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Lifetime costs of invasive meningococcal disease: A Markov model approach

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ABSTRACT

Introduction: Invasive meningococcal disease (IMD) is an uncommon but life-threatening infectious disease associated with high sequelae rates in young children and an increased risk of mortality in adolescents and young adults. Funding decisions to reject inclusion of new meningococcal serogroup B vaccines on national immunisation schedules have been criticised by IMD patients, their families, paediatricians and charity organisations. We aim to estimate the lifetime costs of IMD with the best available evidence to inform cost-effectiveness analyses.
Methods: A Markov model was developed taking healthcare system and societal perspectives. A range of data including age-specific mortality rates, and probabilities of IMD-related sequelae were derived from a systematic review and meta-analysis. All currencies were inflated to year 2017 prices by using consumer price indexes in local countries and converted to US dollars by applying purchasing power parities conversion rates. Expert panels were used to inform the model development process including key structural choices and model validations.
Results: The estimated lifetime societal cost is US$319,896.74 per IMD case including the direct healthcare cost of US$65,035.49. Using a discount rate of 5%, the costs are US$54,278.51 and US$13,968.40 respectively. Chronic renal failure and limb amputation result in the highest direct healthcare costs per patient. Patients aged < 5 years incur the higher healthcare expenditure compared with other age groups. The costing results are sensitive to the discount rate, disease incidence, acute admission costs, and sequelae rates and costs of brain injuries and epilepsy.
Conclusions: IMD can result in substantial costs to the healthcare system and society. Understanding the costs of care can assist decision-making bodies in evaluating cost-effectiveness of new vaccine programs.

1. Introduction

Although invasive meningococcal disease (IMD) is uncommon, the disease causes major public health and societal concerns due to its rapid onset and potentially severe or life-threatening outcomes. Despite advanced clinical management, the disease is still associated with a high disability rate in young children and an increased mortality risk in adolescents and young adults. Up to 58% of adolescents develop sequelae [1] and 9% of young patients have major disabling deficits after the disease [2]. Case fatality rates (CFRs) vary between 5 and 20% [3].

Vaccines are available to protect against five major serogroups: A, B, C, W and Y. New meningococcal serogroup B (MenB) vaccine programs are publicly funded in a limited number of countries or states (e.g. UK, Ireland, Italy and South Australia). Meningococcal serogroup ACWY vaccines have been added to national immunisation schedules or are being considered by national funding bodies in several countries due to the continuing rapid rise in serogroup W disease. Although guidelines developed by funding bodies (e.g. Australia and UK) consider factors such as disease severity and rarity, economic evaluation is one of the key inputs that inform decisions on whether to publicly fund new meningococcal vaccine strategies.

Cost of illness (COI) studies can provide important baseline information for future cost-effectiveness analyses [4]. COI results

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help policy-makers understand the financial impact of IMD on the healthcare system and the potential lifetime cost savings that might arise from new meningococcal vaccine programs [5,6]. Previous costing studies estimating IMD direct healthcare costs were conducted in the US and Australia, but the financial impact of long-term care associated with IMD disabilities were not investigated [7–10]. A recently published COI study estimated lifetime costs for a hypothetical cohort of MenB cases reported from 2001 to 2015 in Germany. The "Sum Diagnosis Specific" - COI method and model-based incidence approach were used [11]. Several case studies using two hypothetical cases of severe meningococcal meningits and septicaemia to calculate lifetime costs of IMD are limiting in their ability to inform policy [12–14]. Although the lifetime costs were estimated in the previous studies with different approaches, decision analytic models (e.g. Markov models) are required to capture all important healthcare and societal costs over a lifetime. Such models predict the experience of health states that are likely to be experienced by the patient, often over the lifetime of a study population. Costs are then applied to the time spent in different health states to estimate lifetime costs.

Decision analytic models have been used to assess cost-effectiveness of meningococcal vaccines [15–26]. However, few studies fully justified the choice of model structure (representing health states included in the model) and approaches to systematically identify the best available evidence to populate the model. It is well noted that the choice of inappropriate model structure, even if we use the true value of inputs, can lead to biased model predictions and, hence, poorly informed policy decisions [27]. Some model-based studies of IMD vaccines excluded important health states such as renal failure or speech/communication problems [16,17,20]. Recent guidelines for good modelling practice highlight the need for the development of a conceptual model (reflecting the current clinical understanding of the condition under study) as a basis for defining the structure of cost-effectiveness models [28]. In terms of populating processes, it was found that wide-ranging parameter values (e.g. total sequelae rates varied from 13% [17] to 77% [22]) were extracted from the published literature and used in these models. Modelling results are sensitive to the choice of model inputs and structure. Two prior modelling studies estimated the rate of cognitive problems as 23–25% [18,22] based on a follow-up study in Iceland. However, the rate of cognitive dysfunction was reported as 1.5% in the original retrospective study [29]. Furthermore, societal costs associated with long-term disabilities and premature death have been considered substantial [30], but some evaluations focused solely on direct healthcare costs [22,24,26].

