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Health State Utilities Associated with Invasive Pneumococcal Disease, Pneumonia, and Recurrent Acute Otitis Media in Young Children

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PLAIN ENGLISH SUMMARY

As new vaccines for pneumococcal disease are considered for use in young children, cost-effectiveness analyses will be needed to examine their value and inform decisions about healthcare funding. Utilities, which are values representing the strength of preference for health states, are needed to quantify health outcomes and health-related quality of life in these analyses. In the current study, utilities were estimated for several pneumococcal infections that are common in children younger than 5 years old. These utilities will be useful in analyses examining the value of pneumococcal vaccines. This study also makes a broader contribution to research on pediatric utility assessment. By piloting several utility assessment methods, the current study identified an effective approach for eliciting utilities associated with temporary medical conditions in children younger than 5 years old. These findings have methodological implications for future research estimating utilities associated with temporary pediatric health conditions.

KEYWORDS

Health state utilities; children; pediatric; time trade-off; cost-effectiveness; pneumococcal infections; *streptococcus pneumoniae*

INTRODUCTION

Streptococcus pneumoniae is a common bacterium with more than 100 identified serotypes [1]. The bacterium can exist harmlessly in the nasopharynx of healthy individuals but can also cause severe disease, particularly in young children [2-9]. If *S. pneumoniae* spreads beyond the nasopharynx, it can cause diseases such as acute otitis media (AOM) and pneumonia. If *S. pneumoniae* invades normally sterile sites, including the bloodstream or cerebrospinal fluid, it can result in invasive pneumococcal disease such as meningitis, bacteremia, and sepsis [4, 6-9].

New vaccines have been introduced to reduce the incidence of pneumococcal disease in young children [10-12]. As these vaccines are considered for use in various countries, cost-utility analyses (CUA) will be needed to examine their value and inform decision-making about allocation of healthcare resources. These economic models will require health state utilities, which are values representing the strength of preference for health states [13].

Two recent reviews suggest several reasons that available utilities for pneumococcal infections are inappropriate or insufficient for use in economic models of pneumococcal vaccines for young children [14, 15]. First, although pneumococcal infections occur most frequently during the first 5 years of life [2-5, 7], almost all published utilities for pneumococcal infections are in adults or older children and adolescents [14, 15]. In addition, some studies used utility assessment methods that are not currently preferred, such as estimating utilities based on input from a small sample of clinicians [16]. Furthermore, utilities were often derived from generic instruments completed by older patients at times when symptoms were not at their peak [14, 17, 18]. Finally, many studies focused on only one type of infection, limiting comparability across the range of infections associated with pneumococcal disease in children [19, 20].

To address these gaps, the purpose of this study was to estimate health state utilities associated with pneumococcal infections that are common in young children. This study raised several challenges. Generic instruments commonly used to derive utilities for adults (e.g., EQ-5D-5L) or older children (e.g., EQ-5D-Y) are not applicable to children under age 5 years. Although measures like the EuroQoL-Toddler and Infant Populations [21] and Health Utilities Preschool [22] are available to estimate utilities for younger children, they have several limitations in this context. For example, they may not be sensitive to key symptoms and features of pneumococcal infections (e.g., fever, cough, fatigue, difficulty breathing, impact of hospitalization), and it may not be feasible to administer these instruments at the time of hospitalization. Therefore, this study uses vignette-based methods to elicit utility values for these infections [23].

Another challenge was that standard utility elicitation methods (e.g., time trade-off [TTO]) are rarely applied to health states for very young children, and it was uncertain how participants would respond when asked to consider mortality of children as young as 2 years old. Furthermore, pneumococcal infections are temporary health events that change over time, and therefore, the TTO task needed to be structured for temporary health states [24, 25]. To identify an appropriate method for addressing these challenges, three methods for valuing temporary pediatric health states were examined in a pilot study. Results from this pilot study informed the study design of the subsequent utility elicitation study.

METHODS

Overview of Study Methods

Health state vignettes were developed based on published literature and clinician interviews, and these vignettes were valued in a TTO utility elicitation study with a general

population sample in two UK locations (London, Edinburgh) in March 2023. The study protocol and materials were approved by the Salus Institutional Review Board (study 22451), and all participants provided informed consent prior to participation.

No consensus exists regarding the optimal method for valuing pediatric health states. There are a range of approaches regarding who should value the health states, who should be imagined living in the health states, whether to specify relationship of the respondent to the child, and how to present the age of this imagined child [26-31]. Consistent with several recent studies [32-35], the current TTO task was conducted with a sample of general population adults who were asked to make choices for a hypothetical child living in each health state at a specified age. Respondents' relationship to the imagined child was not stated.

Another methodological challenge is that pneumococcal infections are temporary. Utility elicitation studies typically focus on chronic health states that do not change over time, and TTO valuations are usually conducted with time horizons of at least 10 years. When estimating utilities associated with temporary conditions, sometimes it is possible to describe and value the temporary condition as if it were chronic. However, a pneumococcal infection involves symptoms and treatments that evolve over a series of days, and these infections could not be presented as a chronic unchanging health state.

Therefore, it was necessary to develop health state vignettes describing temporary experiences that change over time. Previously published studies have estimated utilities of temporary experiences by reducing the time horizon to 1 year and assessing the utility impact of the temporary event on the 1-year period [25, 33, 36-38]. This approach yields a quality-adjusted life year (QALY) decrement for each temporary event that can be used in a CUA. While this approach is useful for temporary adult health states, it has not previously been used

with temporary pediatric states. Three variations of the TTO task were explored in a pilot study to inform the study design for the subsequent utility elicitation study.

