


Costs of Invasive Meningococcal Disease: A Global Systematic Review

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Abstract

Background Invasive meningococcal disease remains a public health concern because of its rapid onset and significant risk of death and long-term disability. New meningococcal serogroup B and combination serogroup ACWY vaccines are being considered for publicly funded immunization programs in many countries. Contemporary costing data associated with invasive meningococcal disease are required to inform cost-effectiveness analyses.

Objective The objective of this study was to estimate costs and resource utilization associated with acute infection and the long-term care of invasive meningococcal disease.

Data Sources and Methods PubMed, EMBASE, The Cochrane Library, health economic databases, and electronically available conference abstracts were searched. Studies reporting any costs associated with acute infection and long-term sequelae of invasive meningococcal disease in English were included. All costs were converted into purchasing power parity-adjusted estimates [international dollars (I\$)] using the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre cost converter.

Results Fourteen studies met our eligibility criteria and were included. The mean costs of acute admission ranged from I\$1629 to I\$50,796, with an incremental cost of I\$16,378. The mean length of hospital stay was reported to be 6–18 days in multiple studies. The average costs reported for readmissions ranged from I\$7905 to I\$15,908. Key variables such as the presence of sequelae were associated with higher hospitalization costs and longer inpatient stay. No studies estimated direct non-healthcare costs and productivity loss. Ten studies reported only unadjusted mean values without using appropriate statistical methods for adjustment.

Conclusions Invasive meningococcal disease can result in substantial costs to healthcare systems. However, costing data on long-term follow-up and indirect costs used to populate health economic models are lacking.

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Key Points for Decision Makers

Invasive meningococcal disease (IMD) is a public health concern worldwide. Assumption and expert opinions have been commonly used in health economic evaluations to estimate unit costs associated with acute admission and long-term care of IMD.

We systematically reviewed and synthesized published evidence of costs and resource utilization relevant to acute infection and long-term sequelae of IMD. The average healthcare costs of acute infection ranged from I\$1629 in Colombia to I\$50,796 in USA with an incremental cost of I\$16,378.

The public health burden of the disease is substantial with significant increases in healthcare costs and resource use for meningococcal patients with sequelae.

1 Introduction

Although the incidence of invasive meningococcal disease (IMD) is relatively low in high-income countries, the disease still causes public health concern and anxiety because of its rapid onset, an increased risk of mortality in adolescents, and high rates of severe sequelae in children [1–4]. Results from retrospective and prospective studies show almost 40% of children had sequelae following IMD infection [2, 5]. Major disabling deficits including amputation, deafness, epilepsy, and learning difficulties were identified in around 10% of pediatric survivors [2]. Among 13 known serogroups, serogroups A, B, C, W, and Y are responsible for most cases of IMD with serogroup X mainly causing disease in Africa [6]. Vaccines against serogroup B disease (MenB), which causes around 40–85% of cases in Australia [7, 8], 64% of cases in Europe [9], and almost 50% in USA [10], have recently been developed. However, the MenB vaccination is publicly funded in a limited number of countries. The recommendation of funding the MenB vaccine under the National Immunisation Program Schedule in Australia has been rejected three times by the Pharmaceutical Benefits Advisory Committee, mainly owing to uncertainty around evidence on the effectiveness of the vaccine and potential for herd immunity response [11–13]. Although initially rejected in the UK [14], the Joint Committee on Vaccination and Immunisation (JCVI) finally recommended inclusion of the

MenB vaccine into the UK immunization schedule at a ‘cost-effective’ price, which was significantly lower than the list price for the MenB vaccine [15]. Changes such as adding litigation costs to the final analysis supported the cost effectiveness of a MenB vaccination program in infants. The JCVI also noted that a similar model with key differences in a number of important parameters including healthcare resources could reach different conclusions on cost effectiveness when comparing an independent study with another unpublished cost-effectiveness study [14]. Because direct and indirect costs associated with acute treatment and long-term care in patients with IMD are important inputs into cost-effectiveness models, detailed costing data are required to inform cost-effectiveness analyses. The paucity of costing data and its potential impact on cost-effectiveness analyses have been acknowledged in recent economic evaluations of the MenB vaccine [16, 17].

By assessing the direct and indirect costs of a particular condition, the results of cost-of-illness (COI) studies can be used to inform public funding decisions such as estimating the magnitude of costs that can potentially be saved by preventative programs (e.g., MenB vaccination). Cost-of-illness studies have also been frequently cited to attract public attention to specific health problems by describing their impact on healthcare resources and productivity loss [18].

To our knowledge, no systematic reviews have been performed to estimate the financial impact associated with acute treatment and long-term follow up of IMD. Anonychuk et al. systematically reviewed the costs related to containment strategies for IMD outbreaks and concluded that the outbreaks result in substantial disruption and costs to society [19]. In a review article, Martín-Torres delineated the extensive clinical and economic burden of IMD including the overlooked family burden, legal costs, and adaptive measures required for IMD survivors with disabilities [20]. However, this narrative review was based mainly on the author’s experience and knowledge, without a description of the literature searching methodology. This review article also used several costing studies related to all-cause bacterial meningitis including pneumococcal and other causes of meningitis to outline the financial burden of IMD.

The aim of the present study is to provide a systematic review of the global evidence on direct or indirect costs of IMD published since 2000. In addition, we compared methodologies used in each study and summarized the key factors affecting healthcare costs.

