods based on HALex[2]	Value while experiencing the disease	0.59	0.57 [0.40,0.79]
Epilepsy/seizures									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	Epilepsy	Parents/caregivers of children with the condition	20	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.6333 (0.5223,0.7442)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.6425 (0.4854,0.7997)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.7904 (0.6934,0.8860)	
		7-14		Patients with the condition	16	Self-reported EQ-5D-Y with Thai weights	Utility value while experiencing the disease	0.6437 (0.5301,0.7617)	
						Self-reported HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.6682 (0.4967,0.8419)	
						Self-reported HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.8174 (0.7238,0.9109)	
Carroll A 2009 [74]	US	0-18	Mild seizure disorder	Parents of children from the general population	413	Direct methods based on SG	Utility	0.85 [0.21/0.01]	0.96; 5th-95th percentile range (0.44,1.00)
						Direct methods based on TTO	Utility	0.86 [0.21/0.01]	0.96; 5th-95th percentile range (0.43,1.00)
			Moderate seizure disorder		439	Direct methods based on SG	Utility	0.84 [0.21/0.01]	0.92; 5th-95th percentile range (0.50,1.00)
						Direct methods based on TTO	Utility	0.83 [0.22/0.01]	0.90; 5th-95th percentile range (0.37,1.00)
			Severe seizure disorder		433	Direct methods based on SG	Utility	0.70 [0.25/0.01]	0.75; 5th-95th percentile range (0.22,1.00)

						Direct methods based on TTO	Utility	0.71 [0.27/0.01]	0.80; 5th-95th percentile range (0.19,1.00)
Petrou S 2009 [88]	UK	5-16 (mean: 12.2; median: 13)	Childhood epilepsies and convulsions	Parents/caregivers of children with the condition	92	Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.334	0.355 [0.063,0.575]
Oostenbrink R 2002 [87]	Netherlands	6	Epilepsy	HCPs (pediatricians)	28	Indirect methods based on vignettes and EQ-5D-3L with UK weights	Utility	0.83 [0.08]	
						Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.88 [0.06]	
						Indirect methods based on vignettes and HUI-3 with Canadian scoring	Utility	0.70 [0.14]	
Stouthard ME 1997 [90]	Netherlands	Unspecified	Epilepsy	HCPs (physician panels)	38	Direct methods based on PTO	Utility, disability weight	0.89 (0.838,0.948)	
VAS outcomes									
Kulpeng W 2013 [84]	Thailand	5-14	Epilepsy	Parents/caregivers of children with the condition	20	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.7381 (0.6502,0.8243)	
		7-14		Patients with the condition	16	Self-reported EQ-VAS	VAS value while experiencing the disease	0.7639 (0.6748,0.8530)	
Disutility									
Petrou S 2009 [88]	UK	5-16 (mean: 12.2; median: 13)	Childhood epilepsies and convulsions	Parents/caregivers of children with the condition	92	Proxy report of HUI-3 with Canadian scoring function	Disutility (vs perfect health)	-0.675 (-0.547,-0.803)	
							Disutility (vs norm)	-0.602 (-0.476,-0.732)	
<u>Mental retardation</u>									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	Mild mental retardation	Parents/caregivers of children with the condition	8	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.6040 (0.5223,0.6857)	