Health State Development

Health state development was informed by published literature and clinician interviews. A targeted literature review focused on infections caused by *S. pneumoniae* including recurrent AOM [39-41], bacteremia [42-44], bacteremic pneumonia [42, 45, 46], meningitis [42, 47, 48], and non-invasive pneumonia [42, 49, 50]. Websites for the American Academy of Pediatrics, the United States Centers for Disease Prevention and Control, and the UK National Health Service were also consulted [51-54].

Multiple rounds of interviews were conducted with six clinicians who had experience managing infections caused by *S. pneumoniae* (four pediatric infectious disease specialists, one pediatrician, and one public health physician/consultant). All clinicians were medical doctors and had an average of 14.8 years of experience with these patients. Five clinicians were based in the United States and one in England. Health states were drafted and refined in an iterative process with these experts. Initial interviews focused on describing the symptoms, treatment, and impact associated with each infection. Follow-up discussions focused on reviewing and editing health state drafts to ensure that the descriptions were clear and accurate representations of typical patient experiences. All clinicians approved the health states before the pilot study and again before the utility elicitation study. Five of the six clinicians are co-authors of the current study, but they were offered co-authorship after they had completed their consultation, and co-authorship was not part of their remuneration or agreement to participate in this research.

Six health state vignettes were developed to be presented to respondents on individual cards, each with bullet point descriptions organized into categories with headings intended to

help the respondents understand the health states (Appendix A). Two chronic health states focused on AOM. Health state A described recurrent AOM infections, occurring four times per year. This infection frequency was selected based on clinician feedback and published literature indicating that a minimum of four infections per year is a common definition of "recurrent AOM" [55].

Health state B described a child who experiences these recurrent AOM infections and is treated with pressure equalization (PE) tubes. Most of the clinicians agreed with published literature suggesting that this procedure can reduce the frequency and severity of AOM infections [56-61]. However, one of the clinicians disagreed based on a recent trial showing that incidence of AOM infections was not significantly lower with PE tube placement than with medical management [62]. The trial authors suggested that previous trials of the PE tube procedure suffer from methodological flaws [62] such as "small sample size, uncertain validity of diagnoses…, short periods of follow-up, and substantial attrition." In light of this recently published information, health state B reflected uncertainty about the effectiveness of the PE tube procedure.

Health states C to F described temporary pneumococcal infections, each lasting for less than 1 month: pneumonia requiring hospitalization, bacteremic pneumonia, bacteremia, and meningitis. A timeline of key experiences (e.g., hospitalization, treatment duration, returning to school/preschool) was included at the bottom of health states A and C through F.

In the pilot study, respondents were asked for feedback on clarity of the health states. Although participants consistently reported no difficulty understanding the health states or the TTO task, some provided suggestions for minor edits. For example, several participants noted

that a commonly used term for PE tubes in the UK is "grommets," and this term was added to health state B. Health states are listed in Table 1, and final health state text is in Appendix A.

Utility Elicitation Study Participants

Participants were recruited via digital advertising (e.g., Facebook, X [previously Twitter], and Google). Interested participants were screened by phone. To be eligible, participants were required to be at least 18 years of age, a UK resident, able to understand study procedures, and able and willing to give informed consent. Because this was a general population sample, there were no inclusion criteria based on clinical characteristics, and efforts were made to reflect the UK's population with regard to gender, age, racial/ethnic background, and rate of unemployment. Participants were remunerated £75 for their time and participation.

Pilot Study: Methods for Valuing Pediatric Health States with Temporary Infections

A pilot study was conducted in January 2023 to refine the health states and inform decisions about interview procedures for temporary pediatric health states (N = 28; mean age = 50.8 years; 50% female). Three variations of the TTO task were explored. In TTO valuations, the amount of time the respondent imagines living in the health state can vary [63, 64]. In the pilot study, both 1-year and 10-year time horizons were attempted. The third approach was lag-time TTO, adding time in full health after the health state being valued [65, 66]. Lag-time TTO was attempted because it mirrors a typical experience in which the pneumococcal infection is followed by a state of good health.

Evaluation of the three methods was based on the pattern of results and qualitative feedback from respondents. Table 2 presents the score pattern for each participant, categorized as "ceiling" (utility $\geq$0.975), "differentiating" (health states did not all receive the same utilities),

"non-differentiating" (health states all received the same utility, but not at ceiling), and "low" (at least one health state received an extremely low utility [<0.30]).

1. TTO with a 1-year time horizon

In this variation of the TTO task, the hypothetical child had a remaining lifespan of only 1 year. For the temporary health states (C to F), participants were told to imagine the infection occurring at some point during the year, with the remainder of the year spent in full health. While this 1-year approach has been effective for valuing temporary adult health states [25, 33, 36-38], it was problematic for these pediatric health states, resulting in minimal differentiation among health states and frequent ceiling effects for participants who were reluctant to sacrifice time from the short lifespan (Table 2). In contrast, other participants traded a large amount of time (resulting in extreme low scores) because they did not see the value in having a child suffer only to be given such a short lifespan.