Our study therefore aims to address these issues to further improve the estimation of the lifetime cost associated with IMD from healthcare system and societal perspectives. Following recent guidelines for good modelling practice [28,31,32], we report on the use of a conceptual framework of the progression of IMD to guide the development of a Markov model to predict IMD costs to a maximum age of 100 years.

2. Methods

A Markov model with yearly cycles was built using TreeAge Pro (version 2018 R2.0). The choice of modelling technique was informed by the findings of the model structuring process (i.e. literature review and expert opinion). Modelling techniques commonly used in costing studies include decision trees and cohort-based state-transition (Markov) models. One of the key limitations of decision trees is their inflexibility to model long-term events (e.g. IMD sequelae over a lifetime horizon) [33,34]. Markov models allow us to evaluate events over a longer period of time [35]. Therefore, a Markov model was used in our study to capture long-term costs in line with the findings of our model structuring process. In the base case, future costs were discounted to their present value at 5% annually and the healthcare system perspective was employed as recommended by Australian guidelines [36].

The healthcare system perspective captures direct healthcare costs associated with IMD and public health management. The analysis was also performed from the societal perspective, including direct healthcare costs, direct non-healthcare costs/government subsidies (e.g. home modification and special education) and indirect costs associated with productivity loss.

Based on the number of births registered in Australia in 2016, a hypothetical birth cohort of 311,104 newborns was followed over a 100-year time horizon. All costs were inflated to price year 2017 based on the Gross Domestic Product deflator index or Consumer Price Indexes in local countries and converted to US dollars using Purchasing Power Parities [37,38].

2.1. Model structure

To inform model structure, we systematically reviewed clinical and health economics literature published after 2000, documenting disease progression and important health states associated with IMD. Based on clinical and health economic literature review, we drafted a conceptual framework (Supplementary Fig. 1).

To further guide the development of model structure, four clinical consultants in immunisation, paediatrics, infectious diseases, and paediatric rehabilitation, two experts in public health, two senior researchers working in the field of IMD, and a health economist were invited to be part of an advisory meeting, in which a focus group discussion was conducted to obtain expert opinions to identify relevant and significant health states (sequelae) (see Supplementary Table 1). The aim of conducting a focus group discussion was to capture an appropriate and comprehensive pooling of expert opinions. The participants were selected purposively for their profound experience in public health, infectious diseases or health economic fields so that the expert opinions elicited would be relevant, robust, and comprehensive. Topic guides and discussion questions were developed and discussed by co-authors. Significant health states were defined with respect to the strength of their relationship with IMD, as well as their impact on associated costs and/or important health outcomes (e.g. life expectancy) [27]. The duration of discussion was around 90 min. The whole session was audio-recorded and subsequently transcribed. The focus group was facilitated by one of co-authors with extensive experience in both quantitative and qualitive research areas. The focus group results involved a transcript of the discussion and a summary of the conclusions that was drawn from a descriptive narrative of the focus group discussion.

The main structure of the draft conceptual model was agreed by the expert panel. Based on the discussion, hearing impairments, amputation and renal failure were further disaggregated. For example, amputation was further classified into three categories - digit, single limb and multiple limb amputations. The rating results were used to assist in excluding health states. We further excluded hepatic dysfunction from the model due to low probability and impact scores derived from the questionnaires (a mean likelihood score ≤ 3 and all mean impact scores ≤ 3).

Owing to a low probability and limited data availability, two health states, bone and joint diseases and vasculitis, were removed from the final conceptual framework (Supplementary Fig. 2) to develop the final costing model (Fig. 1). Based on data availability, motor deficits, cognitive impairments and other neurological impairments were aggregated into one health state, brain injuries. Social functioning problems were specified as severe speech and communication problems. Psychological problems were separated