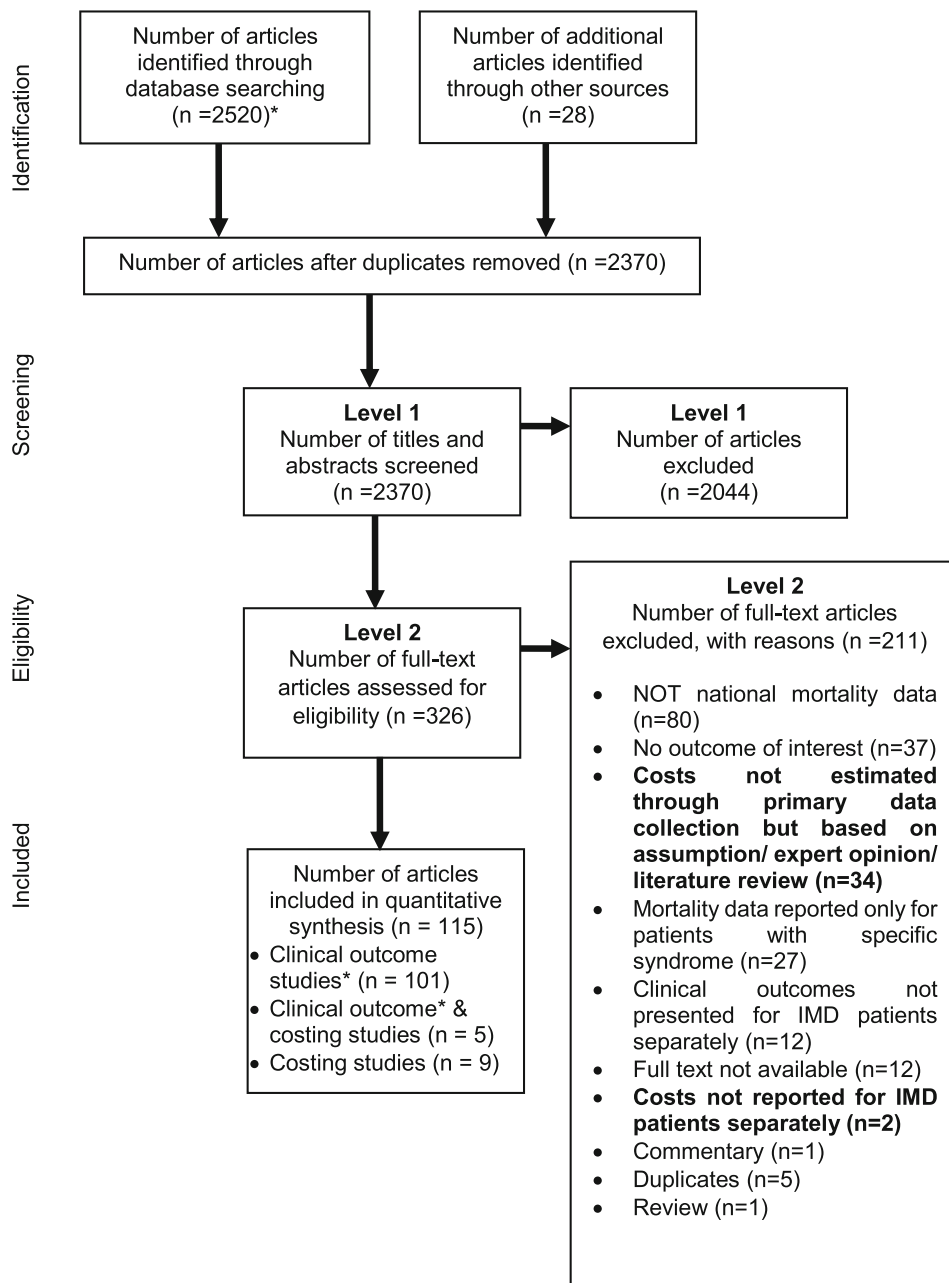
2 Methods

2.1 Literature Search

A search of the literature was conducted using the electronic databases: PubMed, EMBASE, The Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, and the Database of Abstracts of Reviews of Effectiveness. The search terms

included combinations of Medical Subject Headings/ Emtree and text words contained in the title and abstract. Details on search strategies are presented in Table 1 of the Electronic Supplementary Material (ESM). Only studies reporting costing results are included in this review (Fig. 1). Health economic databases were also searched, including the Health Economic Evaluation Database, Cost-effectiveness Analysis Registry, Health Technology Assessment Database, and the Paediatric Economic Database Evaluation. Gray literature available online was

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for article inclusion and exclusion. *IMD* invasive meningococcal disease



* The systematic review covered clinical outcomes and financial costs of IMD. Only the results of costing studies are presented here.

searched for relevant abstracts and/or posters from the following organizations: Meningitis Research Foundation, Infectious Diseases Society of America, International Pathogenic Neisseria Conference, European Society for Paediatric Infectious Diseases, International Congress on Infectious Diseases, World Society for Pediatric Infectious Diseases, and the Australian Society for Infectious Diseases. If conference abstracts were eligible at the title and abstract screen, the first authors were contacted by e-mail and detailed study information was sought. The reference lists of eligible articles and other relevant review articles [19, 20] were searched for additional studies. The search was conducted by one reviewer (BW) from August 2016 to September 2017.

2.2 Inclusion and Exclusion Criteria

The article selection process occurred in two phases: (1) citation screen: titles and abstracts of articles identified from the electronic databases and from Internet searches were reviewed; and (2) full-text screen: the full text of articles selected at the citation screen were obtained and reviewed for eligibility. One reviewer (BW) completed the screening process according to a predefined protocol.

Studies were eligible if direct and/or indirect costs associated with acute infection and long-term complications/sequelae of IMD were reported through primary data collection. We excluded studies only recruiting patients with IMD as part of a larger population but not presenting outcomes for the IMD group separately. Comments, letters, editorials, case reports (fewer than ten patients with IMD), and reviews were excluded. Because the first national meningococcal vaccination (meningococcal C vaccines) program was implemented in the UK in 1999, we expected the vaccination could make significant changes to the epidemiology of IMD. Therefore, the search was restricted to studies published after January 2000. Studies reported in languages other than English were excluded.

Reporting and performing this review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2009 statement [21]. The inclusion and exclusion processes were documented.

2.3 Data Extraction and Quality Assessment

Data were independently extracted by two reviewers (BW and RS) using predefined data fields. Data extracted were: direct and indirect costs, and healthcare resource utilization [e.g., length of hospital stay (LOS), frequency of outpatient services and readmissions], study design, funding, study location, study population (e.g., sample size, serogroup, and age at illness), perspective, data sources, cost items, model type, time horizon, discount rates, cost adjustment

approaches, sensitivity analysis, statistical methods, and limitations considered by authors.

As there are no consensus agreement or validated guidelines explicitly designed to perform critical appraisal for the COI studies, the quality of included studies was assessed using a checklist (Table 2 of the ESM), which was developed on the basis of the Drummond 10-point Checklist [22], the International Society For Pharmacoeconomics and Outcomes Research checklist for retrospective database studies [23], and criteria used in previous COI systematic reviews [24–28]. Two independent reviewers (BW and RS) assessed the quality of the studies and any divergences between reviewers were resolved by discussion.

No studies fulfilled all criteria, as most studies were only conducted from the healthcare system or third-party payer perspective without covering all relevant perspectives, used national hospital discharge or insurance claim databases with no description of data reliability and validity, or reported mean values with no adjustment for confounding variables.

2.4 Data Synthesis

To compare costing data across heterogeneous studies, all cost estimates were converted into international dollars using purchasing power parity according to the recommended guideline [22] and similar studies in the literature [29–31]. Henceforth, all cost estimates are presented with the sign of I\$. The purchasing power parity-adjusted estimates were calculated using the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre cost converter [32]. Because the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre cost converter requires cost estimates reported in the original study's local currency for inflation adjustment, the cost estimates were converted back into the local currency for studies not reporting their results in the study country's local currency but in US\$. If the exchange rate was not presented in the article, the average exchange rate (according to OANDA historical exchange rates [33]) for the reported year was used. If the price year was not specified in the publication, the last year of the study period was utilized. All costs were adjusted to the year 2014, as that was the last price year reported in the included studies.

A meta-analysis was performed using the meta-analytic package [34] in STATA 14.2 (StataCorp LLC., College Station, TX, USA) [35]. Owing to marked variation in data sources, age group, follow-up period, cost items, statistical methods, and confounder adjustment across studies, a significantly high level of heterogeneity ($I^2 = 96.61\%$,

$\tau^2 = 4.6 \times 10^8$) was found in the pooled estimate of unadjusted acute admission costs. Owing to the considerable heterogeneity demonstrated in the meta-analysis, only descriptive results are presented here.