2. TTO with a 10-year time horizon

In this task, participants imagined that the infections described in the health states occurred annually for 10 years. Although these infections do not repeat annually in the real world, this annual repetition allows the disutilities (i.e., decrease from utility of 1) to be conceptualized and used in CUAs as a QALY decrement. This approach was easier for the participants, resulting in reasonable differentiation among health states, without any extreme low scores (Table 2). Participants seemed more comfortable trading time when the overall timeline was longer, and the child would not be dead after only 1 year. For example, one participant said "The 10-year method worked the best. It seemed the most intuitive."

3. Lag-time TTO

In this approach, a 1-year period with the health state was followed by full health for either 5 or 10 years, followed by death [65, 67, 68]. Although this method seems to represent real-world experiences of temporary infections (i.e., occurring once, followed by good health), this method produced extreme low scores for many participants (Table 2). Participants were often willing to trade almost the entire year with the infection because this year was not viewed as a significant amount of time in the context of the 5 or 10 years that followed. Furthermore, some participants found the procedure confusing, and it often required repeated explanations.

Overall, the 10-year approach was clear for participants, while allowing for reasonable differentiation among health states without extreme low scores. Therefore, this approach was used in the subsequent utility elicitation study.

Age of the Imagined Child

Previous studies in which adult respondents valued pediatric health states have often specified the age of the imagined child (e.g., "an 8-year-old child") [35, 69-72]. To identify the age that should be used in the current study, clinicians were asked about the ages when the infections tend to be most common. All agreed with published literature indicating that the infections occur most frequently in children 5 years old and under [2-5, 7], but there was no consensus regarding a single age for the hypothetical child in the TTO task.

During the pilot study, participants were initially instructed to imagine the infections happening to a 2-year-old child. After completing the task while imagining a 2-year-old, some participants were asked if their responses would be different for a 3- or 5-year-old child, and all reported that their TTO choices would be the same for any age from 2 to 5 years. To allow for further examination of utility differences by the age of the imagined child, it was decided to vary

the age of the imagined child in the subsequent utility elicitation study. Participants were randomized to one of four groups and were told that the child was either 2, 3, 4, or 5 years old. This approach has been used in a previous study spanning both childhood and adulthood [73].

Utility Elicitation Study Methods: Valuing Pediatric Health States with Temporary Infections

Trained interviewers conducted in-person utility elicitation interviews in private offices, following a semi-structured interview guide. Participants were first introduced to either the recurrent (A and B) or temporary (C to F) health states. Health state A was always introduced before B because knowledge of health state A was necessary to understand B. Health states C to F were introduced in random order. Instead of using the ordered letters A through F, health states were labeled with letters that did not imply any organization between the states. Interviewers reviewed the health states with participants, who were given an opportunity to read the materials independently and ask questions. Participants were then asked to rank the health states from most to least preferable.

After the ranking, participants valued the health states in a TTO task with a 10-year time horizon [13]. For each health state, participants were given choices between spending a 10-year period in the health state versus spending varying amounts of time in full health, presented in 6-month increments, alternating between longer and shorter periods of time (i.e., 10 years, 0 years [dead], 9.5 years, 6 months, 9 years, 1 year…). Each health state was assigned a utility (u) on a scale with anchors of dead (0) and full health (1) based on the point of indifference between 10 years in the health state and x years in full health (utility = x/10).

Statistical Analysis Procedures

Statistical analyses were conducted with SAS version 9.4. Descriptive statistics were used to summarize demographic data, health state preferences, and utilities (frequencies and percentages for categorical data, means and standard deviations for continuous variables). Disutilities were calculated by subtracting the utility of each health state from full health (i.e., 1.0). Paired *t* tests were conducted to examine differences between utility means (e.g., utility of health state C vs. D), and independent *t* tests were used to test for subgroup differences in utilities by age (median split), gender, employment status (employed vs. not employed), and parental status (has children vs. does not have children). An analysis of variance (ANOVA) was conducted to examine utilities by the age of the hypothetical child.

RESULTS

Sample Characteristics

A total of 229 participants were scheduled, and 211 attended interviews. Three were unable to fully understand the task and health states. Therefore, analyses were conducted with a sample of 208 participants (demographics in Table 3). Almost one-third (30.8%) of the sample reported having children, and some of the children had experienced the conditions described in the health states (frequencies and percentages in Table 3).

Health State Rankings

Participants ranked the recurrent and temporary health states in order of preference. Of the recurrent health states, about half of participants (52.4%) preferred health state A (recurrent AOM) over B (recurrent AOM with PE tube treatment). Among the four temporary states, C (hospitalized pneumonia) was ranked first by 66.3% of participants, and E (bacteremia) was

ranked first by 31.3%. Health state F (meningitis) was almost always perceived as least preferable (97.6%).

Health State Utilities

Health state utilities are presented in Figure 1, along with disutilities calculated by subtracting 1.0 (i.e., the utility associated with full health) from the utility of each health state. Meningitis (health state F) was associated with the greatest utility impact (utility = 0.809), while the other health states had mean utilities ranging from 0.878 to 0.902. There was a significant difference between the utilities of the two recurrent AOM health states, A and B (t=2.9, P<0.01). All utilities of the four temporary health states (C through F) were significantly different from each other (all P<0.0001) except for the comparison of C (hospitalized pneumonia) versus E (bacteremia; t=0.1, P=0.92). No participants perceived any of the health states to be worse than or equal to dead. Therefore, all health states received positive utility scores from all participants.

Participants were randomly assigned to consider the health states for a hypothetical child of ages 2, 3, 4, or 5. An ANOVA found no significant utility differences among these four groups (Table 4).