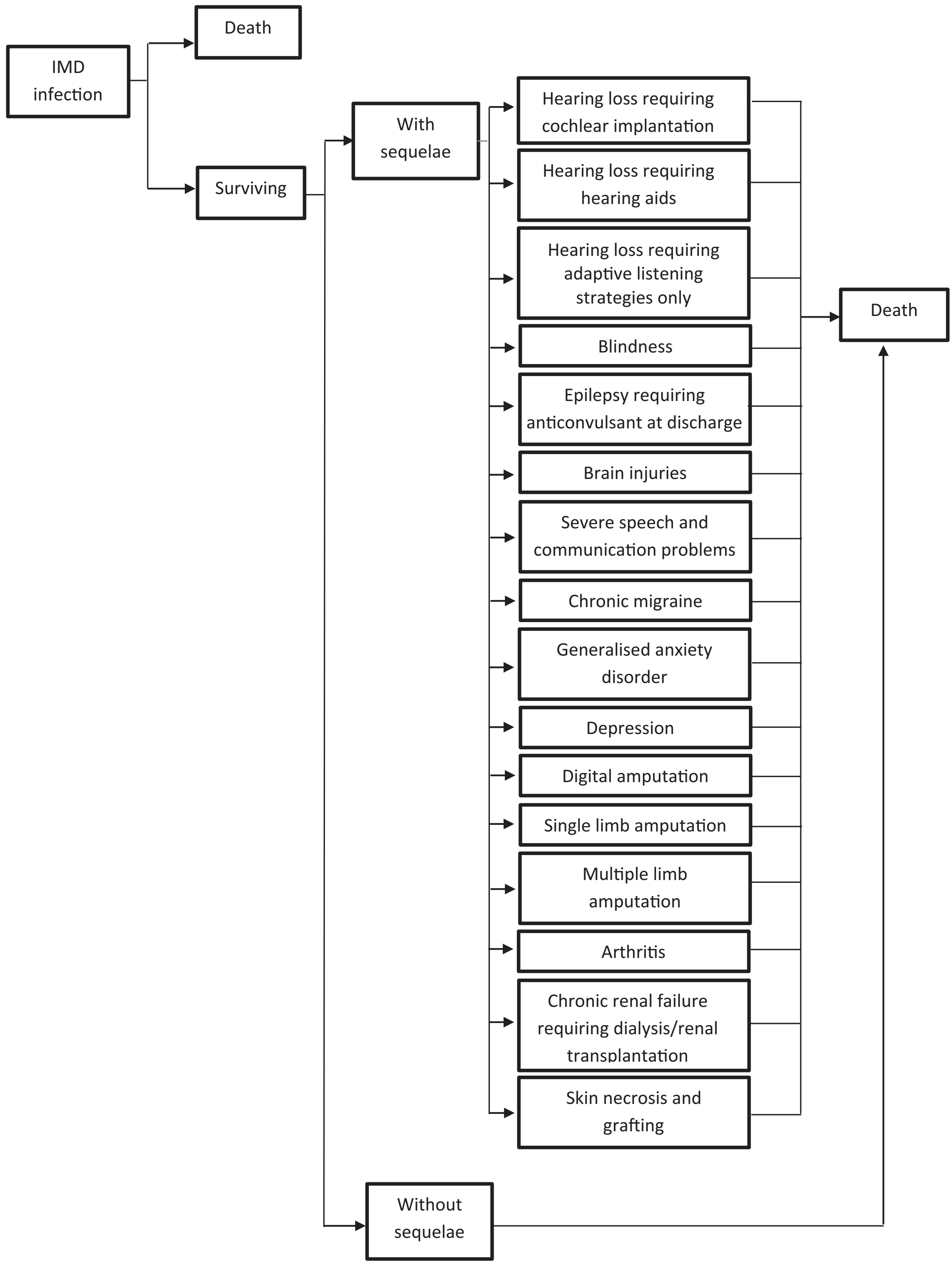

Fig. 1. Revised model structure.

into two health states: depression and generalised anxiety disorder.

2.2. Model inputs and assumptions

We assumed all IMD cases would be hospitalised, as national disease surveillance and hospital morbidity data in Australia show the number of hospitalisations with principal diagnosis of meningococcal infection was higher than the notification number of IMD. As IMD was associated with an increased risk of long-term fatality due to nervous system diseases (mortality rate ratio (MRR): 3.15) and genitourinary diseases (MRR: 6.26) [39], IMD patients with brain injuries and chronic renal failure were assumed to have a higher probability of death. As recurrent IMD is rare [40], each survivor would not have recurrent IMD. Ages of onset of generalised anxiety disorder and depression are 6 and 13 years, respectively [41].

2.2.1. Epidemiological/clinical inputs

A systematic review was performed to identify probabilities of health states, and the best available evidence was used to inform clinical inputs. Given high levels of heterogeneity in the reviewed studies, we were not able to synthesise clinical evidence. Clinical data reported in studies with small sample sizes (n <100) were excluded from data identification, as studies with small sample sizes might produce low quality results with wide variance [42]. We only included studies conducted in developed countries (e.g. UK, US, Australia, etc.) due to applicability issues. Twenty-two studies were used to select clinical parameters (Supplementary Table 2). If more than one study reported a specific sequela rate, the value of the sequelae rate was determined based on the quality of studies (study limitations and imprecision) as suggested by GRADE criteria [43] (Supplementary Table 3).

