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REVIEW ARTICLE

Health Utilities Associated with Pneumococcal Diseases in Children and Adults: A Targeted Literature Review and Meta-analysis

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Abstract

Background Pneumococcal disease and post-meningitis sequelae (PMS) impact health-related quality of life (HRQoL). However, health utility estimates for these conditions vary considerably in the literature, which may affect the outcomes of economic evaluations.

Objectives The aim was to generate pooled estimates of quality-adjusted life year (QALY) decrements per episode for pneumococcal disease and pooled health state utility value (HSUV) estimates for PMS in children and adults.

Methods Global targeted literature reviews were conducted in MEDLINE in June 2024 to identify original studies on the health utilities of pneumococcal disease and PMS. Random-effects meta-analyses were conducted separately for children (< 18 years) and adults (≥ 18 years) to calculate pooled estimates of QALY decrements per episode for pneumococcal disease states and pooled HSUV estimates for PMS.

Results A total of 40 studies, published from 1993–2022, were included. Fifteen were conducted among children, 19 among adults, and six among both age groups. In children, the pooled QALY decrement estimates (95% confidence interval [CI]) per episode were 0.023 (0.017–0.030) for meningitis, 0.010 (0.003–0.017) for bacteremia/sepsis, 0.014 (0.002–0.026) for inpatient pneumonia, 0.010 (0.002–0.017) for outpatient pneumonia, 0.008 (0.003–0.013) for unspecified pneumonia, 0.005 (0.005–0.006) for recurrent/complex acute otitis media (AOM), and 0.003 (0.001–0.005) for simple AOM. The pooled HSUV estimates for PMS in children were 0.485 (0.322–0.649) for neurological deficits, 0.701 (0.563–0.839) for hearing loss, and 0.827 (0.713–0.941) for unspecified PMS. In adults, the pooled QALY decrement estimates per episode (95% CI) were 0.027 (0.018–0.036) for meningitis, 0.013 (0.000–0.027) for bacteremia/sepsis, 0.015 (0.008–0.021) for inpatient pneumonia, 0.007 (0.005–0.008) for outpatient pneumonia, and 0.009 (0.001–0.018) for unspecified pneumonia. The pooled HSUV estimates for PMS in adults were 0.556 (0.447–0.665) for neurological deficits, 0.700 (0.631–0.768) for hearing loss, and 0.778 (0.744–0.812) for unspecified PMS. Moderate to high heterogeneity levels were observed in most of the meta-analyses performed in this study.

Conclusions Pneumococcal disease and PMS substantially reduce HRQoL in children and adults, with the greatest impacts observed with meningitis, inpatient pneumonia, and bacteremia/sepsis. There is considerable variability in utility estimates across studies, likely driven by methodological differences. This analysis provides a comprehensive quantitative synthesis of QALY decrement estimates for pneumococcal disease states and HSUV estimates for PMS, improving our understanding of the HRQoL burden and potentially enhancing the comparability of future economic evaluations of pneumococcal vaccines.

1 Introduction

Streptococcus pneumoniae is a leading cause of morbidity, mortality, and healthcare resource utilization worldwide, particularly among young children and older adults [1–3]. The diseases caused by *S. pneumoniae* are classified as invasive or non-invasive. Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid). Bacteremic pneumonia is the most common presentation of IPD, with other clinical syndromes including bacteremia of unknown source, meningitis, and infection of the pleural space (empyema) or joints. Non-invasive pneumococcal disease includes conditions such as non-bacteremic pneumonia and acute otitis media (AOM) [4].

Pneumococcal disease has a substantial effect on health-related quality of life (HRQoL). Studies have shown that

Extended author information available on the last page of the article

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Key Points for Decision Makers

Pneumococcal disease, particularly meningitis, bacteremia/sepsis, and inpatient pneumonia, significantly reduces health-related quality of life in both children and adults.

The included studies demonstrated considerable variability in their findings, likely because of differences in the methodologies used.

Despite this heterogeneity, combining the evidence allowed us to generate estimates that can guide future research and support more consistent economic evaluations of pneumococcal vaccines.

patients experience significant declines in HRQoL during the acute phase of pneumococcal disease, largely due to symptoms that affect physical and emotional well-being [5, 6]. In addition, recovery from these infections can be prolonged, during which time many patients report lower physical and social functioning [7]. In particular, meningitis often has serious long-term consequences, including neurological deficits and hearing loss. These post-meningitis sequelae (PMS) can substantially decrease HRQoL by affecting daily activities, communication, and social interactions [8].

Preventive measures, such as vaccination, play a crucial role in reducing the burden of pneumococcal disease. Over the last 3 decades, widespread use of pneumococcal conjugate vaccines (PCVs) in routine childhood immunization schedules—particularly 7-valent PCV, 10-valent PCV, and 13-valent PCV—has led to a substantial reduction in the global burden of pneumococcal disease [3]. The United States (US) Centers for Disease Control and Prevention (CDC) Advisory Committee for Immunization Practices (ACIP) recommends pneumococcal vaccination for children younger than 5 years of age, adults 50 years of age or older, and children and adults with chronic medical conditions that increase the risk of pneumococcal disease or predispose to severe pneumococcal infections. In children, ACIP and the American Academy of Pediatrics (AAP) now recommend the use of extended valency PCVs (15-valent PCV [PCV15 or V114] or 20-valent PCV [PCV20]) [9–12]. For adults, the recommendations vary based on the history of prior pneumococcal vaccination, and include PCV20 or 21-valent PCV alone, or PCV15 followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) [13]. Economic evaluations of pneumococcal vaccines are critical to informing vaccine policy decisions in the US and other countries.

While health utilities of pneumococcal disease and PMS are an important component of economic evaluations of pneumococcal vaccines, recent reviews of published cost-utility analyses (CUAs) have found that varied utility estimates from different sources are used in these studies, leading to heterogeneity that can affect study conclusions. Three previously published reviews have summarized the utility outcomes of pneumococcal disease [5, 14, 15]. The most recent of these reviews, Tang et al. and O'Reilly et al., were published in 2022. O'Reilly et al. included studies published through January 2020 and was more comprehensive with regard to the included studies [5], while Tang et al. included studies published through 2019 and was the only review to provide pooled estimates of utilities from identified studies [15].

In order to provide updated estimates of the health utilities of pneumococcal diseases, while leveraging these recent reviews, we conducted two targeted literature reviews in June 2024 to identify published original studies on the health utility of common pneumococcal disease and PMS states in children and adults. These reviews consolidated studies from three key sources: original utility studies used in published CUAs from North America and Europe, utility studies identified in the previously published literature reviews, and new studies identified through a global literature search. As a result, these literature reviews represent the most comprehensive and current summaries of the health utilities of pneumococcal disease and PMS in children and adults conducted to date. In two previous studies, we provided descriptive summaries of the full complement of studies focused on children [16] and adults [17], respectively. These summaries highlighted the substantial variability in utility estimates that exists across studies and demonstrated that published CUAs of pneumococcal vaccines frequently applied the same utility estimates to different pneumococcal disease states or sourced utility estimates from studies published more than 2 decades ago. In addition, only two recent CUAs sourced their utility inputs from the pooled analysis conducted by Tang et al. [18, 19]. Notably, these pooled estimates were based on the averages of utilities reported in the included studies and did not account for data heterogeneity, thus limiting the extent to which they capture variability across studies.