Group Comparisons

There were no significant differences in utility by age, sex, or parental status, although mean utilities for participants with children (i.e., those who responded "yes" to the question "Have you ever been the parent or guardian of a child?") were numerically greater than utilities for participants without children for all health states (mean between-group differences ranging from 0.004 to 0.029). For all health states, mean utilities in London were slightly lower than in Edinburgh. Although these differences between locations were statistically significant for four health states (P<0.05), the magnitude of all differences was small, ranging from 0.023 to 0.039.

DISCUSSION

This study used an innovative approach to estimate utilities of temporary health conditions in young children. In this vignette-based valuation of health states describing pneumococcal infections, lower utilities were associated with health states that had longer treatment periods, described infections that were perceived as more severe, and required more invasive treatments and tests. Consistent with previous research, meningitis had a greater disutility than any of the other pneumococcal infections [17, 74]. The two AOM health states, with and without the PE tube procedure, had similar utilities with participants being almost evenly split regarding their preference for these health states.

When these utilities are included in CUAs, they need to be used in ways that are consistent with how they were valued in the TTO task. Because health state A (recurrent AOM) was valued as a chronic health state, the utility of health state A may be used for any duration of time in a model to represent children suffering from recurrent AOM. Health state B was identical to health state A, other than the addition of an annual PE tube procedure. Therefore, the utility difference between health states A and B represents the QALY impact of receiving the PE tube procedure.

When using these utilities in CUAs, it is also important to know that health states C to F were valued as temporary infections that occur once per year. Therefore, the disutilities of health states C to F (Figure 1) can be interpreted as a QALY decrement of each temporary infection. These QALY decrements may be applied in a model to represent the impact of an individual infection. Because of this temporary health state approach, the current utilities are not necessarily comparable to previously published utilities, which vary widely in their methodological approaches [14, 15].

Several aspects of the study design have methodological implications for assessment of utilities for children under age 5. Available utilities for this age group are limited, and like the current study, previous research has generally used vignette-based methods due to a lack of generic preference-based instruments applicable to younger children. In previous studies, health state valuation methods have varied widely on the basis of who is imagined to be living in the health state (e.g., a hypothetical child, the respondent's own child, or the respondent living in the health state as an adult), the age of the imagined child, the stated relationship between the respondent and the imagined child, the study sample (e.g., parents or general population), and whose time is being traded (e.g., respondent's time or the imagined child's time) [70, 73, 75-77]. The current study adds to this previous research by demonstrating feasibility of a TTO utility elicitation with a 10-year time horizon to value health states for children ages 2 to 5.

This study also provides a new method for valuing temporary health states in young children. The great majority of utility elicitations focus on chronic health states, and temporary health states present methodological challenges [24, 25]. Very few studies have estimated utilities for temporary pediatric states, but there are examples of studies valuing these temporary states as if they were chronic [78] or using a chained standard gamble approach [19]. The current study shows that a method previously used for temporary adult health states can also be applied to pediatric health states [25, 79, 80]. This approach is useful for quantifying the utility impact of an event that changes over time. For example, the meningitis vignette (health state F) describes the infection, initial symptoms, testing procedures, treatment, hospitalization, gradual improvement, and return to school. The resulting QALY decrement is based on consideration of this temporary 3-week sequence.

Another methodological contribution is the approach to specifying the age of the imagined child in the health states. When valuing pediatric health states, adult respondents are often told to imagine a child of a specific age. However, the resulting utilities may need to be applied to children with a range of ages in a CUA. Therefore, respondents in the current study were randomly assigned to consider a child of ages 2, 3, 4, or 5, and no significant differences in utilities were found between the four groups. This approach would be useful for future studies estimating utilities that will be used to represent children of multiple ages in subsequent modeling.

It is often useful to compare newly derived utilities to those that have been previously published. In the current situation, however, this comparison is challenging due to methodological differences between the current and previous studies, as well as substantial variability in utility estimates from previous studies. In a review conducted by O'Reilly et al. [14], the authors found that previously reported utilities for AOM varied widely (0.064 to 0.970), which underscores the methodological variability in previous research. The values for recurrent AOM reported by prior studies include 0.536 [81], 0.418 [82], and 0.534 [83], which are all lower than the utility for AOM in the current study. However, each of these previous values was estimated using responses to a numeric rating scale rather than a preference-based task, and therefore, these values would not typically be considered true utilities. O'Reilly et al. [14] reported previous utilities for outpatient pneumonia ranging from 0.147 to 0.994 and for inpatient pneumonia ranging from -0.054 to 0.998, again reflecting significant variability. These values are not directly comparable to the current results because these previous studies estimated utility at one point in time. In contrast, the "path state" approach in the current study yields

pneumonia disutilities that can be applied to represent the entire infection pathway in a model, rather than a utility at a single point in time.

Limitations of vignette-based methods should be acknowledged [23]. Utilities were derived from general population preferences for hypothetical health states, and comparability between the reported values and utilities derived from patients is unknown. In addition, the current health states describe typical experiences with acute infections. Resulting utilities may underestimate the total impact of these infections because the health states do not describe long-term sequelae that occur in some patients [84, 85]. Furthermore, several aspects of the study design were novel, such as valuation of temporary health states for children under age 5. Therefore, additional research is needed to provide more confidence in these methods.

In summary, the resulting utilities may be useful in models examining cost-effectiveness of treatments and vaccines for infections caused by *S. pneumoniae.* In addition, innovative methods developed in this study have methodological implications for future research on pediatric utilities. Additional studies are needed to further examine and refine methods for estimating utilities for this younger age group, as well as temporary health states in children.