						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.6857 (0.5162,0.8567)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.6841 (0.6009,0.7673)	
		5-14	Severe mental retardation	Parents/caregivers of children with the condition	11	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.2681 (0.0416,0.4961)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.1048 (0.0000,0.3328)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.3945 (0.2234,0.5624)	
Carroll A 2009 [74]	US	0-18	Mild mental retardation	Parents of children from the general population	432	Direct methods based on SG	Utility	0.84 [0.20/0.01]	0.91; 5th-95th percentile range (0.47,1.00)
						Direct methods based on TTO	Utility	0.83 [0.23/0.01]	0.93; 5th-95th percentile range (0.37,1.00)
			Moderate mental retardation		439	Direct methods based on SG	Utility	0.79 [0.22/0.01]	0.86; 5th-95th percentile range (0.40,1.00)
						Direct methods based on TTO	Utility	0.79 [0.23/0.01]	0.87; 5th-95th percentile range (0.37,1.00)
			Severe mental retardation		410	Direct methods based on SG	Utility	0.59 [0.27/0.01]	0.50; 5th-95th percentile range (0.10,1.00)
						Direct methods based on TTO	Utility	0.51 [0.32/0.02]	0.50; 5th-95th percentile range (0.01,1.00)
Oostenbrink R 2002 [87]	Netherlands	6	Mild mental retardation	HCPs (pediatricians)	28	Indirect methods based on vignettes and EQ-5D-3L with UK weights	Utility	0.62 [0.11]	
						Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.55 [0.08]	

						Indirect methods based on vignettes and HUI-3 with Canadian scoring	Utility	0.24 [0.18]
Stouthard ME 1997 [90]	Netherlands	Unspecified	Permanent cognitive impairment after bacterial meningitis	HCPs (physician panels)	38	Direct methods based on PTO	Utility, disability weight	0.75 (0.616,0.881)
VAS outcomes								
Kulpeng W 2013 [84]	Thailand	5-14	Mild mental retardation	Parents/caregivers of children with the condition	8	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.7750 (0.6040,0.9445)
		5-14	Severe mental retardation	Parents/caregivers of children with the condition	11	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.6040 (0.4576,0.7535)
Other neurological sequelae								
Health utility								
Oostenbrink R 2002 [87]	Netherlands	6	Leg paresis	HCPs (pediatricians)	28	Indirect methods based on vignettes and EQ-5D-3L with UK weights	Utility	0.67 [0.12]
						Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.80 [0.10]
						Indirect methods based on vignettes and HUI-3 with Canadian scoring	Utility	0.51 [0.14]
Stouthard ME 1997 [90]	Netherlands	Unspecified	Permanent locomotor impairment after bacterial meningitis	HCPs (physician panels)	38	Direct methods based on PTO	Utility, disability weight	0.83 (0.702,0.964)
Other utility outcomes								

Gold MR 1998 [78]	US	All ages (mean: 41)[1]	Paraplegia	Individuals or proxy respondents from the NHIS 1987-1992	22	Indirect methods based on HALEx[2]	Value while experiencing the disease	0.40	0.43 [0.21,0.52]
		All ages (mean: 63)[1]	Hemiplegia		61		Value while experiencing the disease	0.27	0.21 [0.10,0.38]
Multiple neurological sequelae									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	Mental retardation and epilepsy	Parents/caregivers of children with the condition	18	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.0431 (0.0000,0.1988)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.0031 (0.0000,0.2018)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.2928 (0.1664,0.4206)	
Galante J 2011 [77]	Argentina	Unspecified	Neurological sequelae after meningitis	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	0.508 (0.469,0.547)	0.517 [0.460,0.651]
	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	0.217 (0.164,0.270)	0.230 [0.071,0.455]
	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	0.319 (0.252,0.386)	0.205 [0.082,0.603]
Petrou S 2009 [88]	UK	5-16 (mean: 11.5; median: 11)	Learning and physical disabilities	Parents/caregivers of children with the condition	81	Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.141	0.118 [-0.093,0.361]