To address this gap in the literature, the current study builds on the qualitative summaries from our previously published literature reviews [16, 17] by providing quantitative summaries of utility estimates for specific pneumococcal disease and PMS health states. Specifically, pooled estimates of quality-adjusted life year (QALY) decrements per episode for pneumococcal disease and pooled health state utility value (HSUV) estimates for PMS were generated.

These estimates were assessed separately for children and adults through meta-analyses that accounted for the heterogeneity across the included studies.

2 Methods

2.1 Literature Review

Two targeted literature reviews of utilities related to pneumococcal disease and PMS in children and adults 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, as described previously [16, 17]. These literature reviews aimed to incorporate studies included in recent reviews and CUAs and to identify additional studies not identified in there. The first targeted literature review identified CUAs of pneumococcal vaccines and reviews of CUAs published since 2010 based on search terms including a combination of disease and cost terms (Supplementary Table S1 in the electronic supplementary material). Relevant CUAs published prior to 2010 were also identified by screening the references of the previous reviews. The second targeted literature review updated the existing published reviews through inclusion of additional original research studies estimating health utility values for pneumococcal disease and PMS. The most recently published literature reviews (Tang et al. and O'Reilly et al.) included studies published through January 2020, so this *de novo* literature search—conducted in accordance with guidance from the Centre for Review and Dissemination [20]—identified original full-text publications and reviews of health utilities for pneumococcal disease and PMS published since 2019. The search terms included a combination of disease terms and utility terms and a list of methods used to generate health utilities (Supplementary Table S2).

The references from the identified health utility reviews and CUAs from the first targeted literature review as well as those identified through the *de novo* literature search were screened for eligible studies published prior to 2019 (Supplementary Fig. S1A, B). To be included, studies had to (1) focus on one or more pneumococcal disease states (i.e., meningitis, bacteremia/sepsis, pneumonia, and simple or complex AOM) or PMS (i.e., hearing loss, neurological deficits, unspecified PMS) that are most relevant to economic evaluations; (2) report a measure of health utility, disutility, QALYs, or QALY decrement for one episode of acute disease or long-term sequelae; and (3) be published in a full-text manuscript in English. Studies were excluded if (1) the study population was not representative of the general population (e.g., a population with a comorbidity that impacts HRQoL); (2) the symptoms, disease course, or treatment of the condition evaluated differed from those of pneumococcal disease or PMS health states based on input from a clinical expert (MSK); or (3) the utility estimates included a time period after recovery from the acute episode. These criteria were applied to all original studies identified, including studies identified through review of the references of the previous reviews and CUAs and studies identified through the *de novo* literature search.

2.2 Data Extraction and Preparation

For each of the included studies, the following information was extracted for each pneumococcal disease state: population age category (children < 18 years and/or adults ≥ 18 years); country or geographic region; surveyed population and sample size (i.e., number of individuals queried); utility elicitation method; and measures of health utility, disutility, QALYs, and/or QALY decrement, including means, medians, and available variability information (i.e., standard deviation [SD], confidence interval [CI], interquartile range [IQR]). Missing mean utility measures were imputed using medians, and missing SDs were estimated using the sample size and 95% CI or IQR if available (Supplementary Table S3). If no variability information was provided, missing utility/disutility SDs were assumed to be 75% of the mean, based on observations from studies with both mean and SD data. All studies reporting QALY per year estimates that were retained in the analyses provided measures of variability alongside the point estimates; therefore, no imputation of SDs was required for these studies.

To ensure comparability across studies, utility measures from all eligible studies for IPD, pneumonia, and AOM were converted into QALY decrements per episode for meta-analysis. The mean and SD of the QALY decrement per episode of IPD, pneumonia, and AOM were estimated using the sample size, mean, and SD of the utility measure reported and the mean and SD of the illness duration in years (Supplementary Table S4). The following illness durations from a report published by the US Institute of Medicine were used: 10.6 days for meningitis, 4 days for bacteremia, 7 days for sepsis, 10 days for pneumonia, and 4 days for AOM [21]. The SD of these illness durations was assumed to be equal to its mean based on a hypothetical Poisson distribution. Of note, for studies that directly provided QALY decrement per year estimates, no data conversion was required and the illness duration assumptions mentioned above did not apply. For recurrent/complex AOM, QALY decrements per year were also assessed, assuming four episodes of AOM per year [22, 23]. Given that PMS are frequently long-term or permanent, no QALY decrement estimates were calculated

for these disease states, and utility data were used in the meta-analysis.

For each pneumococcal disease state, every eligible study contributed a single QALY decrement estimate to the corresponding meta-analysis. For studies that reported multiple utility values for the same disease state estimated using different utility elicitation methods, only one of the values was selected. Indirect methods, which estimate utility values through standardized instruments or questionnaires, were prioritized over direct methods, which ask individuals to make decisions or trade-offs about different health states, aligning with guidance from the National Institute for Health and Care Excellence (NICE) that favors instruments such as the EuroQoL 5-Dimension (EQ-5D) for economic evaluation [24]. Among indirect methods, the order of priority was (1) the EQ-5D, in line with guidance from NICE [24]; (2) the Health Utilities Index (HUI)-3; and (3) the HUI-2, given that the HUI-3 is more detailed than the HUI-2 [25]. Among direct methods, the order of priority for methods was (1) time trade-off (TTO), (2) standard gamble (SG), and (3) visual analog scale (VAS) [26]. For studies that reported multiple utility values for the same disease state because of use of the same utility elicitation method in different survey populations (e.g., patients, parents) or different scenarios of the disease (e.g., with or without delayed diagnosis, with or without a requirement for intensive care), a combined estimate was calculated as the weighted average of the QALY decrements of the different populations or scenarios.

2.3 Statistical Analyses

Given the substantial heterogeneity observed between the retained studies [16, 17], random-effects meta-analyses were conducted using the method of DerSimonian and Laird [27] to calculate pooled estimates of QALY decrement and utility per episode of each pneumococcal disease and PMS health state, for children and adults separately. Heterogeneity across data sources was measured using the I^2 statistic, defined as the proportion of the variability that is attributable to between-study heterogeneity and reported along with the associated p value.

For IPD, meta-analyses were conducted separately for meningitis and bacteremia/sepsis. Meta-analyses were also conducted independently for inpatient and outpatient pneumonia; pneumonia studies that did not specify the setting were classified as unspecified pneumonia and analyzed separately. For AOM, meta-analyses were conducted separately for AOM/simple AOM and recurrent/complex AOM; for the latter, pooled QALY decrements per year were also generated. For PMS, meta-analyses were conducted independently for hearing loss and neurological deficits. Studies that focused on PMS but did not describe the specific sequelae were classified as unspecified PMS and analyzed separately.

2.3.1 Primary Analysis

Given that the TTO estimate of QALY decrement per year in Prosser et al. was substantially larger than those reported by other pediatric studies across pneumococcal disease states [28], this study was excluded from primary analyses in children. Details on the methodological aspects of Prosser et al. that likely contributed to the magnitude of the estimated QALY decrements are discussed in Huang et al. (2025) [16].

2.3.2 Sensitivity Analysis Including Prosser et al.

Sensitivity analyses were performed in children with the study conducted by Prosser et al. [28] included in the meta-analysis. The following disease states with data from Prosser et al. were considered: meningitis, bacteremia/sepsis, inpatient and outpatient pneumonia, AOM/simple AOM, and recurrent/complex AOM.