The disease incidence was determined using Australian notification data in 2017. The national life table in the 2014–2016 period was used to predict non-meningococcal mortality after removing premature deaths caused by IMD. The CFRs presented in national surveillance reports in Australia used two different datasets. Those datasets were not linked. The CFRs were relatively lower than other developed countries. Therefore, we used age-specific CFRs derived from a systematic review and meta-analysis [44].

2.2.2. Cost inputs

Direct healthcare costs associated with admissions, rehabilitation, outpatient visits and prostheses were included (Supplementary Table 4). The costs associated with acute admissions were derived from the National Hospital Cost Data Collection reports between 2013 and 2016. Direct healthcare costs relevant to amputations, stump revisions and skin scars were estimated by using cost weights for Australian Refined Diagnosis Related Groups (AR-DRGs). Due to a lack of costing data pertaining to long-term disabilities, costs associated with sequelae were derived from COI studies describing the cost burden on similar medical conditions. A targeted literature search was performed to identify cost parameters. It was assumed that 15% of primary amputations performed before 12 years of age would have two stump revisions at a three year interval [45–48]. Prior estimates of costs associated with amputation and severe speech problems were further modified based on an evaluation of face validity. Expert input was therefore sought and used to derive those cost inputs.

Direct non-healthcare/government subsidies costs associated with long-term care, informal carers, early intervention/special education, home/vehicle modification, and/or personal out-of-pocket costs were included (Supplementary Table 4).

To estimate indirect costs, two approaches were used: human capital (HC) and friction cost (FC) methods [49]. The HC method estimates the reduction in gross earnings due to morbidity and/or premature mortality. The FC method only considers the time span employers need to restore the initial production level [33].

A friction period of 3 months was used for premature death caused by IMD [50,51]. We also considered a friction period of 1.5 months for patients with blindness, brain injuries, multiple limb amputation and renal failure [19].

By using the HC method, the productivity loss associated with acute admissions for patients without sequelae was estimated by multiplying national average weekly income and an average length of stay in hospital [15]. For patients with sequelae, three additional days plus an average length of hospital stay were considered due to the severity of the disease. The value of lifetime income foregone due to premature death was calculated on an annual basis from the age of death to the retirement age using age-specific wage weighted by age-specific employment rate.

2.3. Model validation

Three clinical consultants in infectious diseases or paediatrics (not involved in the previous focus group discussion) were invited to investigate the model's face validity. A focus group methodology was used again to collect expert opinions on the model structure, model inputs, assumptions and results. They concluded the lifetime costs generated from our model were highly likely to be underestimated. To address this concern, we further investigated onset ages of depression/generalised anxiety disorder and economic parameter values relevant to amputation and severe speech problems. The onset ages of depression/generalised anxiety disorder were revised based on a large survey study in the US [41]. The costs associated with amputation and severe speech problems were revised after interviewing a paediatric rehabilitation consultant, senior speech pathologist and senior prosthetist/orthotist. The costs associated with prostheses, surgical revisions and rehabilitation services were considered for patients with amputation.

Verification was performed by BW and HHAA independently to examine and confirm whether all equations and parameters populated the model correctly. External validity was checked through comparison of population figures predicted in the model against the Australian population in 2016. Cross validation of our final model was assessed by comparing costing results with previous modelling studies.

2.4. Sensitivity analyses

One-way sensitivity analyses were conducted to test the sensitivity of the base case model predictions to model inputs. Australian historically low and high incidence rates in 2013 and 2002 respectively, and 95% confidence intervals of CFRs were used. Due to lack of estimates of precision (e.g. confidence intervals), all other model inputs were varied between 75% and 125% of their point estimates. Discount rates of 0%, and 3.5% were also considered in the analyses.

3. Results

The model predicted 419 IMD cases with a total direct healthcare cost of US$5,860,991.21 (discounted at 5%) or US $27,288,190.17 (no discounting) after following a birth cohort of 311,104 newborns over the model's 100-year horizon (Table 1). At the population level, the cross-sectional costs associated with direct healthcare services reached a peak of $374,972.38 (discounted at 5%) or $455,781.27 (no discounting) at year 4 (Fig. 2). The expected direct healthcare cost per IMD case is US$13,968.40 (discounted at 5%) or US$65,035.49 (no discounting) over a lifetime. The societal cost estimate using HC method is much higher than the estimate using FC methods.

With a discount rate of 5%, the first-year healthcare cost is US $19,236.91 in patients aged one and decrease gradually by age

Table 1
Lifetime costs per IMD case (US$) estimated from the healthcare system and societal perspectives and discounted at 5, 3.5 and 0%.