Oostenbrink R 2002 [87]	Netherlands	6	Epilepsy, mental retardation, and leg paresis	HCPs (pediatricians)	28	Indirect methods based on vignettes and EQ-5D-3L with UK weights	Utility	0.47 [0.25]	
						Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.46 [0.07]	
						Indirect methods based on vignettes and HUI-3 with Canadian scoring	Utility	0.02 [0.14]	
		6	Severe mental retardation and tetraplegia	HCPs (pediatricians)	28	Indirect methods based on vignettes and EQ-5D-3L with UK weights	Utility	-0.15 [0.13]	
						Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.12 [0.03]	
						Indirect methods based on vignettes and HUI-3 with Canadian scoring	Utility	-0.33 [0.02]	
Bennett JE 2000 [72]	US	3-36 months	Meningitis with minor brain damage	Parents with children presented in an urban hospital ED	94	Direct methods based on SG	Utility	0.7393 [0.29]	0.8681 [0.5694,0.9851]
			Meningitis with severe brain damage				Utility	0.3903 [0.37]	0.4650 [0.0000,0.7643]
IOM 2000 [80]	US	0-5 and ≥5	Meningitis with neurologic sequelae	Experts	14	Indirect methods based on vignettes and HUI-2 with Canadian scoring function	Utility	0.6	
Stouthard ME 1997 [90]	Netherlands	Unspecified	Permanent locomotor and cognitive impairment after	HCPs (physician panels)	38	Direct methods based on PTO	Utility, disability weight	0.24 (0.139,0.348)	

			bacterial meningitis						
VAS outcomes									
Kulpeng W 2013 [84]	Thailand	5-14	Mental retardation and epilepsy	Parents/caregivers of children with the condition	18	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.5562 (0.4823,0.6302)	
Galante J 2011 [77]	Argentina	Unspecified	Neurological sequelae after meningitis	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.434 (0.469,0.547)	0.400 [0.305,0.510]
Kramer MS 1994 [82]	Canada	3-24 months	Major neurologic effect	Parents of well children	100	Direct methods based on vignettes rated using VAS	VAS value	0.232	
				Parents of febrile children	61		VAS value	0.22	
				HCPs (Attending staff physicians in ED)	56		VAS value	0.241	
Disutility									
Petrou S 2009 [88]	UK	5-16 (mean: 11.5; median: 11)	Learning and physical disabilities	Parents/caregivers of children with the condition	81	Proxy report of HUI-3 with Canadian scoring function	Disutility (vs perfect health)	-0.858 (-0.727,-0.989)	
							Disutility (vs norm)	-0.783 (-0.656,-0.918)	
Hearing loss									
Health utility									
Kulpeng W 2013 [84]	Thailand	5-14	Hearing loss	Parents of children with the condition	22	Proxy report of EQ-5D-3L with Thai weights	Utility while experiencing the disease	0.6934 (0.6456,0.7381)	
						Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.5455 (0.4284,0.6595)	
						Proxy report of HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.6672 (0.5901,0.7442)	

		7-14	Hearing loss	Patients with the condition	15	Self-reported EQ-5D-Y with Thai weights	Utility while experiencing the disease	0.6414 (0.5412,0.7416)	
						Self-reported HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.3586 (0.1470,0.5657)	
						Self-reported HUI-2 with Canadian scoring function	Utility while experiencing the disease	0.5724 (0.4477,0.6971)	
Galante J 2011 [77]	Argentina	Unspecified	Auditory sequelae after meningitis	General population in Argentina	73	Indirect methods based on vignettes and EQ-5D-3L with Argentina local TTO weights	Utility	0.727 (0.687,0.768)	0.802 [0.482,0.850]
	Chile					Indirect methods based on vignettes and EQ-5D-3L with Chile local TTO weights	Utility	0.582 (0.543,0.622)	0.672 [0.456,0.682]
	UK					Indirect methods based on vignettes and EQ-5D-3L with UK local TTO weights	Utility	0.635 (0.578,0.691)	0.725 [0.378,0.812]
Carroll A 2009 [74]	US	0-18	Mild hearing loss	Parents of children from the general population	452	Direct methods based on SG	Utility	0.92 [0.16/0.01]	0.99; 5-95 percentile (0.58,1.00)
						Direct methods based on TTO	Utility	0.92 [0.17/0.01]	0.99; 5-95 percentile (0.53,1.00)
			Moderate hearing loss		486	Direct methods based on SG	Utility	0.91 [0.18/0.01]	0.99; 5-95 percentile (0.53,1.00)
						Direct methods based on TTO	Utility	0.92 [0.18/0.01]	0.99; 5-95 percentile (0.51,1.00)
			Severe hearing loss		459	Direct methods based on SG	Utility	0.86 [0.19/0.01]	0.94; 5-95 percentile (0.50,1.00)
						Direct methods based on TTO	Utility	0.86 [0.20/0.01]	0.94; 5-95 percentile (0.50,1.00)
Petrou S 2009 [88]	UK	5-16 (mean: 12.2;	Deafness	Parents/caregivers of children with the condition	104	Proxy report of HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.420	0.410 [0.227,0.644]