2.3.3 Leave-One-Out Sensitivity Analysis

To explore the robustness of the pooled estimates, sensitivity analyses were conducted using a leave-one-out approach for the pneumococcal disease and PMS states. For each primary meta-analysis with at least three contributing studies, each individual study was excluded one at a time while all remaining studies were retained, and the pooled estimates of QALY decrements per episode for pneumococcal disease and pooled HSUV estimates for PMS, and corresponding I^2 statistics, were re-estimated. The resulting ranges of pooled estimates and heterogeneity measures were reported to assess the influence of any single study on the overall results.

2.3.4 Subgroup Analyses

Given that direct and indirect elicitation methods tend to result in different utility estimates [16, 17], stratified analyses based on this methodological classification were conducted separately for children and adults for pneumococcal disease and PMS states for which at least two studies provided data for each category of method. Studies that measured utilities using both direct and indirect methods contributed to the meta-analysis for each respective method. These analyses were conducted for the pneumococcal disease and PMS states with at least two studies in each subgroup. This included meningitis, AOM/simple AOM, and post-meningitis hearing loss and neurological deficits in children, and inpatient and outpatient pneumonia in adults.

To further understand the variability across different elicitation methods, analyses were also conducted stratified by specific elicitation method (e.g., EQ-5D, HUI-3, SG, TTO). For studies that measured utilities using multiple methods, the results for each method were included separately in the

Table 1 Counts of the original studies included in this review and meta-analysis

	Total	Age group of population of interest		
		Children only	Adults only	Both children and adults
Overall	**40**	**15**	**19**	**6**
IPD	**7**	**5**	**0**	**2**
Meningitis[a]	7	5	0	2
Bacteremia/sepsis[a]	5	3	0	2
Pneumonia	**19**	**3**	**12**	**3**
Inpatient[a]	9	1	6	2
Outpatient[a]	10	1	7	2
Unspecified	4	2	1	1
AOM	**10**	**10**	**0**	**0**
AOM/simple AOM[a]	7	7	0	0
Recurrent/complex AOM[a]	4	4	0	0
PMS	**22**	**9**	**7**	**6**
Hearing loss	16	8	6	2
Neurological deficits	11	6	1	4
Unspecified	3	1	0	2

AOM acute otitis media, *IPD* invasive pneumococcal disease, *PMS* post-meningitis sequelae

[a]The number of studies conducted in children includes the study by Prosser et al. [28] that was not included in the primary analysis

subgroup analyses. These analyses were conducted for all disease states, with the exception of recurrent/complex AOM in children, for which only VAS scores were used to measure utilities.

Finally, subgroup analyses were conducted to generate US-specific pooled estimates when at least two US studies were available. In children, these subgroup analyses were conducted for meningitis, bacteremia/sepsis, AOM/simple AOM, post-meningitis hearing loss, post-meningitis neurological deficits, and unspecified PMS. In adults, analyses were conducted for inpatient and outpatient pneumonia, post-meningitis hearing loss, and unspecified PMS. Subgroup analyses were not performed for other countries or regions because fewer than two studies were available for most pneumococcal disease states.

All statistical analyses were conducted in R (version 4.2.2).

3 Results

3.1 Studies Included from Targeted Literature Reviews

Overall, 40 studies that reported health utility measures and that were published between 1993 and 2022 were included in the current meta-analyses [16, 17]. Of these, 15 studies were conducted among children, 19 studies were conducted among adults, and six studies included individuals from both age groups. Table 1 shows the number of studies per disease state by age group of interest. Of studies that focused only on children, ten assessed AOM, nine assessed PMS, five assessed meningitis or bacteremia, and three assessed pneumonia. Of studies that focused only on adults, 12 assessed pneumonia and seven assessed PMS. Of studies that considered both children and adults, six assessed PMS, three assessed pneumonia, and two assessed meningitis or bacteremia.

A summary of the countries/regions, surveyed populations, and utility elicitation methods by age group and disease state is provided in Table 2. The studies were conducted in 20 different countries or regions, with the most common locations being the US ($n = 10$ studies), the United Kingdom (UK) ($n = 9$), and the Netherlands ($n = 8$). Different populations were surveyed across the studies, including patients ($n = 26$ studies), parents/caregivers ($n = 15$), healthcare providers (HCPs) ($n = 5$), and the general population ($n = 2$). A variety of elicitation methods were used to assess the utility outcomes. Among direct methods, VAS ($n = 17$ studies) and TTO ($n = 4$) were the most frequently used methods in both children and adults. Among indirect methods, EQ-5D-3L ($n = 10$), EQ-5D-5L ($n = 6$), and HUI-3 ($n = 8$) were the most frequently used in studies of both children and adults. In addition to these standard methods, other less common elicitation methods were also used: one study applied a direct person trade-off (PTO) method to estimate utility values

Table 2 Studies included in the main analyses[a]

Age group (years)	Disease state		Sources	Countries	Surveyed populations	Method used to generate utilities
Children (0–17)	IPD	Meningitis	[21, 40, 44–47]	Argentina; Canada; Thailand; UK; US	General population; HCPs; parents; patients; parents of well/febrile children	EQ-5D-3L; HUI-2; HUI-3; SG; VAS
		Bacteremia/sepsis	[21, 40, 46, 47]	Argentina; Thailand; US	General population; HCPs; parents; patients	EQ-5D-3L; HUI-2; SG
	Pneumonia	Inpatient pneumonia	[21, 46]	Argentina; US	General population; HCPs	EQ-5D-3L; HUI-2
		Outpatient pneumonia	[21, 46]	Argentina; US	General population; HCPs	EQ-5D-3L; HUI-2
		Unspecified pneumonia	[29, 44, 47]	Canada; Netherlands; Thailand	HCPs; parents; patients; parents of well/febrile children and HCPs	EQ-5D-3L; PTO; VAS
	AOM	AOM/simple AOM	[21, 46–50]	Argentina; Canada; Malaysia; Thailand; US	General population; HCPs; parents; patients	EQ-5D-3L; HUI-2; TTO; VAS
		Recurrent/complex AOM	[51–53]	Denmark; Finland; Netherlands	Parents	VAS
	PMS	Hearing loss	[29, 40, 44–47, 49, 54–56]	Argentina; Canada; Netherlands; Thailand; UK; US	Caregivers; general population; HCPs; parents; patients	EQ-5D-3L; HUI-3; PTO; SG; TTO; VAS
		Neurological deficits	[21, 29, 30, 40, 44–47, 49, 55]	Argentina; Canada; Netherlands; Thailand; UK; US	General population; HCPs; parents; parents of well/febrile children and HCPs; patients; patients/parents	EQ-5D-3L; HALex; HUI-2; HUI-3; PTO; SG; TTO; VAS
		Unspecified PMS	[57–59]	Netherlands; UK	Parents; patients; patients/parents	EQ-5D-5L; HUI-2; HUI-3
Adults (≥ 18)	IPD	Meningitis	[21, 46]	Argentina; US	General population; HCPs	EQ-5D-3L; HUI-2
		Bacteremia	[21, 46]	Argentina; US	General population; HCPs	EQ-5D-3L; HUI-2
	Pneumonia	Inpatient pneumonia	[7, 21, 31, 32, 46, 60–62]	Argentina; Australia; Denmark; Netherlands; Serbia; US	General population; HCPs; patients	EQ-5D-3L; EQ-5D-5L; HUI-2; SG; VAS
		Outpatient pneumonia	[21, 31, 32, 46, 63–67]	Argentina; Belgium; England; Europe; Finland; Germany; Netherlands; Spain; Sweden and Norway; US; Wales	General population; HCPs; patients	EQ-5D-3L; HUI-2; SG; TTO
		Unspecified pneumonia	[29, 68]	Japan; Netherlands	HCPs; patients	EQ-5D-5L; PTO
	PMS	Hearing loss	[29, 33, 46, 69–73]	Argentina; Colombia/Poland; Netherlands; UK; US; US, UK, and France	General population; HCPs; patients	EQ-5D-3L; EQ-5D-5L; HUI-2; HUI-3; HUI, VAS, and QWB; PTO
		Neurological deficits	[21, 29, 30, 46, 74]	Argentina; Japan; Netherlands; US	General population; HCPs; patients; patients/parents	EQ-5D-3L; EQ-5D-5L; HALex; HUI-2; PTO
		Unspecified PMS	[58, 59]	UK	Patients; patients/parents	EQ-5D-5L; HUI-3