3 Results

3.1 Overview of Studies

The search strategy identified 2370 studies that met the inclusion criteria (Fig. 1). After title and abstract screening, full manuscripts of 326 articles were reviewed so as to exclude additional articles. Among 115 articles retained to assess the clinical and financial burden of IMD, 14 articles reported costing results (Table 1). The majority of the studies were conducted in high-income countries, including six studies in USA, two in Spain, one in Belgium, one in Italy, and another study in Australia. Three studies reported costs associated with IMD outbreaks in the UK, Colombia, and Brazil.

3.2 Methodological Heterogeneity

Although all studies were conducted from the perspective of the healthcare system or third-party payers with a bottom-up approach, the range of cost items included in each study varied considerably (Table 2). Except for three outbreak studies, all other studies used retrospective insurance claim or hospital discharge databases. Five studies did not provide detailed cost breakdowns with three of them reporting costs based on Diagnosis Related Group codes [36, 38, 41, 45, 48]. Five studies provided a breakdown of healthcare costs by age groups. The main cost item reported was inpatient costs. Some studies also included other cost components such as emergency department, hospital outpatient services, physician office visits, nursing home services and rehabilitation facilities, pharmacy claims, and associated costs. Cost adjustment was not documented in three studies [36, 41, 45]. One study compared costing data and resource utilization between cases and controls [38]. Four studies reported healthcare costs relevant to medical follow-up after hospital discharge [39, 40, 43, 49]. The follow-up period varied between 0 and 3659 days. Serogroup information was only available for six studies.

Only four studies used statistical models to adjust cost and resource utilization data [38, 39, 43, 49]. Among those, a generalized linear model was commonly used for costing data adjustment, with three studies fitting a generalized linear model with a log link function and a gamma distribution. Resource utilization was analyzed using negative binomial regression, Cox proportional hazard, or Poisson

regression models. Two studies chose the same set of confounding variables [39, 43]. There is considerable variability in selecting confounding variables between the aforementioned two studies and other studies. Both unadjusted and adjusted analyses were presented in three studies [39, 43, 49]. Except for patients without sequelae in two US studies, all adjusted costs were reported to be lower than unadjusted costs. For those performing only unadjusted analyses, four of them presented mean and/or median values with no variability measures (e.g., range, interquartile range, 95% confidence interval or standard deviation) [40, 41, 45, 46].

3.3 Direct Medical Cost Estimates and Healthcare Resource Utilization

The unadjusted acute admission costs per patient ranged from I\$1629 in Colombia [47] to I\$50,796 in USA [39] (Tables 3, 4). The unadjusted mean cost of follow-up care during 1-year post-admission was reported as I\$23,565 in USA including readmission costs and other healthcare expenses [40]. The unadjusted total healthcare cost for initial admission, readmissions, and other healthcare services was around I\$60,000 on average in USA during 1-year post-admission [39, 40, 43]. Readmissions resulted in I\$15,908 in USA [40] and I\$7905 in Australia [49] in unadjusted analyses with varied follow-up periods. The adjusted mean costs associated with acute admission were reported in four studies ranging from I\$8571 in Australia [49] to I\$23,792 in USA [38]. The adjusted mean cost relevant to IMD readmissions was estimated to be I\$935 in Australian pediatric patients with sequelae [49]. Both unadjusted and adjusted healthcare costs including inpatient costs almost doubled in patients with sequelae compared with patients without sequelae [38, 43, 49]. The incremental cost and LOS of acute admission (I\$16,378, 4.3 days) could only be inferred from a case-control study [38].

Of the 14 included studies, ten reported an estimated hospital resource use. The mean LOS during acute admission was reported from 8 to 18 days in unadjusted analyses with around 1 week in adjusted analyses. Approximately 40% of patients with IMD had sequelae after discharging from hospital. Those patients were 1.5–3 times more likely to stay in hospital longer and visit outpatient clinics during the acute admission and/or in the year following admission [39, 43, 49].

The total cost associated with an outbreak was reported as I\$55,778 in Brazil and I\$7873 in Colombia [37] (Table 4). As MenB vaccines were not available for the outbreak in Colombia, the cost of managing the outbreak was lower in Colombia than the one in Brazil. It was

Table 1 Characteristics of costing studies included in the systematic review

Study	Location	Currency	Study period (year of pricing)	Follow-up period	Sample size	Age group, years	Age and sex of IMD cases	Clinical diagnosis	Serogroup
Clarke and Mallonee [36]	Oklahoma, USA	US\$	2002–2004	Not stated	46	All	Not stated	Laboratory confirmed and probable cases of IMD	Not stated
Constenla et al. [37]	Vila Brandina in Brazil and Cartagena de Indias in Colombia	US\$	2011 and 2012 (2014 US\$)	3 months (Brazil); 18 days (Colombia)	3 in Brazil; 6 in Colombia (outbreak)	All	Brazil: 2 children (aged 3 years) and an adult (aged 36 years); Colombia: 6 children	Laboratory confirmed, probable or clinically suspected IMD	2 confirmed IMD cases in Brazil: C (100%); 4 confirmed IMD cases in Colombia: B (100%)
Davis et al. [38],	USA	US\$	2006 (2009 US\$)	Not stated	447 (735 [weighted])	≤ 20	Female: 42%; age category: < 1 year (25.99%), 1–4 years (23.67%), 5–10 years (13.74%), 11–18 years (26.94%), 19–20 years (9.66%)	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Davis et al. [39]	USA	US\$	1998–2009 (2009 US\$)	12 months	173	All	Mean age, year (SD): 33.2 (24.7); female: 52%	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Davis et al. [40]	USA	US\$	1999–2007 (2009 US\$)	12 months	Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS): (<i>n</i> = 349, 1710 [weighted]); Perspective Comparative Database (PCD): (<i>n</i> = 1058 [weighted]); LifeLink Health Plan Database: (<i>n</i> = 268 [weighted])	All	Mean age, year (SD): NIS: 25.10 (55.59), PCD: 31.52 (26.27), LifeLink: 35.18 (26.82); female: 47–49%	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Gil-Prieto et al. [41]	Spain	€	1997–2008	Not stated	11,611 discharges	All	Mean age, year (SD): 16 (22); median age, year (interquartile range): 5 (1, 20); female: 48.8%	Diagnosis of IMD defined by ICD-9-CM codes 036	Not stated