Discount rate	Direct healthcare cost	Societal cost (HC method)	Societal cost (FC method)
5%	$13,968.40 **(base case)**	$54,278.51	$24,109.56
3.5%	$19,072.94	$84,189.32	$32,066.91
0%	$65,035.49	$319,896.74	$96,809.26

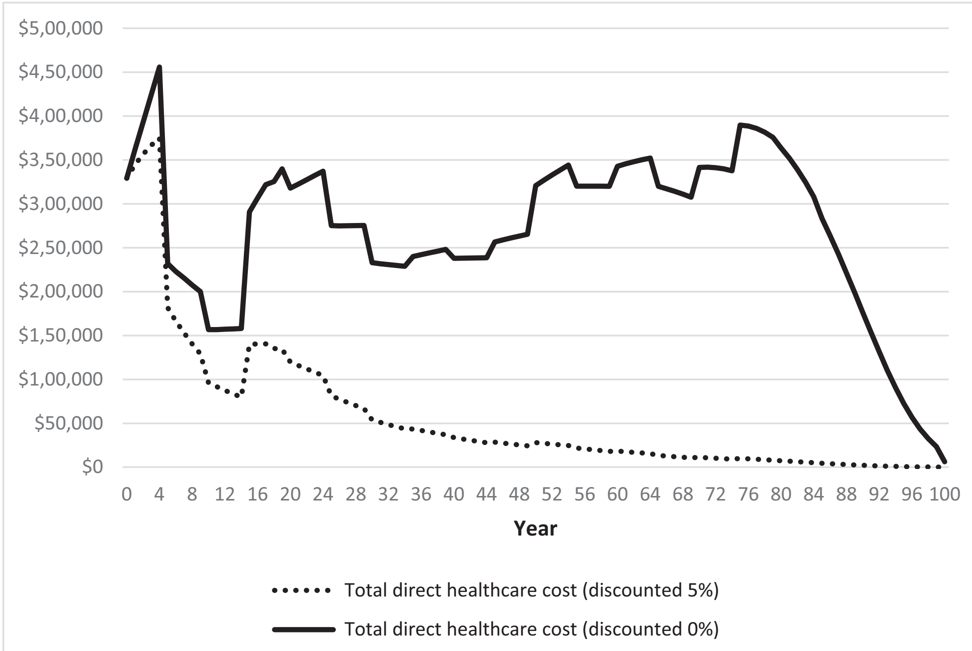

Fig. 2. Total direct healthcare costs of all IMD cases by year.

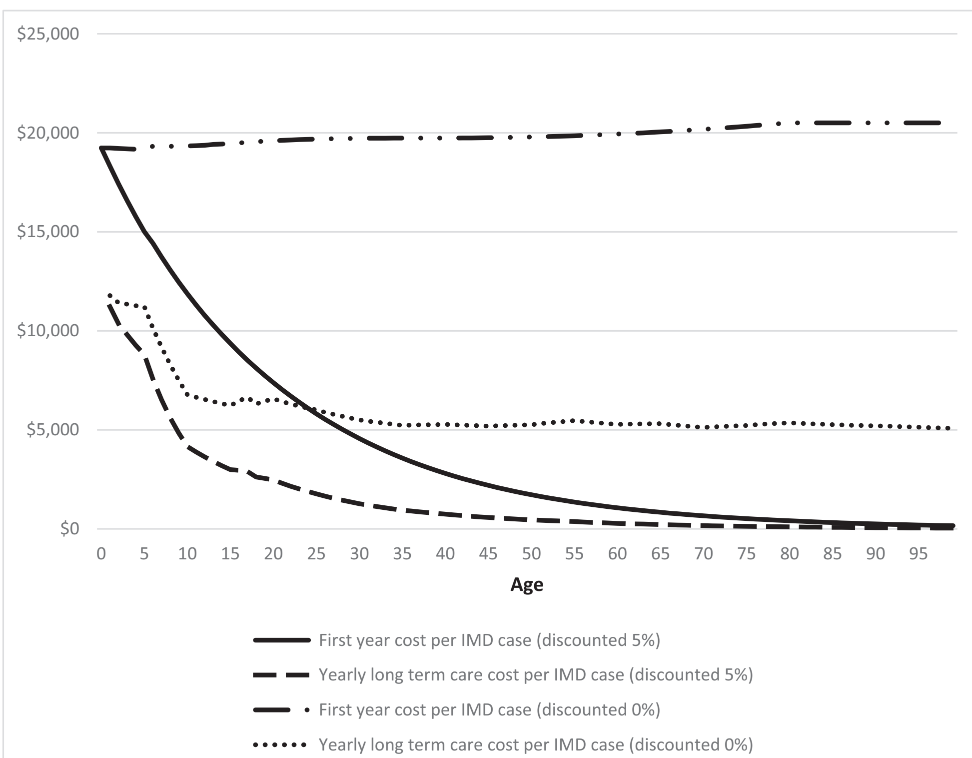

Fig. 3. Direct healthcare cost per IMD case by age group.