		median: 12.5)						
Barton GR 2006 [71]	UK	0-17	Permanent bilateral hearing impairment - moderate (AHL 40–70 dB)	Parents/caregivers of children with the condition	260	Proxy report of revised HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.667 (0.652,0.702)
			Permanent bilateral hearing impairment - severe (AHL 71–95 dB)		464	Proxy report of revised HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.616 (0.598,0.634)
			Permanent bilateral hearing impairment - Profound (AHL 96–105 dB)		259	Proxy report of revised HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.497 (0.469,0.525)
			Permanent bilateral hearing impairment - profound (AHL >105 dB)		290	Proxy report of revised HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.353 (0.327,0.379)
			Permanent bilateral hearing impairment - implanted		403	Proxy report of revised HUI-3 with Canadian scoring function	Utility while experiencing the disease	0.575 (0.553,0.598)
Oostenbrink R 2002 [87]	Netherlands	6	Deafness	HCPs (pediatricians)	28	Indirect methods based on vignettes and EQ-5D-3L with UK weights	Utility	0.81 [0.15]
						Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.79 [0.06]

						Indirect methods based on vignettes and HUI-3 with Canadian scoring	Utility	0.28 [0.14]	
			Mild hearing loss	HCPs (pediatricians)	28	Indirect methods based on vignettes and EQ-5D-3L with UK weights	Utility	0.91 [0.08]	
						Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.84 [0.07]	
						Indirect methods based on vignettes and HUI-3 with Canadian scoring	Utility	0.65 [0.14]	
Bennett JE 2000 [72]	US	3-36 months	Deafness	Parents with children presented in an urban hospital ED	94	Direct methods based on SG	Utility	0.8611 [0.22]	0.9688 [0.8255,0.9985]
Cheng AK 2000 [75]	US	0-18 (mean: 7.5/SD: 4.5)	Pre-cochlear implant	Parents of profoundly deaf children	78	Proxy report of VAS	Utility while experiencing the disease	0.59 [0.24] (0.53,0.64)	
		0-18 (mean: 7.4/SD: 5.3)	Pre-cochlear implant	Parents of profoundly deaf children	40	Direct methods based on TTO	Utility while experiencing the disease	0.75 (0.67,0.83)	
		0-18 (mean: 10.0/SD: 4.9)	Pre-cochlear implant	Parents of profoundly deaf children	22	Proxy report of HUI-3	Utility while experiencing the disease	0.25 (0.16,0.34)	
		0-18 (mean: 7.5/SD: 4.5)	Post-cochlear implant	Parents of profoundly deaf children	78	Proxy report of VAS	VAS value while experiencing the disease	0.86 [0.14] (0.83,0.89)	
		0-18 (mean: 7.4/SD: 5.3)	Post-cochlear implant	Parents of profoundly deaf children	40	Direct methods based on TTO	Utility while experiencing the disease	0.97 (0.93,1.00)	
		0-18 (mean: 10.0/SD: 4.9)	Post-cochlear implant	Parents of profoundly deaf children	22	Proxy report of HUI-3	Utility while experiencing the disease	0.64 (0.57,0.70)	