AOM acute otitis media, *EQ-5D* EuroQoL 5-Dimension, *HALex* Health and Activities Limitation Index, *HCP* healthcare provider, *HUI* Health Utilities Index, *IPD* invasive pneumococcal disease, *PMS* post-meningitis sequelae, *PTO* person trade-off, *QWB* quality of well-being scale, *SG* standard gamble, *TTO* time trade-off, *UK* United Kingdom, *US* United States, *VAS* visual analog scale

[a]The primary analyses excluded the study conducted by Prosser et al.[28]

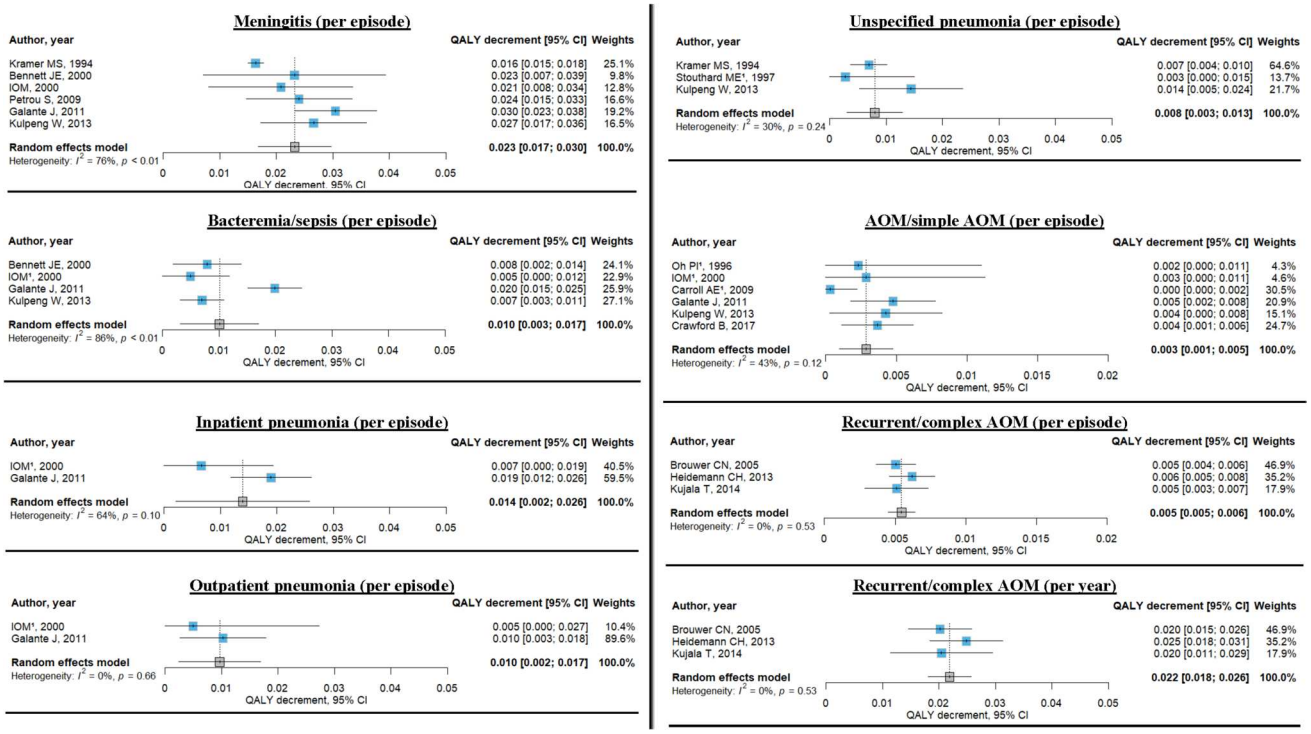

Fig. 1 Forest plots for the meta-analyses of QALY decrements for pneumococcal disease states in children. *AOM* acute otitis media, *CI* confidence interval, *IOM* Institute of Medicine, *QALY* quality-adjusted life year. [1] The lower bound of the 95% CI for QALY decrements was truncated at 0

of pneumonia and PMS [29], while another study used the Health and Activities Limitation Index (HALex) to estimate HRQoL scores for PMS [30].

3.2 Meta-analysis Results in Children

A total of 20 studies contributed to the primary meta-analyses of health utility measures in children [28]. Forest plots of the primary meta-analyses for IPD, pneumonia, and AOM in children are presented in Fig. 1 (additional information on the included studies, including sample size, can be found in Supplementary Table S5 in the electronic supplementary material). The pooled QALY decrement estimates per episode in children were 0.023 (95% CI 0.017–0.030) for meningitis and 0.010 (95% CI 0.003–0.017) for bacteremia/sepsis. For pneumonia, the pooled QALY decrement estimates per episode in children were 0.014 (95% CI 0.002–0.026) for inpatient pneumonia, 0.010 (95% CI 0.002–0.017) for outpatient pneumonia, and 0.008 (95% CI 0.003–0.013) for unspecified pneumonia. For AOM, the pooled QALY decrement estimate per episode of AOM/simple AOM in children was 0.003 (95% CI 0.001–0.005). For recurrent/complex AOM, the pooled QALY decrement estimates in children were 0.005 (95% CI 0.005–0.006) per episode and 0.022 (95% CI 0.018–0.026) per year.

Forest plots of the meta-analyses for PMS in children are presented in Fig. 2 (additional information on the included studies, including sample size, can be found in Supplementary Table S6). Pooled HSUV estimates in children were 0.701 (95% CI 0.563–0.839) for hearing loss, 0.485 (95% CI 0.322–0.649) for neurological deficits, and 0.827 (95% CI 0.713–0.941) for unspecified PMS.

In the primary analyses in children, between-study heterogeneity was high for post-meningitis hearing loss (I^2 = 100%), neurological sequelae (I^2 = 100%), unspecified PMS (I^2 = 97%), bacteremia/sepsis (I^2 = 86%), and meningitis (I^2 = 76%), substantial for inpatient pneumonia (I^2 = 64%), moderate for AOM/simple AOM (I^2 = 43%) and unspecified pneumonia (I^2 = 30%), and low for outpatient pneumonia and recurrent/complex AOM (I^2 = 0%).