(Fig. 3). For patients with disabilities requiring long term care, the average clinical follow-up cost is estimated to be US$11,225.79 for children aged two and has shown a steady decline by age.

Without discounting, the first-year healthcare cost is around US $20,000 on average (Fig. 3). The average long-term healthcare cost is expected to be US$11,787.08 for two-year old children and remains stable for adult patients aged greater than 25 years.

Patients with chronic renal failure, limb amputation, epilepsy and brain injuries are predicted to have higher healthcare costs than other patients (discounted at 5%) (Fig. 4).

The discount rate and disease incidence are key drivers of uncertainty in the one-way sensitivity analyses. A tornado diagram presents model inputs with at least 5% impact on the base case result, including the discount rate, disease incidence, acute

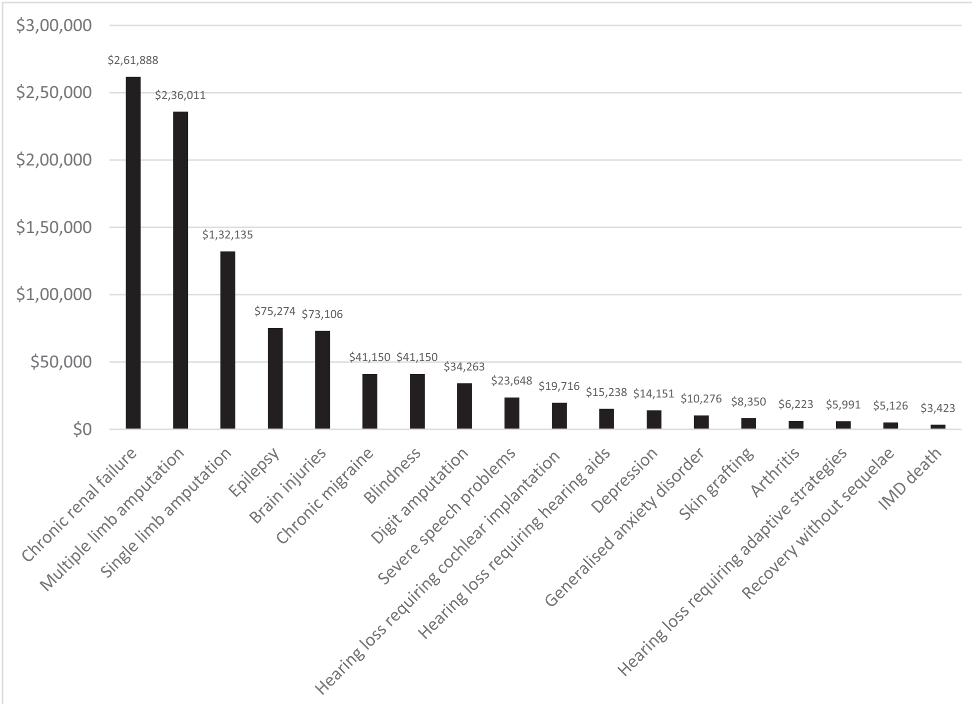

Fig. 4. Direct healthcare cost per IMD case by sequelae type (discounted at 5%).

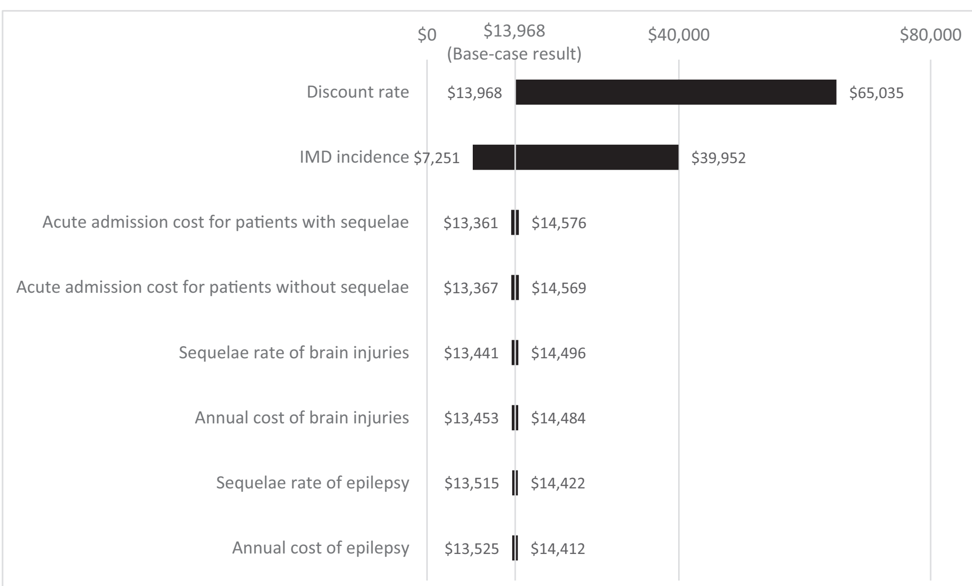

Fig. 5. Tornado diagram of the most influential input parameters in the one-way sensitivity analysis.