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TABLES AND FIGURES

Table 1. Health States Developed and Valued in This Study

Health state	Infection	Number of days in hospital	Number of days on antibiotics
Recurrent AOM health states			
A	Recurrent AOM	0	10 days per episode
B	Recurrent AOM treated with PE tubes	0	10 days per episode
One temporary infection valued in the context of a year			
C	Pneumonia	2–3	10 per year
D	Bacteremic pneumonia	3–4	10–14 per year
E	Bacteremia	2–3	10 per year
F	Meningitis	10–14	10–14 per year

Abbreviations: AOM = acute otitis media; PE = pressure equalization

Table 2. Pilot Study Score Profiles: Three Variations of the Time Trade-off Procedure (N=28)

	Recurrent health states (A/B)			Temporary health states (C/D/E/F)		
	1 year[a]	10 year[b]	Lag time[c]	1 year	10 year	Lag time
Ceiling[d]	9	11	9	8	3	3
Difference[e]	4	8	4	12	19	11
Low[f]	3	0	8	3	0	11
No difference[g]	12	9	7	5	6	3

[a] In TTO with the 1-year time horizon, respondents were given choices between one year that included the infection(s) described in the health states vs. a shorter amount of time in full health. The recurrent health states described AOM recurring throughout the year, while the infections described in the temporary health states occurred only once during the year.

[b] In TTO with the 10-year time horizon, respondents were given choices between 10 years that included the infection(s) described in the health states vs. a shorter amount of time in full health. The recurrent health states described AOM recurring throughout the 10 years, while the infections described in the temporary health states occurred once per year for the 10-year period.

[c] For lag time TTO, the time in the health state was the same as described in the 1-year approach. However, after the year in the health state, the child had an additional 5 or 10 years in full health.

[d] Ceiling = Health states all received the same utility, which was considered to be at the ceiling (i.e., 0.975 or 1.0).

[e] Difference = Health states were not all rated equally.

[f] Low = At least one health state was rated at what was considered to be an unusually low utility given the severity of the health state (below 0.30).

[g] No difference = Health states all received the same utility, but not at the ceiling.

Table 3. Sample Characteristics

Characteristic	London (N=100)	Edinburgh (N=108)	Total Sample (N=208)	*P* value[a]
Age (mean, SD) (years)	40.5 (14.0)	41.5 (15.7)	41.0 (14.9)	0.632
Gender, n (%)				0.363
Male	51 (51.0%)	47 (43.5%)	98 (47.1%)	
Female	48 (48.0%)	60 (55.6%)	108 (51.9%)	
Nonbinary	0 (0.0%)	1 (0.9%)	1 (0.5%)	
Prefer not to answer	1 (1.0%)	0 (0.0%)	1 (0.5%)	
Ethnicity, n (%)				0.135
Asian/Asian British	14 (14.0%)	6 (5.6%)	20 (9.6%)	
Black/African/Caribbean/Black British	2 (2.0%)	3 (2.8%)	5 (2.4%)	
White	71 (71.0%)	91 (84.3%)	162 (77.9%)	
Mixed/Multiple ethnic groups	8 (8.0%)	4 (3.7%)	12 (5.8%)	
Other	5 (5.0%)	4 (3.7%)	9 (4.3%)	
Marital status, n (%)				0.512
Single	52 (52.0%)	50 (46.3%)	102 (49.0%)	
Married	21 (21.0%)	30 (27.8%)	51 (24.5%)	
Other	27 (27.0%)	28 (25.9%)	55 (26.4%)	
Employment status, n (%)				<.001
Full-time work	63 (63.0%)	35 (32.4%)	98 (47.1%)	
Part-time work	14 (14.0%)	38 (35.2%)	52 (25.0%)	
Other	23 (23.0%)	35 (32.4%)	58 (27.9%)	
Education level, n (%)				0.043
Less than university degree	20 (20.0%)	35 (32.4%)	55 (26.4%)	
University degree or higher	80 (80.0%)	73 (67.6%)	153 (73.6%)	
Parent or guardian of a child[b], n (%)				0.008
Yes	22 (22.0%)	42 (38.9%)	64 (30.8%)	
No	78 (78.0%)	66 (61.1%)	144 (69.2%)	
Parents/guardians with at least one child who has had any of the following infections/procedures[c], n (%; not mutually exclusive)				
Otitis media	9 (40.9%)	18 (42.9%)	27 (42.2%)	
Pneumonia	2 (9.1%)	4 (9.5%)	6 (9.4%)	
Bacteremia	0 (0.0%)	2 (4.8%)	2 (3.1%)	
Meningitis	2 (9.1%)	1 (2.4%)	3 (4.7%)	
PE tubes	1 (4.5%)	3 (7.1%)	4 (6.3%)	

[a] *P* values are for comparisons between the London and Edinburgh subgroups, based on *t* tests for continuous variables and chi-square analyses for categorical variables.

[b] Participants were responding to the question "Have you ever been the parent or guardian of a child?"

[c] Participants were responding to the question "To the best of your knowledge, has the child even had any of the following infections/procedures?". Participants responded for each of their children. Percentages were calculated as number of parents/guardians with at least one child who experienced each infection divided by the total number of parents/guardians in the sample.