Table 1 continued

Study	Location	Currency	Study period (year of pricing)	Follow-up period	Sample size	Age group, years	Age and sex of IMD cases	Clinical diagnosis	Serogroup
Hanquet et al. [42]	Belgium	€	2004–10 (2012 Euros)	Up to discharge	698	All	By age group (n): < 1 year (117), 1–4 years (169), 5–9 years (77), 10–19 years (165), 20+ years (170)	Diagnosis of IMD defined by ICD-9-CM codes 036	B: n = 597
Karve et al. [43]	USA	US\$	1997–2009 (2009 US\$)	12 months	343	All	Mean age in years (SD): 34.2 (22.6); female: 44.6%	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Letouze et al. [44], 2014	England, UK	£	2012 (2012 £)	Up to discharge	2 (outbreak)	All	2 female primary school pupils aged 10 and 8 years	Laboratory confirmed IMD	B
Montero et al. [45]	Spain	€	1997–2005	Not stated	9479	All	Median age, year (range): 6 years (0–102); female: 49.2%	Diagnosis of IMD defined by ICD-9-CM codes 036	Not stated
O'Brien et al. [46]	California, Florida, Massachusetts and Washington States, USA	US\$	1999–2001 (2003 US\$)	Up to discharge	1634	All	Mean age, year: 24; median age, year (range): 17 (0–96); female: 48%	Admissions of IMD defined by ICD-9-CM codes 036	Not stated
Pinzon-Redondo et al. [47]	Cartagena de Indias, Colombia	US\$	2012 (2011 US\$)	3 week following the outbreak	6 (outbreak)	All	Mean age, year (SD): 4.6 (3.5); female: 50%	Laboratory confirmed IMD	B (100%)
Tirani et al. [48]	Lombardia and Piemonte, Italy	€	2007–012 (2013 €)	Not stated	341	All	Female: 51.9%	Discharge diagnosis of IMD defined by ICD-9-CM codes 036	B (59.2%), C (29.6%), others (11.1%)

Table 1 continued

Study	Location	Currency	Study period (year of pricing)	Follow-up period	Sample size	Age group, years	Age and sex of cases	Clinical diagnosis	Serogroup
Wang et al. [49]	Adelaide, SA, Australia	AUS\$	2000–11 (2011 AUS\$)	5–3659 days	109	< 18	Mean age, year (SD): 3.9 (4.5); female: 54.1%	Laboratory confirmed and probable cases of IMD	B (70.6%), C (9.2%), Y (0.9%), W (1.8%)

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, *IMD* invasive meningococcal disease, *SD* standard deviation

reported in the UK study that the incremental cost of managing a second case of IMD was I\$7815 [44].

3.4 Direct Non-medical Costs and Indirect Costs

We have not found any studies reporting direct non-medical costs and indirect costs relevant to IMD. We excluded studies that estimated productivity loss based on assumption or expert opinions without any primary data collection.

3.5 Factors Impacting Healthcare Costs

Studies in USA and Australia suggested sequelae/complications, serogroup B infection, male sex, and previous medical history were significantly associated with higher healthcare costs and resource use compared with their counterparts [5, 38, 39, 43]. Infants aged less than 1 year had the highest healthcare costs and LOS in pediatric patients and young patients aged < 21 years [38, 49]. However, unadjusted mean costs or LOS reported in other studies did not show a similar trend. In contrast, adolescents or adults were reported as having higher costs and longer LOS than other age groups [41, 42, 45, 46, 48].

4 Discussion

This systematic review included 14 studies that reported costs associated with acute infection and/or long-term care of patients with IMD, and descriptively described and compared study results and methodologies. To our knowledge, this is the first study to systematically review and investigate the financial impact of IMD.

The results show a considerable impact of IMD on healthcare resources, which reflects severe outcomes associated with the disease requiring resource-intensive treatments. The costs of acute treatment and readmissions were the most important components of total healthcare costs. The national costs per year were estimated to be around €5 million in Spain [41, 45] and US\$50 million in USA [40, 46]. Although total costs of controlling IMD outbreaks are not significant in Brazil and Colombia, the management of outbreaks cost 2.7 times more than the annual gross domestic product per capita in Brazil including vaccination costs and 9.5% of Colombia's annual gross domestic product per capita without using any vaccination [37].

The financial impact of long-term sequelae on the healthcare system has not been well investigated. The included studies consistently reported that the presence of sequelae is an important predictor of high healthcare costs and resource use. Clinical data show that around 10% of patients with IMD had severe long-term sequelae such as

Table 2 Summary of study designs and methods used in included studies

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Clarke and Mallonee [36]	Incidence; bottom up	Healthcare system	State-wide hospital discharge data	Hospital charges	Not stated	No	Not stated	No
Constamla et al. [37]	Incidence; bottom up	Healthcare system	Interviews with structured standardized questionnaires administered to health authorities involved in the outbreak	Personnel, office supplies, gasoline consumption, chemoprophylaxis, and vaccines	Expressed costs in 2014 US dollars using the IMF official exchange rate	No	Not stated	No
Davis et al. [38]	Incidence; bottom up	All payers (private insurance, self-pay, government)	2006 HCUP Kids' Inpatient Database	Total cost per admission	All cost data were converted from charges using facility-specific, cost-to-charge ratios provided by the HCUP and inflated to \$US, year 2009 values using the medical component of the US Consumer Price Index.	Demographically matched admissions: $n = 4573$	Healthcare costs: GLM with a log-link function and Gamma distribution; LOS data: zero-truncated negative binomial and Poisson regression models	A binary IMD indicator (IMD admission vs. control), sex (female vs. male), race (white vs. non-white), geographic location, admission source (ED vs. other), urban/rural status of the hospital, teaching/non-teaching status of the hospital, payer type (private insurance vs. non-private) and discharge status (routine vs. dead)
Davis et al. [39]	Incidence; bottom up	Third-party payer	LifeLink database (formerly the PharMetrics Integrated Outcomes Database)	Medical claims and associated costs for various service categories, including inpatient, ED, hospital outpatient services, physician office visits, nursing home services and rehabilitation facilities, pharmacy claims, and associated costs	Adjusted to 2009 US dollars	No	Healthcare costs: GLM with a log-link function and gamma distribution; resource utilization data: negative binomial regression models	Presence of IMD-related sequelae and patient baseline demographic characteristics including age, gender, region, payer type, insurance type and the Charlson Comorbidity Index score

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Davis et al. [40]	Incidence; bottom up	All payers (private insurance, self-pay, government)	HCUP NIS 2005, PCD 2000–2007, and LifeLink (formerly PharMetrics) Health Plan Database 1999–2000	NIS: all-payer inpatient care; PCD: principal and secondary procedures, medications, laboratory tests, and diagnostic and therapeutic services at the individual patient level, as well as the hospital ward (e.g., ICU); LifeLink: actual paid (i.e., reimbursed) amounts for medical services and prescription drugs utilized, and costs of non-facility (i.e., professional and other ancillary) services rendered	All cost data were converted from charges using facility-specific, cost-to-charge ratios provided by the HCUP and inflated to \$US, year 2009 values using the medical component of the US Consumer Price Index.	No	Not stated	No
Gil-Prieto et al. [41]	Incidence; bottom up	Healthcare system	National surveillance system for hospital data	The cost to the healthcare system of these hospitalizations was calculated by considering the diagnostic cost group, the total cost, and the number of discharges. Diagnostic cost group was based on the DRG codes for hospitalized patients depending on discharge ICD classification, age, sex, and resource consumption.	Not stated	No	Descriptive analysis only	No