admission cost, sequelae rate and annual healthcare cost of brain injuries, and sequelae rate and annual healthcare cost of epilepsy (Fig. 5). Those parameters modified the cost results by more than 5% and generated the wider uncertainty. The cost result was most strongly affected by discount rates, which produced the largest cost difference of US$51,067.09. The variation in incidence rates also greatly impacted the cost result with a cost difference of US $32,701.70. Other parameters modified the cost result by<5% (Supplementary Table 5).

The single birth cohort population shows a steady decline in the model after the cohort reached the age of 50 (Supplementary Figure 3) and presents a similar trend to the Australian population in 2016. Variation in cost results was observed when comparing our results with prior modelling studies.

4. Discussion

The aim of this study was to estimate the lifetime cost from IMD admission until death. Using a Markov model, we found that the undiscounted societal cost could be more than 0.3 million US dollars per case. Young children and severe disabilities such as chronic renal failure and limb amputations were associated with higher costs. Based on literature review, very few studies estimated lifetime costs associated with IMD from healthcare system and societal perspectives using a decision analytic model. A cohort-based state-transition (Markov) model was developed in our study to predict the average lifetime cost of IMD. Markov models were commonly used in previous health economic studies evaluating cost-effectiveness of meningococcal vaccines. Those models were thoroughly reviewed and critically appraised. To address limitations identified in previous modelling studies, the best available published evidence as well as expert panels were used to develop model structure and select model inputs, potentially improving the transparency and accuracy of our model predictions.

In a German COI study, the undiscounted societal costs were estimated at €364,914 (US$496,935) and €105,780 (US$144,050) using HC and FC methods, respectively [11]. Although their results are similar to our study, there were important differences between the methods used in this study and in our study. A "Sum Diagnosis Specific"-COI study design was used in the German study, with a slightly different model structure which included attention deficit hyperactivity disorder (ADHD). The probability of ADHD was estimated to be 9.7% in their model. However, a diagnosis of ADHD can be controversial, and the identification and definition of ADHD cases may be subject to uncertainties in the psychological tools/criteria used in research studies. Therefore, ADHD was not considered in our model. Moreover, their costing parameters associated with long-term disabilities are considerably different, which may explain why the average direct healthcare cost of hearing loss was the highest among all sequelae in the German study. Skin scarring and blindness were costed (up to €500 (US$ 658)) as much less than other sequelae in their study. In addition, lifetime costs were calculated for a hypothetical, cross-sectional cohort consisting of 343 IMD cases occurred between 2001 and 2016 in the German study. In our study, we theoretically followed up a birth cohort of newborn infants. Meningococcal infections can occur at any stage of their lifetime based on incidence rates. All costs associated with acute admissions that occur in the future were discounted at 3.5% and 5% in discounting scenarios. Since all MenB infections occurred during the first year in the German study, no future costs incurred by acute admissions. Unsurprisingly, their societal costs discounted at 5% are almost twice as high as ours. In a Canadian cost-effectiveness study, the cumulative direct healthcare costs were C$56.3 million (approx. US$47 million) for 7037 cases or 80.7 million (approx. US$68 million) for 11,438 cases, equating an average of C$7055 (US$5770) – C$8001 (US$6544) per case discounted at 5% [17]. After adjusting inflation and converting to US dollars, the direct healthcare cost per case was only half of our estimated cost. The Markov model with three health states (dead, alive with sequelae and alive without sequelae) was used in this Canadian study. The sequelae rate was estimated as 13.2% for children aged <18 years and 20% for adults with a treatment cost of C $19,124 (US$15,641) for children and C$4085 (US$3341) for adults. The treatment cost during the acute infection phase was C$14,144 (US$11,568) across all age groups. However, in another Canadian study, the average direct healthcare cost of MenB cases was estimated to be around C$27,410 (US$23,250) with a discount rate of 5% [26]. The undiscounted treatment cost (C$64,755 (US $52,961)) is similar to our estimate. Sequelae rates were obtained from the MOSAIC study in the UK, which is also our main source of the probability of sequelae [2]. Sequelae were classified as minor single/multiple sequelae or major single/multiple sequelae in their model with non-specific treatment costs used to estimate costs of those sequelae. In a cost-effectiveness study conducted in the Netherlands, the direct healthcare cost per case could be approximately €16,667 (US$22,489) discounted at 4% with a total cost of €0.65 million (approx. US$0.88 million) for 39 cases [21]. Hearing loss, motor deficit, neurological sequelae, scars and amputation were included in their Markov model after MenB infection with or without septic shock. Although the model structure and parameters used in their study are different to those in our study, the discounted treatment cost is comparable to our result. A French cost-effectiveness study reported that the cumulative direct healthcare cost could be €600 million (approx. US$800 million) for 52,800 cases which would equal €11,036 (US$15,024) per case (discounted at 4% within the first 30 years and 2% thereafter) [20]. Besides hearing loss, blindness, epilepsy and amputation, IQ < 85 and ADHD were also included in their Markov model. Although their epidemiological and costing parameters are dissimilar to our study, the treatment cost is not vastly different to our result.