Table 4. Health State Utilities by Age of the Imagined Child[a]

Health state	Age of Imagined Child in the Utility Elicitation				F statistic	*P* value
	(A) 2-year-old child (n=50) Mean (SD)	(B) 3-year-old child (n=54) Mean (SD)	(C) 4-year-old child (n=54) Mean (SD)	(D) 5-year-old child (n=50) Mean (SD)		
Recurrent Health States[b]						
A: AOM	0.91 (0.08)	0.88 (0.11)	0.90 (0.09)	0.90 (0.12)	0.65	0.59
B: PE tubes	0.89 (0.08)	0.87 (0.11)	0.88 (0.10)	0.88 (0.13)	0.42	0.74
Temporary Health States[c]						
C: Hospitalized pneumonia	0.89 (0.10)	0.90 (0.10)	0.90 (0.09)	0.92 (0.09)	0.60	0.62
D: Bacteremic pneumonia	0.86 (0.12)	0.87 (0.11)	0.88 (0.09)	0.90 (0.11)	0.90	0.45
E: Bacteremia	0.90 (0.08)	0.89 (0.10)	0.90 (0.08)	0.92 (0.08)	1.59	0.19
F: Meningitis	0.79 (0.16)	0.79 (0.15)	0.81 (0.12)	0.84 (0.15)	1.13	0.34

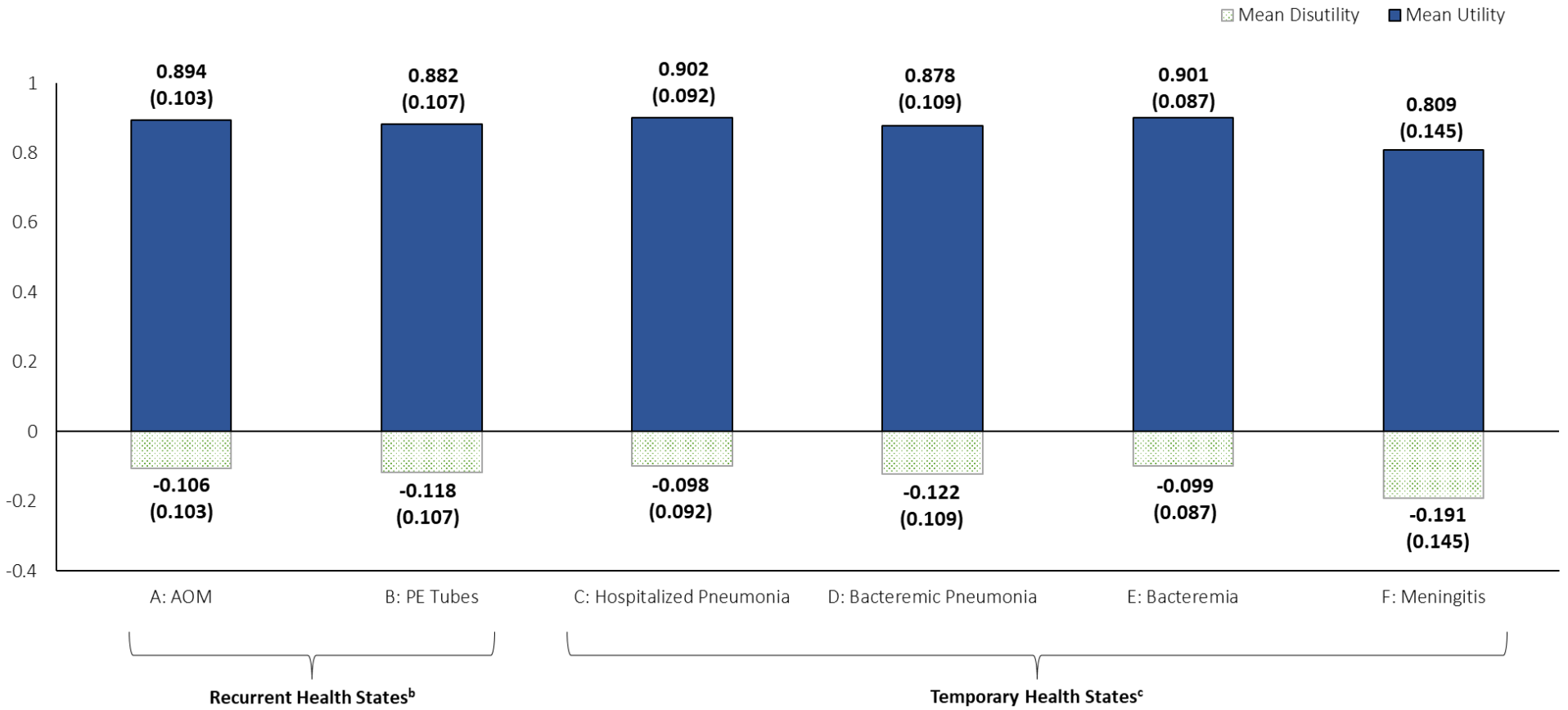
Abbreviations: AOM = acute otitis media; PE = pressure equalization; TTO = time trade-off

[a] Prior to ranking and valuing the six health states in the TTO task, respondents were randomly assigned to think about either a 2-, 3-, 4-, or 5-year-old living in the health states.

[b] Health states in which the infection occurred multiple times in the same year were called "recurrent."

[c] Health states in which each temporary infection occurred only once per year were called "temporary."

Figure 1. Mean (SD) Health State Utilities and Disutilities (N=208)[a]



Abbreviations: AOM = acute otitis media; PE = pressure equalization; SD = standard deviation

[a] Utilities are on a scale with 0 representing dead and 1 representing full health. Disutilities were calculated by subtracting the utility of each health state from 1, which represents full health.