3.3 Meta-analysis Results in Adults

A total of 25 studies contributed to the meta-analysis of health utility measures in adults. Forest plots of the meta-analyses for IPD and pneumonia in adults are depicted in Fig. 3 (additional information on the included studies, including sample size, can be found in Supplementary Table S7). For IPD, the pooled QALY decrement estimates per episode in adults were 0.027 (95% CI 0.018–0.036) for meningitis and 0.013 (95% CI 0.000–0.027) for

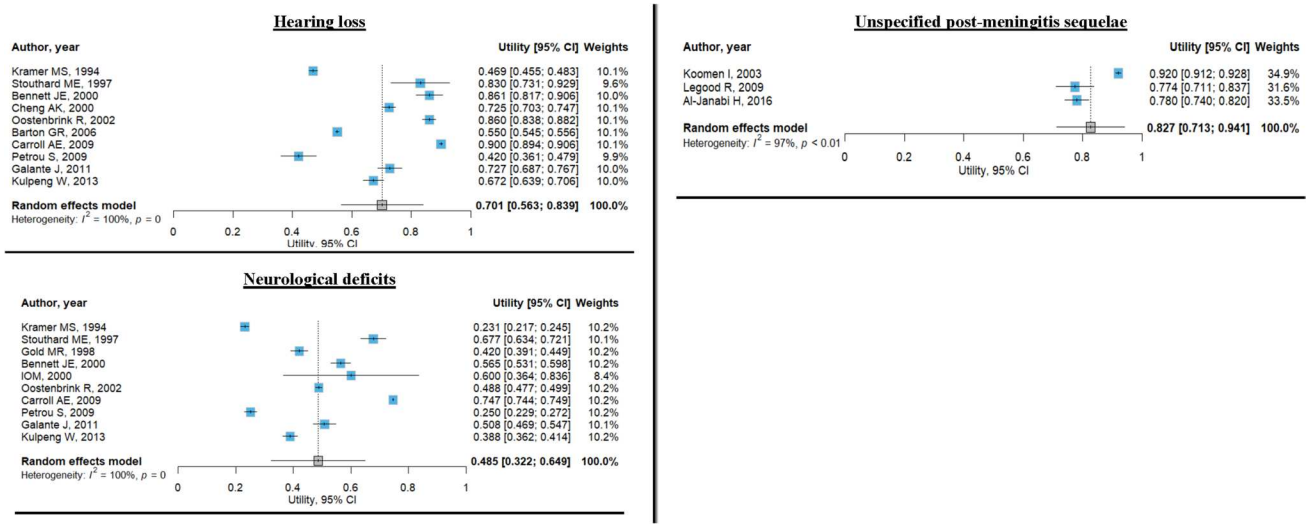

Fig. 2 Forest plots for the meta-analyses of utility for post-meningitis sequelae in children. *CI* confidence interval

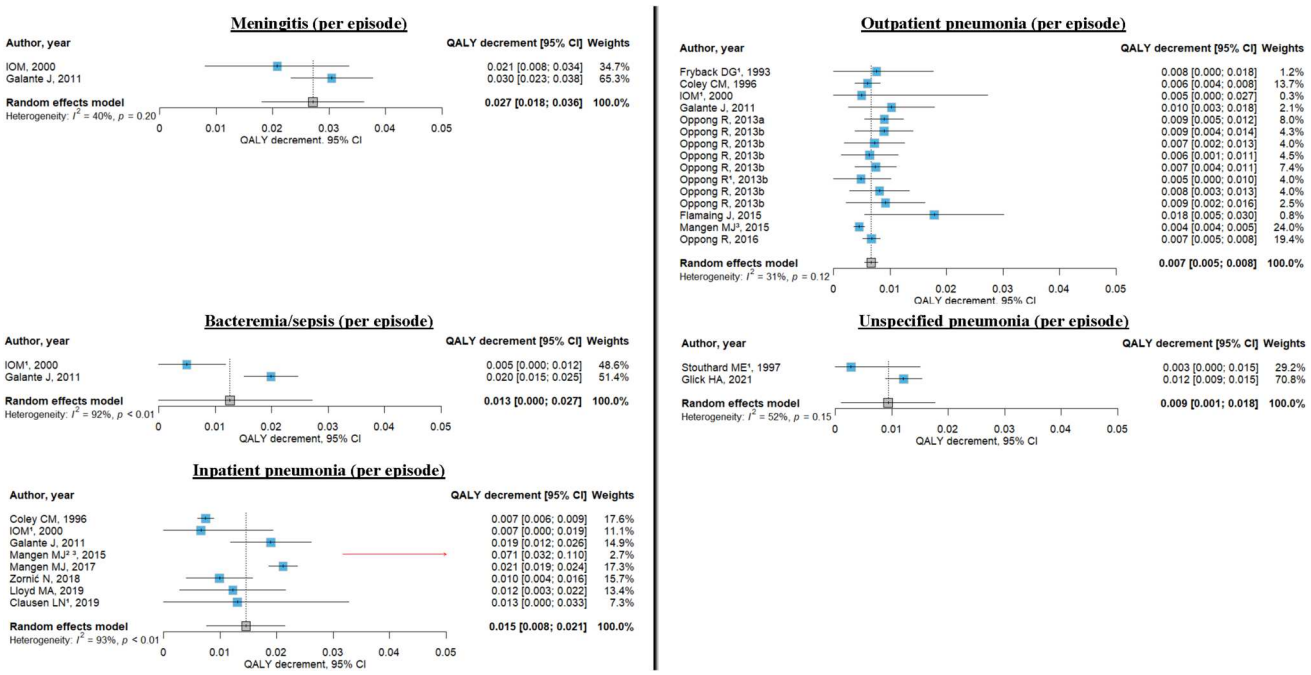

Fig. 3 Forest plots for the meta-analyses of QALY decrements for pneumococcal disease states in adults. *CI* confidence interval, *QALY* quality-adjusted life year. [1] The lower bound of the 95% CI for QALY decrements was truncated at 0. [2] Results from Mangen et al. (2015) [32] were not shown in the forest plot as the mean QALY decrement point estimate was substantially larger than that of the other studies and was outside the range of the plot. [3] This study provided the estimates or formula to calculate QALY decrements

bacteremia/sepsis. For pneumonia, the pooled QALY decrement estimates per episode in adults were 0.015 (95% CI 0.008–0.021) for inpatient pneumonia, 0.007 (95% CI 0.005–0.008) for outpatient pneumonia, and 0.009 (95% CI 0.001–0.018) for unspecified pneumonia.

Forest plots of the meta-analyses for PMS in adults are depicted in Fig. 4 (additional information on the included studies, including sample size, can be found in Supplementary Table S8). Pooled HSUV estimates in adults were 0.700 (95% CI 0.631–0.768) for hearing loss, 0.556 (95% CI