The costs are sensitive to changes in the discount rate. This factor was reported to be most influential parameters in other cost-effectiveness analyses [16,17,20]. The more time that has elapsed between birth and predicted events, the higher the reduction in the current value of costs. How and whether to use discounting is controversial when evaluating vaccine programs with potentially long time lags between the time of vaccination and time of its prevention effects [52].

Our study showed the disease incidence is another key driver of differences in costs. The disease incidence is highest in infants, which may partially explain why the infant vaccination was more cost-effective than other strategies without considering carriage reductions and indirect protection [15]. In our study, the highest direct healthcare cost was predicted to be incurred in infants, consistent with the highest disease incidence occurring in this age group. Despite widespread vaccination providing protection against serogroup C disease, there are unpredictable natural fluctuations in the incidence of other serogroup diseases over time. In Australia, the number of IMD notifications declined to 147 in 2013 and rose to 381 in 2017. Although the number of IMD cases might be low over a short period of time, the disease burden should not be underestimated in the long term. Since the national notification incidence was used, both laboratory confirmed and clinically suspected cases of IMD were included in the model. However, 96% of notified cases of IMD were laboratory confirmed in Australia in 2016. The differences between confirmed and probable cases would not substantially affect the outcome of the study.

Our model was developed based on a thorough review of clinical and modelling literature and expert engagement. Unlike previous health economic analyses, surgical revision costs were included in our model. Multiple surgical reinterventions after initial amputation are often required to treat bony outgrowth, growth arrest, and skin contracture in young children [53].

Clinical inputs including incidence are based on the best available published evidence. A few costing parameters were revised based on expert opinions as a result of face validation. In the absence of evidence this is routine practice in model-based studies. Moreover, the effect of assumptions was tested in the sensitivity analysis. However, model inputs were collected from the published literature, which may not represent the current treatment guidelines and costs associated with IMD. Limited epidemiological and costing studies exist especially in paediatric population to inform clinical and economic parameters. Several parameter estimates were derived from the adult population which may underestimate the higher disease burden in children. Moreover, in large observational studies, most patients with disabilities were followed for less than five years. Psychological and social behaviour problems associated with the disease and permanent disabilities (e.g. scaring and amputation) could not be fully investigated. The additional costs resulting from long-term disabilities are highly likely to be underestimated. Owing to difficulties in estimating frequency and combinations of sequelae, we assumed each patient would have one sequela, consistent with other modelling studies. In reality, among patients with sequelae, around one third had multiple sequelae [54]. To minimise this bias, we attempted to include all important sequelae identified in the literature and suggested by experts. However, the costing impact of multiple sequelae might be enormous, which could not be investigated in sensitivity analyses. Overall, the cost results in our study are conservative. Costs were not measured from the different perspectives such as the government, or patients and their families due to limited costing data.

5. Conclusions

IMD can result in substantial costs to the healthcare system and society especially in young children. Further COI and epidemiological studies on long-term disabilities associated with IMD are warranted to improve model accuracy and reduce parameter uncertainty.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Professor Helen Marshall is an independent investigator on clinical trials of investigational vaccines manufactured by pharmaceutical companies including GlaxoSmithKline, Novavax and Pfizer. Her institution has received funding for investigator-led research from GlaxoSmithKline, Sanofi-Pasteur, Pfizer and Novartis Vaccines. There are no other conflicts of interest to declare.

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Contributors

BW conceived and designed the study, developed the costing model, and produced the first draft of the manuscript. HHAA conceived and designed the study, instructed BW in model development, and contributed to, reviewed and edited the manuscript. LG contributed to, reviewed, and edited the manuscript. HM conceived and designed the study, and contributed to, reviewed and edited the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.060.

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