[b] Health states in which the infection occurred multiple times in the same year were called "recurrent."

[c] Health states in which each temporary infection occurred only once per year were called "temporary."

SUPPLEMENTARY MATERIAL

APPENDIX A. HEALTH STATE VIGNETTES

Health State A: Recurrent AOM

Infections

- The child has **ear infections every three months** (about four times per year).
- These infections are caused by a common type of bacteria that is found in the nose and throat but can spread to other parts of the body and cause illness.
- For these infections, the bacteria **spread to the area behind the child's eardrums.**

Symptoms of Each Infection

- Symptoms begin as a **typical cold or flu-like infection**.
- Fluid builds up behind the eardrum, causing **pain, redness, and swelling of the eardrum.**
- With about a third of these infections, the child **develops a fever**.
- The child is **irritable and fussy**.

Impact During Each Infection

- The child is **not as active as usual**.
- While the child has a fever, they cannot attend pre-school (or school) or participate in other activities.
- Because the child is uncomfortable, they have **difficulty sleeping** during these infections.

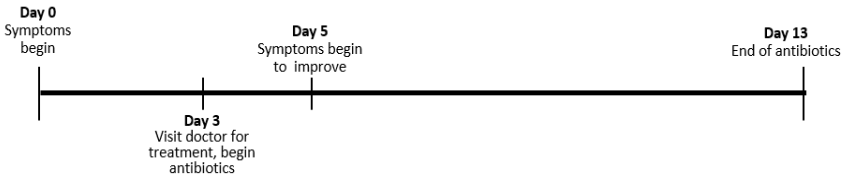
Treatment

- A **10-day course of oral antibiotics** is prescribed for each infection. For some children, these antibiotics can have **mild side effects** (most commonly diarrhoea and upset tummy).

Duration of Each Infection

- Each episode usually **starts with a cold** (runny nose and cough).
- **After about two or three days**, symptoms of the **ear infection begin**, and the child is taken to the doctor, who diagnoses the ear infection and **prescribes the antibiotics**.
- The pain and other **symptoms resolve after about two days** of treatment, but the child must **finish the full 10-day course** of antibiotics.
- Including treatment, the **total episode lasts about two weeks**.

Timeline for Each Infection



Health State B: Recurrent AOM with PE Tube Procedure

Infections

- The child has **ear infections every three months** (about four times per year).
- These infections are similar to the ones described in **health state A.**

Treatment and Procedure

- In an effort to reduce the number of infections, the child is **treated with a surgical procedure** to insert small plastic "pressure equalisation" tubes (also called "grommets") into their eardrums.
    - These tubes allow the fluid in the child's ears to drain more completely, which **may help prevent infections**.
- The surgery takes place **in hospital under general anaesthesia**, but the child does not have to stay in hospital overnight.
- The surgeon makes a **small incision in the eardrum**, drains any fluid from the ear, and **inserts the tube**.

After the Procedure: Frequency of Infections

- After the procedure, children usually experience a short-term reduction in the rate of ear infections. For this child, the onset of the next infection after the procedure is **delayed by about 2 months**.
- In general, the **rates of ear infections decrease as children get older**. Over the long-term, this procedure has not been shown to be better than antibiotic treatment for reducing the rate of ear infections.
- With the tubes, it is possible to treat the infections with antibiotic ear drops **instead of oral antibiotic medication**. The ear drops are less likely than oral antibiotics to have side effects.

Impact

- The tubes are **very small and are not visible or noticeable**.
- The child **cannot go swimming** with the tubes because they could allow water to get into the ear.

Resolution

- The tubes **fall out painlessly on their own about one year** after being placed, and the hole in the **eardrum heals on its own**.

Health State C: Hospitalised Pneumonia

Infection

- The **child has an infection** caused by a common type of bacteria that is found in the nose and throat but can spread to other parts of the body and cause illness.
- In this case, the bacteria have **spread into the lungs**.

Symptoms

- Symptoms begin as a **typical cold or flu-like infection**.
- Over the next few days, the child develops **high fever, fatigue, cough, congestion, difficulty breathing, and decreased appetite**.
- The child is **not as active** as usual.

Treatment and Hospitalisation

- The child is **admitted to hospital** and is put on **intravenous (IV) antibiotics**.
    - This means a needle is inserted into the child's arm and is attached to a tube, through which medication flows into the child.
- At times, the child requires **supplemental oxygen**, which is given by a small tube placed under the nose.
- Symptoms **begin to improve after about 2-3 days**. At this point, antibiotic **treatment is changed from IV to oral (liquid or tablets)** and the child is **discharged from hospital**.
- For some children, these IV and oral antibiotics can have **mild side effects** (most commonly diarrhoea and upset tummy).
- The full course of **antibiotic treatment is 10 days**, including the IV and oral treatment.

Return to School

- The child is able to return to pre-school (or school) once they are feeling better, **about a week after being discharged from hospital**.

Timeline Starting at Hospitalisation

Health State D: Bacteremic Pneumonia

Infection

- The **child has an infection** caused by a common type of bacteria that is found in the nose and throat but can spread to other parts of the body and cause illness.
- In this case, the bacteria have **spread to the lungs and into the blood**.

Symptoms

- Symptoms begin as a **typical cold or flu-like infection**.
- Over the next few days, the child develops a **high fever, fatigue, cough, congestion, difficulty breathing, decreased appetite, and an increased heartrate**.
- The child is **tired and lethargic**.
- The child is **not as active** as usual.