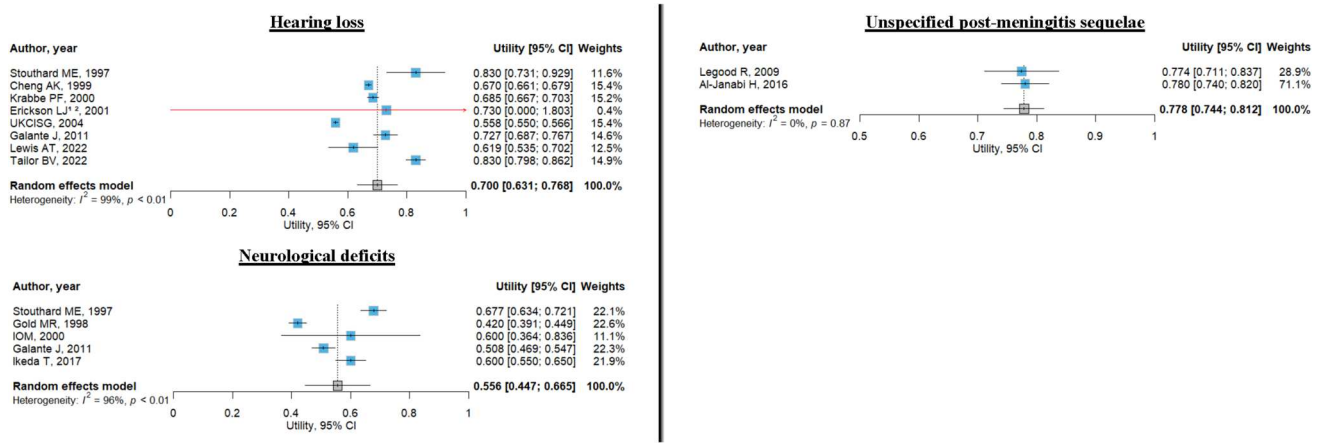

Fig. 4 Forest plots for the meta-analyses of utility for post-meningitis sequelae in adults. *CI* confidence interval. [1] The lower bound of the 95% CI for utility was truncated at 0. [2] The 95% CI from the study conducted by Erickson et al. (2001) [33], which included a single patient, was not shown in the forest plot because it was outside the range of the plot

0.447–0.665) for neurological deficits, and 0.778 (95% CI 0.744–0.812) for unspecified PMS.

In adults, between-study heterogeneity was as substantial as in children, with higher levels observed for post-meningitis hearing loss (I^2 = 99%), neurological sequelae (I^2 = 96%), inpatient pneumonia (I^2 = 93%), and bacteremia/sepsis (I^2 = 92%).

3.4 Sensitivity Analysis Including Prosser et al.

A total of 21 studies contributed to the sensitivity analyses in children with the inclusion of the study by Prosser et al. [28]. These results are presented in Supplementary Table S9. In this sensitivity analysis, very low weights were assigned to the study by Prosser et al. for meningitis, bacteremia/sepsis, AOM/simple AOM, and recurrent/complex AOM (0.3–2%) due to the high variability associated with the provided estimates as well as the relatively high number of other studies contributing to the meta-analysis in these pneumococcal disease states. As a result, this sensitivity analysis led to pooled QALY decrements per episode that were similar to those from the primary analysis for meningitis (0.026 [95% CI 0.015–0.037] vs. 0.023 [95% CI 0.017–0.030]), bacteremia/sepsis (0.011 [95% CI 0.003–0.019] vs. 0.010 [95% CI 0.003–0.017]), AOM/simple AOM (0.003 [95% CI 0.001–0.005] vs. 0.003 [95% CI 0.001–0.005]), and recurrent/complex AOM (0.006 [95% CI 0.003–0.009] vs. 0.005 [95% CI 0.005–0.006]). However, for inpatient and outpatient pneumonia, only two other studies contributed to the meta-analyses, resulting in moderate weights assigned to the study by Prosser et al. (9–10%), leading to pooled QALY decrements per episode that were substantially larger in the sensitivity analyses than in the primary analyses (inpatient pneumonia: 0.051 [95% CI 0.007–0.095] vs. 0.014 [95% CI 0.002–0.026]; outpatient pneumonia: 0.017 [95% CI 0.000–0.040] vs. 0.010 [95% CI 0.002–0.017]). Heterogeneity was consistently higher in all pneumococcal disease states in the sensitivity analyses, compared with the primary analysis.

3.5 Leave-One-Out Sensitivity Analysis

Across disease states, leave-one-out analyses found limited variation in point estimates for both children (Supplementary Table S5 and S6) and adults (Supplementary Table S7 and S8). In contrast, heterogeneity levels varied depending on the contribution of individual studies, particularly in children. For example, for meningitis in children, the pooled QALY decrement per episode was 0.023 (I^2 = 76%); the leave-one-out sensitivity ranges were 0.021–0.027 for the QALY decrement and 0–81% for I^2. For inpatient pneumonia in adults, the pooled QALY decrement per episode was 0.015 (I^2 = 93%), with leave-one-out sensitivity ranges of 0.012–0.016 for the QALY decrement and 72–94% for I^2.

3.6 Subgroup Analyses

Results of the meta-analyses stratified by use of direct or indirect methods are presented in Supplementary Tables S10 and S11 for children and Supplementary Table S12 for adults. Indirect methods were associated with numerically smaller utility estimates, and thus larger QALY decrements, than direct methods. The pooled QALY decrement estimates in children for meningitis were 0.027 (95% CI 0.022–0.031) for indirect methods and 0.016 (95% CI 0.015–0.018) for direct methods. For AOM/simple AOM, the pooled

QALY decrement estimates in children were 0.004 (95% CI 0.002–0.006) and 0.003 (95% CI 0.001–0.004) for indirect and direct methods, respectively. For PMS, the pooled estimates of HSUV for hearing loss in children were 0.647 (95% CI 0.494–0.800) for indirect methods and 0.756 (95% CI 0.535–0.978) for direct methods, while these estimates were 0.431 (95% CI 0.314–0.547) and 0.555 (95% CI 0.235–0.875) for children with neurological deficits. In adults, the pooled QALY decrement estimates for inpatient pneumonia were 0.016 (95% CI 0.009–0.023) for indirect methods and 0.007 (95% CI 0.006–0.009) for direct methods, while these estimates were 0.007 (95% CI 0.006–0.008) and 0.006 (95% CI 0.004–0.008) for outpatient pneumonia.

Results of the meta-analyses stratified by utility elicitation method are presented in Supplementary Tables S13–S16. Among indirect methods, EQ-5D led to consistently larger pooled QALY decrements across pneumococcal disease states in both children and adults. For example, the pooled QALY decrements for meningitis in children were 0.029 (95% CI 0.023–0.035) for the EQ-5D, 0.021 (95% CI 0.014–0.028) for the HUI-3, and 0.016 (95% CI 0.008–0.024) for the HUI-2. For PMS, the HUI generally produced the largest pooled HSUV estimates in children, while the largest pooled HSUV estimates in adults were obtained using the EQ-5D. For instance, the pooled HSUV estimates for post-meningitis hearing loss in adults were 0.779 (95% CI 0.682–0.876) for the EQ-5D and 0.573 (95% CI 0.522–0.625) for the HUI-3. Among direct methods, VAS was associated with larger pooled QALY decrement estimates compared to TTO and SG across all pneumococcal disease states except meningitis, in both children and adults. For example, the pooled QALY decrement estimates for inpatient pneumonia in adults were 0.016 (95% CI 0.014–0.018) for VAS, while the only study that used SG as a utility elicitation method reported an HSUV estimate of 0.007 (95% CI 0.006–0.009) [31]. VAS also consistently led to smaller pooled HSUV estimates for PMS in both children and adults. For instance, the pooled HSUV estimates for post-meningitis hearing loss in children were 0.608 (95% CI 0.440–0.777) for VAS, 0.883 (95% CI 0.844–0.922) for TTO, and 0.886 (95% CI 0.854–0.918) for SG.

Results of the meta-analyses of utility estimates for the subgroup of studies conducted in the US are presented in Supplementary Tables S17–S20. In children, the pooled QALY decrement estimates per episode were 0.022 (95% CI 0.012–0.032) for meningitis, 0.007 (95% CI 0.002–0.011) for bacteremia/sepsis, and 0.000 (95% CI 0.000–0.002) for AOM/simple AOM; the pooled HSUV estimates were 0.829 (95% CI 0.702–0.955) for hearing loss and 0.582 (95% CI 0.386–0.778) for neurological deficits. In adults, the pooled QALY decrement estimates per episode were 0.007 (95% CI 0.006–0.009) for inpatient pneumonia and 0.006 (95% CI 0.004–0.008) for outpatient pneumonia; the pooled HSUV estimate for neurological deficit was 0.470 (95% CI 0.312–0.629).