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Hanquet et al. [42]	Incidence; bottom up	Healthcare payers	Hospital Clinical Records (MZG-RHM: Minimale Ziekenhuisgegevens-Résumé Hospitalier Minimum); Hospital Billing Records database (AZV-SHA: Anoniem Ziekenhuis Verbljif - Séjour Hospitalier Anonyme); database of the National Reference Centre	Healthcare costs of each hospital stay including the extrapolated lump sums for laboratory testing, medical imaging and drugs	Adjusted to 2012 values using the health Consumer Price Index. Before aggregating the costs recorded in each IMD stay, the following adjustments were performed: extrapolation to 100% per diem costs; extrapolating the lump sums for laboratory testing, and medical imaging, and drugs.	No	Descriptive analysis only	No
Karve et al. [43]	Incidence; bottom up	Third-party payer	An administrative claims database in USA (Ingenix Impact (formerly the Integrated Healthcare Information Services) database)	Medical claims and associated costs for different service categories including inpatient, ED, outpatient, physician office, nursing home, and rehabilitation services, as well as details on pharmacy utilization and associated costs	Adjusted to 2009 US\$	No	Healthcare costs: GLM with a log-link function and gamma distribution; risk of rehospitalization; Cox proportional hazard models; number of hospitalizations or physician office visits; negative binomial regression models	Presence of IMD-related sequelae and patient demographic characteristics including age, sex, region, payer type, insurance type, and co-morbidity burden via the Charlson Comorbidity Index score
Letouze et al. [44]	Incidence; bottom up	Public health management	Published unit costs used to estimate the total cost	Time and cost attributed to staffing, microbiology, pharmacy, and media liaison	Adjusted to 2012 price in pounds	No	Not stated	No

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Montero et al. [45]	Incidence; bottom up	Healthcare system	National surveillance system for hospital data	The cost to the healthcare system of these hospitalizations: calculated by considering the diagnostic cost group, the total cost and the number of discharges. Diagnostic cost group: based on the DRG codes for hospitalized patient depending on discharge ICD classification, age, sex, and resources consumption	Not stated	No	Descriptive analysis only	No
O'Brien et al. [46]	Incidence; bottom up	Healthcare payers	Claims databases maintained by each individual state, patient discharge databases	Acute hospital costs include all accommodations (e.g., routine, ICU, ancillary services (e.g., pharmacy, laboratory), ED, and observation unit care prior to admission where appropriate, and physician services.	Older values were inflated using rates based on the medical care component of the US Consumer Price Index, supplied by the Federal Bureau of Labour Statistics for the appropriate years. Hospital charges were adjusted to costs using a 0.61 cost-to-charge ratio. State costs [where data from a single state were used (i.e., Florida Medicaid physician fees)] were adjusted to national values using ratios based on published national and state cost data.	No	Not stated	No

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Pinzon-Redondo et al. [47]	Incidence; bottom up	National health system	Interviews with experts involved in the outbreak and medical notes review	Direct treatment costs and costs associated with outbreak control including personnel costs, measured in time and estimated as a fraction of the salary of each. An outbreak care team consisted of two pediatricians, two nurses, an epidemiologist, and two public health experts.	All costs are expressed in US\$ (2011) as cost per 1000 inhabitants.	No	Not stated	No
Tirani et al. [48]	Incidence; bottom up	Healthcare system	National Invasive Bacterial Diseases Surveillance System; Italian Hospital Discharge Dataset	All hospital-related expenditures (i.e., costs for acute standard care and complications) used the DRG codes reported for each patient record.	Adjusted to 2013 € price level	No	Descriptive analysis only	No
Wang et al. [49]	Incidence; bottom up	Healthcare system	Costing data were provided by the hospital Health Informatics, Performance, Planning and Outcomes Unit. Clinical data were extracted from medical records.	Direct medical costs included costs of medical ward, pathology, imaging, allied health, pharmacy, use of theatre suite, paediatric intensive care unit, prosthesis, medical and surgical supplies, hotel services, direct goods, and services and overheads.	Inflated to 2011 AUS\$ using the medical and hospital services component of the Australian Consumer Price Index	No	Healthcare costs: GLM; LOS during the acute admissions: zero-truncated negative binomial regression models; LOS of readmission, the number of outpatient visits and readmission frequencies: negative binomial regression models	Serogroup, age, sex, diagnosis type, previous medical history and sequelae

DRG Diagnosis Related Group, ED emergency department, GLM generalized linear model, ICD International Classification of Diseases, ICU intensive care unit, LOS length of hospital stay, MIS Nationwide Inpatient Sample, PCD Perspective Comparative Database

Table 3 Summary of included studies reporting healthcare costs and resource utilization

References	Unadjusted healthcare costs	Adjusted healthcare costs	Incremental costs	Unadjusted healthcare utilization results	Adjusted healthcare utilization results	Incremental healthcare utilization
Clarke and Mallonee [36]	Mean hospital charges per patient: \$46,006 (median: \$22,431, range: \$946–\$328,506)	No	No	Mean LOS per patient in days: 12 (median: 8, range: 1128)	No	NA
Davis et al. [38]	Not stated	Mean costs per admission by age group (95% CI): < 1 year: \$39,620 (\$35,704–\$43,537), 1–4 years: \$13,437 (\$12,875–\$13,999), 11–18 years: \$21,656 (\$20,788–\$22,524), 19–20 years: \$34,163 (\$30,647–\$37,680), all ages \$23,792 (\$22,985–\$24,601)	\$16,378	Not stated	Mean LOS per admission by age group in days (95% CI): < 1 year: 9.0 (7.7–10.3), 1–4 years: 5.51 (5.07–5.95), 5–10 years: 5.55 (4.64–6.46), 11–18 years: 6.20 (5.84–6.56), 19–20 years: 8.99 (7.53–10.45), all ages: 6.4 (6.0–6.8)	LOS per patient in days: 4.3
Davis et al. [39]	Mean healthcare costs during 12 mo per patient (SD): \$60,540 (\$132,314) including inpatient costs of \$50,796 (\$119,472) for all patients, \$83,923 (\$145,990) including inpatient costs of \$70,660 (\$133,151) for patients with complicated IMD, \$44,263 (\$119,961) including inpatient costs of 36,969 (\$107,469) for patients with uncomplicated IMD	Mean healthcare costs during 12 mo per patient (95% CI): \$78,364 (\$67,592–\$89,134) including inpatient cost of \$67,633 for patients with complicated IMD, \$45,521 (\$41,162–\$49,880) including inpatient cost of \$38,342 for patients with uncomplicated IMD	No	Mean LOS during 12 mo per patient in days (SD): 17.8 (26.8) for all patients, 26.7 (31.7) for patients with complicated IMD, 11.5 (20.7) for patients with uncomplicated IMD; mean number of rehospitalization per patient (SD): 0.64 (1.30) for all patients, 1.1 (1.7) for patients with complicated IMD, 0.3 (0.9) for patients with uncomplicated IMD	Inpatient admissions during 12 mo: IRR = 1.5 (95% CI 1.2–1.9) for patients with complicated IMD vs. patients with uncomplicated IMD; hospital outpatient visits: IRR = 3.2 (95% CI 1.7–5.8) for patients with complicated IMD vs. patients with uncomplicated IMD; home health and durable medical equipment services: IRR = 2.7 (95% CI 1.0–6.9) for patients with complicated IMD vs. patients with uncomplicated IMD	No
Davis et al. [40]	Mean acute admission costs per patient: \$48,146; mean follow-up care costs following discharge from initial admission: \$23,565 including costs attributed to repeat hospitalizations of \$15,908; mean 1-year cost: \$71,711	No	No	Mean LOS during acute admission per patient in days: 9; mean ICU stay in days: 1.7	No	No
Gil-Prieto et al. [41]	Mean costs per admission: \$7843	No	No	Mean LOS per admission by age group in days (SD): < 1 year: 10 (9), < 2 years: 10 (9), 0–4 years: 10 (10), 5–9 years: 9 (8), 10–14 years: 11 (11), 15–19 years: 12 (11), 20–24 years: 12 (14), 25–29 years: 13 (11), 30–49 years: 15 (21), 50–54 years: 17 (18), 55–59 years: 16 (17), 60–64 years: 19 (25), 65–69 years: 16 (15), 70–74 years: 15 (14), 75–79 years: 17 (19), 80–84 years: 14 (12), ≥ 85 years: 12 (8), all ages: 11 (12)	No	No