Treatment and Hospitalisation

- The child is **admitted to hospital** and is put on **intravenous (IV) antibiotics**.
    - This means a needle is inserted into the child's arm and is attached to a tube, through which medication flows into the child.
- At times, the child requires **supplemental oxygen**, which is given by a small tube placed under the nose.
- Symptoms **begin to improve after about 3-4 days**. At this point, antibiotic **treatment is changed from IV to oral (liquid or tablets)** and the child is **discharged from hospital**.
- For some children, these IV and oral antibiotics can have **mild side effects** (most commonly diarrhoea and upset tummy).
- The full course of **antibiotic treatment is 10-14 days**, including the IV and oral treatment.

Return to School

- The child is able to return to pre-school (or school) once they are feeling better, **about a week after they are discharged from hospital.**

Timeline Starting at Hospitalisation

Health State E: Bacteremia

Infection

- The **child has an infection** caused by a common type of bacteria that is found in the nose and throat but can spread to other parts of the body and cause illness.
- In this case, the bacteria have **spread into the blood**.

Symptoms

- Symptoms begin as a **typical cold or flu-like infection**.
- Over the next few days, the child develops a **high fever, fatigue, decreased appetite, and an increased heart rate**.
- The child is **tired and lethargic**.
- The child is **not as active** as usual.

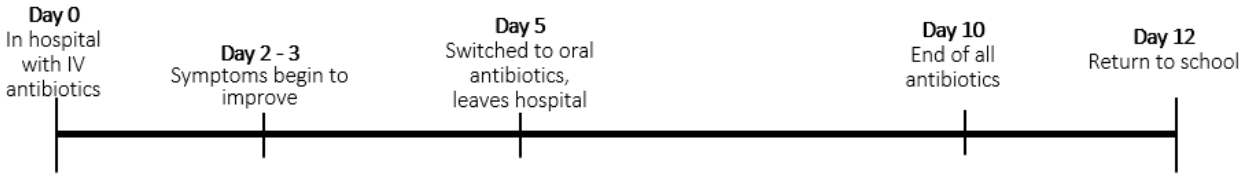
Treatment and Hospitalisation

- The child is **admitted to hospital** and is put on **intravenous (IV) antibiotics**.
    - This means a needle is inserted into the child's arm and is attached to a tube, through which medication flows into the child.
- Symptoms **begin to improve after about 2-3 days**. After 3-5 days, the **antibiotic treatment is changed from IV to oral (liquid or tablets)** and the child is **discharged from the hospital**.
- For some children, these IV and oral antibiotics can have **mild side effects** (most commonly diarrhoea and upset tummy).
- The full course of **antibiotic treatment is about 10 days**, including the IV and oral treatment.

Return to School

- The child is able to return to pre-school (or school) once they are feeling better, **about a week after they are discharged from hospital**.

Timeline Starting at Hospitalisation



Health State F: Meningitis

Infection

- The **child has an infection** caused by a common type of bacteria that is found in the nose and throat but can spread to other parts of the body and cause illness.
- In this case, the bacteria have **spread to the fluid around the brain**.

Symptoms

- The child has a **high fever, headache, sensitivity to light, and neck stiffness**.
- The child is **sleepy and difficult to wake up**.
- The child is **irritable**.

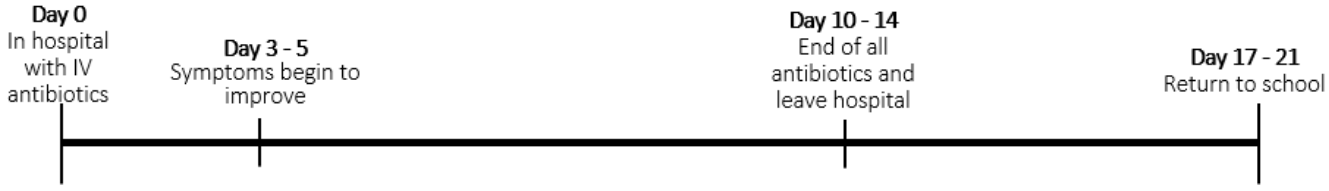
Treatment and Hospitalisation

- The diagnosis is confirmed with a **lumbar puncture**.
  - In a lumbar puncture, a **large needle is inserted into the child's lower back** so some fluid can be removed from the area surrounding the spinal cord. This fluid is then tested for bacteria.
  - For this procedure, **the area is numbed with a local anaesthetic**. This anaesthetic is given with a smaller needle inserted into the child's back.
  - During the lumbar puncture, the **child feels pressure, but not the needle.**
- After confirmation of the diagnosis, the child is put on **intravenous (IV) antibiotics for 10-14 days.**
  - This means a needle is inserted into the child's arm and is attached to a tube, through which medication flows into the child.
- Symptoms **begin to improve after 3-5 days**.
- The child's **hearing is tested** several times throughout the illness to make sure there is no hearing loss.
- The child is **in hospital for 10-14 days** during the IV antibiotic treatment and is discharged after completion of the IV antibiotic treatment.

Return to School

- The child is able to return to pre-school (or school) once they are feeling better, **about a week after they are discharged from hospital**.

Timeline Starting at Hospitalisation



Full Health

- The child is healthy.
- The child does NOT have any health problems.
- The child can perform their usual activities without difficulty (getting around the community, pre-school (or school), social, family, and physical activities).