4 Discussion

The current study provides a comprehensive quantitative summary of utility outcomes of pneumococcal disease and PMS in children and adults based on a global review of 40 original studies. These studies were published between 1993 and 2022, were conducted in 20 countries or regions, and queried patients, parents, and HCPs using a variety of utility elicitation methods, including standard direct and indirect methods.

This targeted literature review employed a combined search approach to comprehensively capture relevant studies while avoiding unnecessary duplication of previously conducted reviews. In addition to screening all original studies identified in previously published targeted and systematic literature reviews against the inclusion and exclusion criteria applied in the current study, a *de novo* literature search was conducted to identify original studies of health utilities for pneumococcal disease and PMS published after the period covered by the most recent reviews. Furthermore, CUAs of pneumococcal disease retrieved through a separate literature search were examined to identify any additional original utility studies used in those analyses that may not have been captured in the prior reviews.

Our current literature review uncovered a substantially larger number of original utility studies for pneumococcal disease and PMS in children and adults relative to the meta-analyses conducted by Tang et al., which included 18 studies published between 1980 and 2017 [15]. In addition to incorporating more recent studies, the current review identified additional original utility studies published within the timeframe considered by Tang et al. Additionally, some studies included in the literature review by Tang et al. were excluded from the current review, because the disease states examined were deemed not to be representative of acute pneumococcal disease states or the studies did not estimate utilities based on actual patient data [16].

As discussed in our two literature review summary studies [16, 17] and consistent with the previous literature reviews on this topic [5, 14, 15], the studies included in the current review demonstrate a high level of heterogeneity, with utility estimates for pneumococcal disease and PMS health states ranging from worse than death to nearly perfect health. This

variability is reflected in the moderate to high heterogeneity levels observed in most of the meta-analyses performed in this study, underscoring the importance of using random-effects meta-analyses to appropriately account for this heterogeneity. Notably, leave-one-out sensitivity analyses showed that pooled estimates were generally stable across disease states in both children and adults, with relatively narrow ranges of QALY decrement or HSUV point estimates despite substantial variability in I^2 values. These findings suggest that while heterogeneity is influenced by the contribution of individual studies, the overall pooled estimates may not be driven by a single influential study.

The findings from our primary analyses are consistent with the known clinical severity of the pneumococcal disease states considered [3, 4]. In both children and adults, we found that meningitis was associated with the largest pooled QALY decrement per episode (0.023 and 0.027, respectively); bacteremia/sepsis (0.010 in children and 0.013 in adults) and inpatient pneumonia (0.014 in children and 0.015 in adults) were also associated with substantial QALY decrements. Trends in pooled HSUV estimates for PMS were similar in children and adults, with neurological deficits having smaller pooled HSUV estimates (0.485 in children and 0.556 in adults) than hearing loss (0.701 in children and 0.700 in adults).

In the sensitivity analysis for children that included the study by Prosser et al. [28], the pooled QALY decrements per episode for inpatient and outpatient pneumonia were particularly impacted by the inclusion of the larger estimates from that study, due to the low number of other studies included for these pneumococcal disease states. This led to substantially larger pooled QALY decrements per episode for inpatient and outpatient pneumonia than in the primary analyses, resulting in inconsistencies with regard to the recognized clinical severity of these pneumococcal disease states, with larger pooled estimates of QALY decrement for inpatient pneumonia than for meningitis (0.051 and 0.026, respectively) and for outpatient pneumonia than bacteremia/sepsis (0.017 and 0.011, respectively). Notably, Prosser et al. used TTO and deviated from the preference elicitation literature by asking parents or members of the general population to trade their own life to prevent their child (or a hypothetical child, if they did not have children) from experiencing the condition [28]. Additionally, the respondents were asked to sacrifice a certain number of days each year for the remainder of their lives to avoid the condition, rather than being asked to give up days at the end of their life as is commonly assumed in TTO studies. Our findings suggest that such an approach may overestimate the QALY decrements associated with pneumococcal disease states. This is also reflected in the higher between-study heterogeneity and wider CIs for pooled estimates in the sensitivity analyses as compared to the primary analyses. Thus, for future CUAs in children, we recommend using the pooled estimates from the primary analyses rather than those that were estimated in the sensitivity analyses of this study.

In adults, the study by Mangen et al. directly provided a QALY decrement estimate of 0.071 for inpatient pneumonia, which is nearly five times larger than the pooled estimate of 0.015 obtained for this disease state in meta-analyses [32]. However, given the low weight assigned to this study (2.7%), it is unlikely that this had a substantial impact on the overall results. In addition, the study by Erickson et al. assessed the utility of hearing loss using data collected from a single adult patient, resulting in a large degree of uncertainty regarding this estimate [33]. Consequently, this study contributed minimally to the meta-analysis for PMS, with a weight of just 0.4%.

Utilities are measured with either direct or indirect methods. Using direct methods, preferences are mapped directly onto a utility scale using techniques such as SG, TTO, and VAS. Using indirect methods, preferences are derived from responses on generic HRQoL questionnaires, which are converted to utility values. Indirect methods streamline the process by avoiding the need for respondents to repeatedly engage in time-consuming trade-offs, allowing utilities to be calculated efficiently through standardized questionnaires [34]. Previous literature has shown that direct methods tend to result in larger HSUV estimates, and thus smaller QALY decrements, compared to indirect methods [34]. Consistent with these findings from prior studies, we found that use of direct methods resulted in smaller pooled QALY decrements in both children and adults for pneumococcal disease states. Similarly, for post-meningitis hearing loss and neurological deficits, the pooled HSUV estimates obtained through direct methods were larger than those obtained through indirect methods in both age groups. At the utility elicitation method level, we found that the EQ-5D consistently produced larger pooled QALY decrements compared to other indirect methods across pneumococcal disease states, while VAS generally yielded larger pooled QALY decrement values compared to other direct methods. This highlights the significant impact of choice of methodology on utility estimates of HRQoL and the need for caution when comparing utilities generated by different instruments that may capture distinct dimensions of the disease burden. Utilities generated by instruments are also likely to differ from utilities elicited directly from the patient for their own health. For this reason, many health technology agencies stipulate a preferred method or instrument for generating utilities to enable consistency across assessments conducted in different patient groups and interventions [35, 36]. For example, the NICE recommends the use of the EQ-5D to generate health utilities [24].

Subgroup analyses estimated smaller QALY decrements for certain pneumococcal disease states in the US compared

to the overall findings. For example, the pooled QALY decrements for bacteremia/sepsis in children were 0.007 in the US and 0.010 across all studies, and the pooled estimates for inpatient pneumonia in adults were 0.007 in the US and 0.015 overall. However, due to the limited number of studies available for most pneumococcal disease states in other countries or regions, subgroup analyses were not conducted for these locations, hindering the ability to provide a comprehensive interpretation of the findings. One factor that stands out, however, is the potential impact of methodological variation across studies, which may partially explain the difference between US-specific and overall results. For instance, studies conducted in the US that focused on inpatient pneumonia in adults utilized vignettes, whereas studies from other countries that assessed this disease state and population surveyed patients directly.