Table 3 continued

References	Unadjusted healthcare costs	Adjusted healthcare costs	Incremental costs	Unadjusted healthcare utilization results	Adjusted healthcare utilization results	Incremental healthcare utilization	
Hanquet et al. [42]	Mean acute admission costs per patient (SD): serogroup B only by age group: < 1 year: \$8998 (\$10,193), 1–4 years: \$7655 (\$6061), 5–9 years: \$6774 (\$2553), 10–19 years: \$9752 (\$8,430), 20+ years: \$12,278 (\$9,874), all ages: \$9182 (\$8211); any serogroup by age group: < 1 year: \$8844 (\$9665), 1–4 years: \$7674 (\$6017), 5–9 years: \$7326 (\$4305), 10–19 years: \$9733 (\$8238), 20+ years: \$12,926 (\$13,643), all ages: \$9597 (\$9574)	No	No	No	No	No	
Karve et al. [43]	Mean healthcare costs during 12 mo per patient (SD): \$59,779 (\$118,314) including inpatient costs of \$45,162 (\$104,901) for all patients, \$108,406 (\$187,826) including inpatient costs of \$81,383 (\$168,945) for patients with complicated IMD, \$534,605 (\$34,972) including inpatient costs of \$26,410 (\$31,238) for patients with uncomplicated IMD	Mean healthcare costs during 12 mo per patient (95% CI): \$105,235 (\$96,360–\$114,113) including inpatient costs of \$77,868 (\$71,741–\$83,996) for complicated patients, \$35,229 (\$33,502–\$36,957) including inpatient costs of \$26,995 (\$25,667–\$28,322) for uncomplicated patients	No	Mean LOS during 12 mo in days (SD): 14.0 (27.6) for all patients, 25.6 (42.3) for patients with complicated IMD, 8.1 (11.3) for patients with uncomplicated IMD; mean number of rehospitalization (SD): 0.5 (1.3) for all patients, 1.0 (2.0) for patients with complicated IMD, 0.2 (0.6) for patients with uncomplicated IMD; mean number of hospital outpatient visits (SD): 6.4 (11.9) for all patients, 12.7 (17.9) for patients with complicated IMD, 3.1 (4.5) for patients with uncomplicated IMD	Inpatient admissions during follow-up: IRR = 1.5 (95% CI 1.3–1.9) for complicated patients vs. uncomplicated patients; outpatient visit: IRR = 3.1 (95% CI 2.4; IRR 4.0) for complicated patients vs. uncomplicated patients; rehospitalization after initial IMD admission: hazard ratio = 1.7 (95% CI 1.0; IRR 2.7) for complicated patients vs. uncomplicated patients	No	No
Montero et al. [45]	Mean cost per admission: \$7791	No	No	Mean LOS per admission by age group in days (95% CI): 0–4 years: 9.81 (9.53–10.09), 5–9 years: 9.10 (8.66–9.53), 10–14 years: 10.54 (9.69–11.39), 15–19 years: 11.32 (10.65–11.98), 20–24 years: 12.03 (10.98–13.08), 25–29 years: 12.53 (11.14–13.91), ≥ 30 years: 15.56 (14.71–16.40), all ages: 11.10 (10.86–11.33)	No	No	
O'Brien et al. [46]	Mean acute admission cost per patient by age group: < 1 year: \$21,043, 1–10 years: \$25,418, 11–17 years: \$35,339, 18–22 years: \$32,908, 22–49 years: \$33,958, ≥ 50 years: \$26,816, all ages: \$29,189 (median: \$14,591)	No	No	Mean LOS per survivor in days: 8.8 (median: 6.5)	No	No	

Table 3 continued

References	Unadjusted healthcare costs	Adjusted healthcare costs	Incremental costs	Unadjusted healthcare utilization results	Adjusted healthcare utilization results	Incremental healthcare utilization
Tirani et al. [48]	Mean admission costs per patient (range): pediatric (≤ 18 years): \$9067 (\$3334–\$50,671), adult (> 18 years): \$11,001 (\$3600–\$60,005)	No	No	Mean LOS per patient in days: 11.40 for subjects ≤ 18 years (pediatric) and 21.64 for those > 18 years (adult); by age group: < 1 year: 10.92, 1–4 years: 12.29, 5–9 years: 10.88, 10–14 years: 10.15, 15–19 years: 12.76, 20–24 years: 13.90, 25–44 years: 28.34, 45–64 years: 22.08, 60+ years: 22.25	No	No
Wang, et al. [49]	Mean acute admission costs per patient (95% CI): \$14,855 (\$8618–\$25,064) for all patients, \$29,140 (\$13,573–\$54,868) for patients with sequelae, \$11,529 (\$4,558–\$36,075) for patients without sequelae, \$17,644 (\$9288–\$32,827) for MenB patients, \$8144 (\$5207–\$13,571) for non-MenB patients, \$22,451 (\$9451–\$49,725) for patients < 1 year, \$11,698 (\$6783–\$22,350) for patients ≥ 1 year; mean readmission costs for patients with sequelae (95% CI): \$7905 (\$1041–\$17,439)	Mean acute admission costs per patient (95% CI): \$8571 (\$7317–\$9824) for all patients, \$24,591 (\$22,212–\$26,968) for patients with sequelae, \$5743 (\$5352–\$6135) for patients without sequelae, \$16,550 (\$13,647–\$19,453) for MenB patients, \$7191 (\$6150–\$8232) for non-MenB patients, \$16,511 (\$13,360–\$19,662) for patients < 1 year, \$12,864 (\$10,544–\$15,183) for patients ≥ 1 year; mean readmission costs for patients with sequelae (95% CI): \$935 (\$248–\$1621)	No	Mean LOS during acute admissions in days (95% CI): 9.6 (7.1–13.6) for all patients, 16.5 (10.0–27.3) for patients with sequelae, 5.3 (4.7–6.0) for patients without sequelae, 11.3 (7.6–17.3) for MenB patients, 5.5 (4.6–7.0) for non-MenB patients, 12.5 (7.8–21.6) for patients < 1 year, 8.4 (5.9–13.6) for patients ≥ 1 year; mean readmission LOS in days (95% CI): 4.8 (0.7–10.6) for patients with sequelae	Mean LOS during acute admissions in days (95% CI): 7.2 (6.1–8.4) for all patients, 14.3 (13.3–15.3) for patients with sequelae, 5.2 (4.9–5.6) for patients without sequelae, 10.3 (9.1–11.6) for MenB patients, 5.3 (4.7–6.0) for non-MenB patients, 10.1 (8.8–11.4) for patients < 1 year, 8.5 (7.4–9.6) for patients ≥ 1 year; mean readmission LOS in days (95% CI): 1.1 (0.2–2.1) for patients with sequelae	No