Stouthard ME 1997 [90]	Netherlands	Unspecified	Hearing disorders in childhood, mild to moderate congenital or early acquired	HCPs (physician panels)	38	Direct methods based on PTO	Utility, disability weight	0.89 (0.832,0.944)	
			Hearing disorders in childhood, severe congenital or early acquired	HCPs (physician panels)	38	Direct methods based on PTO	Utility, disability weight	0.77 (0.669,0.877)	
VAS outcomes									
Kulpeng W 2013 [84]	Thailand	5-14	Hearing loss	Parents of children with the condition	22	Proxy report of EQ-VAS	VAS value while experiencing the disease	0.7889 (0.7180,0.8613)	
		7-14	Hearing loss	Patients with the condition	15	Self-reported EQ-VAS	VAS value while experiencing the disease	0.8330 (0.7327,0.9354)	
Galante J 2011 [77]	Argentina	Unspecified	Auditory sequelae after meningitis	General population in Argentina	73	Indirect methods based on vignettes and EQ-VAS	VAS value	0.601 (0.567,0.635)	0.605 [0.520,0.700]
Kramer MS 1994 [82]	Canada	3-24 months	Unilateral hearing loss	Parents of well children	100	Direct methods based on vignettes rated using VAS	VAS value	0.516	
				Parents of febrile children	61		VAS value	0.492	
				HCPs (Attending staff physicians in ED)	56		VAS value	0.652	
			Bilateral hearing loss	Parents of well children	100		VAS value	0.379	
				Parents of febrile children	61		VAS value	0.368	
				HCPs (Attending staff physicians in ED)	56		VAS value	0.451	
Disutility									

Legood R 2009 [85]	UK	5.4-20.4 (mean: 9.9)	Hearing impairment	Patients or parents of children with the condition	69	Proxy- or self-reported HUI-3 with Canadian scoring	Disutility while experiencing the disease	-0.117
Petrou S 2009 [88]	UK	5-16 (mean: 12.2; median: 12.5)	Deafness	Parents or caregivers of children with the condition	104	Proxy report of HUI-3 with Canadian scoring function	Disutility (vs perfect health)	-0.583 (-0.454,-0.712)
							Disutility (vs norm)	-0.509 (-0.383,-0.641)
Unspecified PMS states								
Health utility								
Al-Janabi H 2016 [70]	UK	0-65 (mean: 23/SD: 16)	After-effects post meningitis on survivors, including cognitive problems, seizures, hearing loss, motor limitations, amputations, vision problems, and behavioral problems	Family members (survivors' utility)	816	Proxy report of EQ-5D-5L without specifying weights used	Utility while experiencing the disease	0.78
				Family members (family members' utility)	1,053	Self-report of EQ-5D-5L without specifying weights used	Family members' utility	0.87
Legood R 2009 [85]	UK	5.4-20.4 (mean: 9.9)	Meningitis survivors	Patients or parents	69	Proxy- or self-reported HUI-3 with Canadian scoring	Utility while experiencing the disease	0.774 (0.711,0.837)

Koomen I 2003 [81]	Netherlands	4.3-13.6 (mean: 8.5)	Meningitis survivors	Parents	680	Indirect methods based on vignettes and HUI-2 with Canadian scoring	Utility	0.92 [0.11]

Abbreviations: PMS=Post-meningitis sequelae; SD=Standard deviation; SE=Standard error; CI=Confidence interval; IQR=Interquartile range; IOM=Institute of Medicine; UK=United Kingdom; US=United States; HCP=Health care provider; ED=Emergency department; SG=Standard gamble; TTO=Time trade-off; EQ-5D=EuroQol-5 Dimensions; HUI=Health utilities index; NHIS=National Health Interview Survey; HALex=Health and Limitations Index; EQ-VAS=EuroQol visual analogue scale; VAS=Visual analogue scale; PTO=Person trade-off; AHL=Average hearing level; dB=Decibel.

Notes:

1. The study used the National Health Interview Survey, which included a nationally representative sample. Children with <18 years old accounted for 7.7% of the sample. The results were reported for the overall population. Proxy respondents were used for all children, while individuals or proxy respondents were used among adults, depending on their ability to respond to the questionnaire.

2. HALex is not a preference-based measure but has been used to generate estimates to represent utilities.