We compared our findings to those of the review by Tang et al. by converting the pooled estimates of QALY per year reported in that study into QALY decrements per episode for IPD, pneumonia, and AOM, assuming one episode of acute disease per year [15]. While Tang et al. generally found smaller pooled estimates of QALY decrements for pneumococcal disease states in children, the pooled estimates for adults reported in this study were generally larger than in the current meta-analyses. For instance, the reported pooled estimates of QALY per year for meningitis in the study by Tang et al. were equivalent to a QALY decrement of approximately 0.01 in children and 0.05 in adults, while the corresponding values in our study were 0.023 and 0.027, respectively. There are several potential explanations for the differences in the results of the current study and those of Tang et al. [15]. First, the sets of studies included in these literature reviews differed, as described above. Most notably, Tang et al. included the study by Prosser et al., which we showed to be an important outlier among pediatric studies [28]. Second, Tang et al. conducted a pooled analysis based on averages, while we performed meta-analyses that accounted for heterogeneity across the included studies [15]. While the authors attempted to address this limitation by presenting results using sample size-weighted and inverse variance-weighted averages in addition to the arithmetic average, the obtained pooled estimates still did not account for the substantial heterogeneity present across studies.

Our study provides robust utility estimates for pneumococcal disease and PMS health states for future economic evaluations. Previous CUAs have often relied upon data from a small number of utility studies that are often outdated [16, 17]. For example, most CUAs of pneumococcal vaccines in children applied QALY decrements of 0.0232 for meningitis, 0.0079 for non-meningitis IPD, 0.006 for inpatient pneumonia, 0.004 for outpatient pneumonia, and 0.005 for AOM with tympanostomy tube placement, which were all sourced from a single CUA conducted in the UK [37]. In adults, the most common QALY decrement values used in CUAs of pneumococcal vaccines have been 0.0745 for IPD and inpatient pneumonia based on an assumption, and 0.004 for outpatient pneumonia, using data from a pediatric study [17, 38–40]. Compared to the pooled estimates from the current study, QALY decrement values used in previous CUAs appear to have underestimated the HRQoL impact of non-meningitis IPD, inpatient pneumonia, and outpatient pneumonia in children and outpatient pneumonia in adults, but overestimated the HRQoL impact of IPD and inpatient pneumonia in adults. Similarly, most CUAs that focused on PMS in children or adults used HSUV inputs of 0.4 for neurological deficits and 0.8 for hearing loss, values that were sourced neither from empirical studies nor studies that used preference-based measures [17, 30, 41, 42]. Based on the pooled estimates from the current study, these values may underestimate the health utility of neurological deficits while overestimating the utility associated with hearing loss.

Based on the most recent literature, our study furthers our understanding of the HRQoL burden of pneumococcal disease and PMS and addresses a key knowledge gap by providing a comprehensive set of pooled utility estimates for these conditions. These data can serve as inputs for future economic evaluations of pneumococcal vaccines in both children and adults, aligning with recommendations from health technology assessment bodies to use utility values that have been systematically estimated from the available literature [24]. This contribution will promote greater consistency and comparability across studies, thereby strengthening the accuracy and reliability of cost-effectiveness analyses of pneumococcal vaccines.

The QALY decrement estimates reported in this study were calculated relative to perfect health (HSUV = 1), reflecting absolute, disease-specific losses in HRQoL associated with an episode of pneumococcal disease. As a result, these values should be interpreted as absolute reductions from full health rather than incremental changes from baseline population health. In contrast, many CUAs anchor QALY calculations to age- or population-specific baseline HSUVs that are typically less than 1. When incorporated into economic models that use population norms, the QALY decrements presented in this study may therefore require appropriate adjustment or consistent application across health states to ensure valid estimation of incremental QALY outcomes. However, in pediatric populations where baseline HSUVs are generally close to 1, such adjustments may have a limited impact on estimated QALY losses for acute, short-duration conditions.

This study has several limitations. First, this review did not encompass all of the conditions that can be caused by *S. pneumoniae*, but rather focused on the specific pneumococcal disease states and PMS that are most relevant to economic evaluations. Second, consistent with the conceptual

framework of most CUAs, this review only considered utility estimates during the acute phases of pneumococcal disease states and did not assess their long-term impacts. Third, the substantial heterogeneity in the methodology, reporting, and quality across the included studies could affect the results, although the random-effects model used in this meta-analysis accounted for this variability to some extent. Fourth, to convert utility measures into a format suitable for meta-analysis, data transformations and imputations were performed, requiring a number of assumptions, such as imputing missing SDs and specifying illness durations for acute conditions. However, imputation of SDs was needed for only a small subset of studies (seven of 40 included studies), as most studies reported measures of variability, and sensitivity analyses indicated that pooled estimates were not sensitive to variation in imputed values of SDs (see Supplementary Table S21 for an illustrative example for meningitis in children). In addition, the assumed illness durations used in this study were sourced from a single, well-established reference published by the US Institute of Medicine [21], and sensitivity analyses indicated that reasonable variation in assumed illness duration had a limited impact on the pooled results (see Supplementary Table S21 for an illustrative example for meningitis in children). Fifth, for some disease states, including pneumonia in children and IPD in adults, only a few studies contributed to the meta-analysis, limiting the precision of the utility estimates. This limitation is particularly evident in secondary analyses, including the subgroup analysis that focused on studies conducted in the US. Sixth, it is unclear if utility measures generated using different elicitation methods or study populations are reasonably comparable for inclusion in the same meta-analysis [43]. In this study, utility estimates were pooled across valuation methods because of the limited number of available studies for each disease state and the lack of a standard methodology to assess utilities for temporary health states. Finally, a formal quality or risk-of-bias assessment of the included utility studies was not conducted because there is currently no standard quality appraisal checklist specifically designed for utility studies, particularly for temporary health states. Given the limited number of studies available for several disease states, applying additional exclusion criteria based on quality scoring could have further reduced the evidence base without necessarily improving interpretability. To address these limitations, we complemented the primary analyses with extensive sensitivity analyses. In addition, subgroup analyses by method were performed, although our conclusions from these analyses were limited by the small number of studies that used some methods.

5 Conclusions

In conclusion, pneumococcal disease negatively impacts HRQoL in both children and adults, with the greatest impact observed with meningitis, bacteremia/sepsis, and inpatient pneumonia. In our meta-analysis, we found considerable variability in study results driven primarily by differences in methodology, resulting in substantial between-study heterogeneity. This underscores the need for future research that adopts more rigorous methodologies to estimate the HRQoL of patients with pneumococcal disease. By providing comprehensive, updated pooled utility estimates, our study advances knowledge regarding the HRQoL burden of pneumococcal disease and PMS. These data can inform future economic evaluations of pneumococcal vaccines in children and adults, improving consistency and reliability of cost-effectiveness analyses of these products.

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Declarations

Conflict 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. HR, YS, and DL are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Merck & Co., Inc. SS was an employee of Analysis Group, Inc. at the time of study conduct. JX is an employee of XL Source, Inc., a consulting company that has provided paid consulting services to this research project. MSK is a consultant for Merck & Co., Inc. and provided paid consulting services to this research project.

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data/Materials All data generated or analyzed during this study are included in this published article and its supplementary information files.

Code Availability The code used in this study is not publicly available.

Author Contributions MH, EE, and SM contributed to the conceptualization of the study. All authors contributed to the study design and methodology. HR, DL, and JX conducted the literature search and data extraction. MH and HR 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.

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