CI confidence interval, IMD invasive meningococcal disease, IRR incidence rate ratio, LOS length of hospital stay, NA, SD standard deviation

Table 4 Summary of included studies reporting healthcare costs and resource utilization during outbreaks

References	Cost items and type of resource	Unadjusted costs and resource utilization	Incremental costs
Constenla et al. [37]	Personnel, office supplies, gasoline consumption, chemoprophylaxis, and vaccines	Colombia: total cost of investigation and outbreak management: I\$1239 (I\$207 per notified case); total cost of disease surveillance: I\$6634 Brazil: total cost of investigation and outbreak management: I\$46,728 (I\$15,576 per notified case), total cost of disease surveillance: I\$9050	No
Letouze et al. [44]	Time and cost attributed to staffing, microbiology, pharmacy, and media liaison	Total cost of managing an outbreak (two cases): I\$8286, total cost of managing a single case: I\$471	I\$7815
Pinzon-Redondo et al. [47]	Direct treatment costs and costs associated with outbreak control including personnel costs, measured in time and estimated as a fraction of the salary of each. An outbreak care team consisted of two pediatricians, two nurses, an epidemiologist, and two public health experts.	Mean cost of hospital care per patient: I\$1629 (median: I\$1332); total cost of the disease response phase: I\$1216; total cost of disease surveillance: I\$6511	No

amputation, skin scarring, or neurological disabilities [1, 2, 5]. However, most patients were only followed up until discharge, and costs for other healthcare services such as rehabilitation associated with long-term care were not included. Studies in USA followed patients up to 12 months post-discharge [39, 43] and one study in Australia assessed readmission costs in one tertiary pediatric hospital [49]. Including costs relevant to care and clinical management of long-term sequelae may lead to substantially higher cost estimates. A few case studies show that the discounted lifetime cost associated with severe long-term sequelae could be more than €1 million. However, those severe IMD cases were developed on the basis of expert opinions and interviews with patients and their families [50–52]. Future studies are warranted to investigate the longer term financial burden imposed on the healthcare system, patients, their families, and society as well as the negative effect on economically meaningful health outcomes (e.g., quality of life) [53, 54]. The cost and quality of life are key inputs into health economic evaluation, and therefore reliable data on the costs of long-term care would be valuable in reducing parameter uncertainty.

Undertaking studies to follow patients with IMD over a long period of time (e.g., lifetime) could be time and resource consuming. It might be problematic to link different administrative, costing, and clinical databases, as researchers would need to follow ethics, privacy, and legal guidelines and fulfill local and national requirements. Because the incidence rate of IMD peaks in infants [55], those infant survivors with neurological sequelae and motor deficits would need multiple hospital readmissions, special education, and long-term carers. The time frame of follow-up is a critical point to consider. For example, following adult patients until their conditions stabilize may

only take 2 years. It may take at least 3–5 years to confirm diagnoses of permanent neurological and psychological sequelae in infant survivors. Given the previous literature indicating that around 20–40% of IMD survivors had multiple sequelae following IMD [1, 56], determining the long-term effect of each single sequela separately could be very difficult. The cost associated with individual sequela has been used to develop decision analytical models to assess the cost effectiveness of meningococcal vaccines. Those parameters were determined mainly on the basis of data collected for similar medical conditions, assumptions, or expert opinions [42, 48, 57, 58].

The impact of the disease on individuals and the community has been widely discussed and considered substantial [19, 20], but we have not found any studies reporting data associated with direct non-healthcare costs and indirect costs. The financial burden of the disease estimated in our review was relatively conservative, as third-party payers were the only perspective taken by the included studies. The measurement of reduced employment, absenteeism, presenteeism, and productivity loss associated with informal carers is controversial [59]. In a small number of cost-effectiveness studies taking the societal perspective, the productivity costs were based on assumptions or average national employment data [57, 58, 60].

Our review found that around one third of included studies reported costing results by serogroup [37, 42, 44, 47, 49]. One study compared serogroup B with non-B and reported serogroup B disease was likely to result in the highest costs to the healthcare system in pediatric patients [49]. Clinical literature indicated serogroup C disease was associated with high rates of morbidity and mortality [1, 61]. The serogroup may be an important

factor in predicting the disease severity and hence healthcare expenditures. Cost-of-illness analyses should reflect the epidemiology of the disease and variations in serogroup distribution in relation to time period and geographical region. Serogroup comparison may be necessary to consider in COI analyses to support cost-effectiveness evaluations assessing vaccines against certain serogroups. Because of the limited number of COI studies examining the effect of serogroups on healthcare costs, some cost-effectiveness studies used the average acute admission cost for all IMD cases derived from International Classification of Diseases codes [48, 62]. Several studies estimated the average acute hospitalization cost based on Diagnosis Related Group costs associated with meningococcal diagnosis [57, 58].

Although the new MenB vaccines are protein based, the preliminary results obtained from studies evaluating the impact of meningococcal vaccines on disease carriage prevalence show that MenB vaccines could potentially offer a certain level of protection against non-B serogroup disease [63]. All MenB vaccines are licensed to provide protection against serogroup B disease only. Serogroup-specific COI analyses may still be warranted to provide useful information on disease burden for cost-effectiveness evaluations. Pentavalent vaccines that protect against five serogroups (A, B, C, W, and Y) causing the majority of IMD are currently in phase III clinical trials. It may be less important to compare and evaluate healthcare resource use by serogroup in a decade.

Invasive meningococcal disease has become uncommon especially in industrialized countries, which may be owing to vaccine pressure, a reduction in smoking, or natural fluctuations of disease incidence [55]. However, outbreaks of IMD continue to occur in schools and universities [64, 65]. Surveillance networks have closely monitored capsule switching and capsule replacement after implementing meningococcal vaccination programs. The impact of the new protein-based MenB vaccines on clearing carriage and interrupting transmission in adolescents remains unclear. It is too early to envisage eradication of the meningococcus bacteria at the current stage, when most developing countries have not implemented meningococcal vaccine programs because of the high costs of vaccines [66]. Although inclusion of the MenB vaccine on the government-funded National Immunisation Program was rejected by the Pharmaceutical Benefits Advisory Committee in Australia, the Australian Technical Advisory Group on Immunisation provided clinical advice to the Pharmaceutical Benefits Advisory Committee and recommended routine MenB vaccination of infants, young children, and adolescents owing to their higher risk of MenB infection [11, 67]. The COI analyses would still be required to inform a cost-effectiveness review of a new submission

or resubmission to national decision-making bodies for publicly funding new meningococcal vaccines. However, we acknowledge that the evaluation of the true costs of IMD may be more challenging in the future because of a reduced number of patients infected with IMD.

The incremental cost-effectiveness ratios derived from the estimate of costs and quality-adjusted life-years are one of the key inputs to inform public funding decisions in countries such as the UK and Australia. An evaluation of IMD vaccines by national funding bodies in Australia and the UK found that the results of economic evaluations of meningococcal prevention strategies were, among others, highly sensitive to herd immunity and vaccine effectiveness [12, 15]. After considering new evidence in 2014, the JCVI recommended the MenB vaccine for inclusion on the UK national immunization program with a reduced dose schedule at a very low price of £7 per dose based on the revised analysis [16]. Including litigation costs associated with the disease, updating cost data relevant to long-term care, and using a quality-of-life adjustment factor affected the outcome of a cost-effectiveness analysis in the UK [15]. With very limited COI analyses conducted for this severe but uncommon disease, there may be a risk of underestimating the true disease burden. The results of model-based evaluations are subject to a significant level of parameter uncertainty as emphasized by the Global Meningococcal Initiative [68]. Because of considerable uncertainty around the duration of protection against IMD and potential for reduction in the carriage in adolescents, the JCVI rejected the inclusion of the routine MenB vaccine schedule in adolescents. If the true value of COI is ultimately shown to be high enough, for example, considering all important direct and societal costs, it may be argued that this could potentially offset the significance of indirect protective effects/herd immunity that play an important role in determining the cost effectiveness of new meningococcal vaccine programs.

Therefore, comprehensive COI analyses could provide important inputs into economic evaluations of meningococcal vaccines to better inform public funding decisions. It is worth noting that individuals, charity organizations, and clinicians strongly criticized the JCVI's initial rejection and called for re-evaluation of the vaccine program. Subsequently, the JCVI reviewed and revised the analysis that included more favorable assumptions, optimized parameters, and additional costs associated with the disease, thereby amending its interim position [69]. Economic evidence is only one of several inputs into decision making. Guidelines developed by decision-making bodies in countries such as Australia and Canada recommend considering less-readily quantifiable factors for health technology funding decisions [70, 71]. In Australia, for example, national funding bodies consider factors such as

severity and rapid onset of the condition under study, the age at which a person with the condition might die, and rarity of the condition. Such societal values are all relevant to IMD and hence should be considered in evaluating IMD-related vaccines. However, as reported by Drew et al., there is a lack of transparency and consistency in defining and integrating these values into decision making [72].

The quality and methodologies varied significantly between studies. Although we converted costs from original studies to international dollars, extremely high heterogeneity including differences in the treated population, study design, cost items, or data analysis hinders direct comparison between studies, which may also explain the conflicting results of inpatient costs and healthcare resource use in infants. The included studies used insurance claims, hospital charges, or payments to estimate costs that may not represent the same 'market value' between studies. Only four out of 14 studies reported adjusted mean values using a regression model to adjust for confounding factors including sociodemographic characteristics, disease outcomes, comorbidities, and/or medical history. Differences between unadjusted and adjusted mean values were apparent within the same study, reflecting the importance of consideration of potential confounders in any analyses.

It is of concern that overlooking the nature of highly skewed costing data and not using any appropriate statistical models to deal with skewness and adjusting for potential confounders could lead to biased results [18, 26, 73]. Among those studies presenting only unadjusted results, four studies reported average costs and/or LOS without any variability measures. Incremental costs are commonly recommended for health economic analyses and have been frequently reported in the COI studies of other diseases [26, 28, 74]. The incremental costs were only reported in one included study through a comparison of patients with IMD with matched controls.

We understand various methodologies are used to generate estimates in the COI studies to serve different purposes [75]. However, this variation in study conduct may also reflect a lack of guidelines to standardize COI study designs and methodologies [76]. A review of COI studies highlighted the need for standardized methods of cost calculation, mathematical modeling, choice of cost components, disease classification, and selection of study perspective [77]. The findings of COI studies are often used to support funding decisions and attract public attention. Developing and implementing best-practice recommendations will improve the comparability and generalizability of the costing studies.

As some studies enrolled patients with meningitis caused by a range of bacteria, including *Haemophilus influenzae* type B, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, we were unable to separate the costs

for patients with meningococcal meningitis from those with other bacterial meningitis. We excluded studies describing the financial burden of meningitis during epidemics of serogroup A meningococcal disease in the meningitis belt of sub-Saharan Africa because those studies did not report costs associated with meningococcal meningitis specifically. Because the authors' first language is English and not all languages were included, there may be important studies not included in this review, resulting in regional or English-language bias.

5 Conclusions

Despite the variability in estimates of medical costs and hospital resource use, all included studies concluded IMD resulted in substantial costs to healthcare systems or third-party payers. The public concerns and fears caused by IMD have been frequently reported. However, few have implemented appropriate research methods, for example, using micro-costing methodology and collecting primary data prospectively from the societal perspective [22], to investigate the true costs of the disease. This systematic review provides important information for the selection of an appropriate unit cost for future cost-effectiveness studies, identifying the financial burden of the disease in prioritizing healthcare policies, and estimating potential cost savings accrued from the introduction of new vaccines, and also reinforces the need to standardize methodology and improve the quality of the COI studies.

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Author contributions BW, HM, LG, and HA conceived and designed the study. BW conducted the database searches, extracted, analyzed, and interpreted the data, performed a quality assessment, and produced the draft of the manuscript. RS extracted data and performed a quality assessment. HM, RS, LG, and HA contributed to, reviewed, and edited the manuscript. HM acts as the overall guarantor.

Data Availability Statement The full dataset including data extracted from the full-text review and quality assessment results that support the findings of this study are available from the corresponding author upon request. The authors declare that all other data supporting the findings of this study are available within the article and its supplementary information files.

Compliance with Ethical Standards

Conflict of interest 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. Bing Wang, Renee Santoreneos, Hossein Afzali, and Lynne Giles

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