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ORIGINAL RESEARCH

Cost of Illness Analysis of Invasive Meningococcal Disease Caused by *Neisseria Meningitidis* Serogroup B in the Netherlands—a Holistic Approach

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ABSTRACT

Introduction: Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* is a rapidly progressing, rare disease that often presents as meningitis or sepsis. It mostly affects infants and adolescents, with high fatality rates or long-term sequelae. In the Netherlands, serogroup B (MenB) is most prevalent. We aimed to estimate the economic burden of MenB-related IMD between 2015 and 2019, including direct and indirect medical costs from short- and long-term sequelae, from a societal perspective.

Methods: IMD incidence was based on laboratory-based case numbers from the Netherlands Reference Laboratory for Bacterial Meningitis (Amsterdam UMC, Amsterdam, the Netherlands); there were 74 MenB cases on average per

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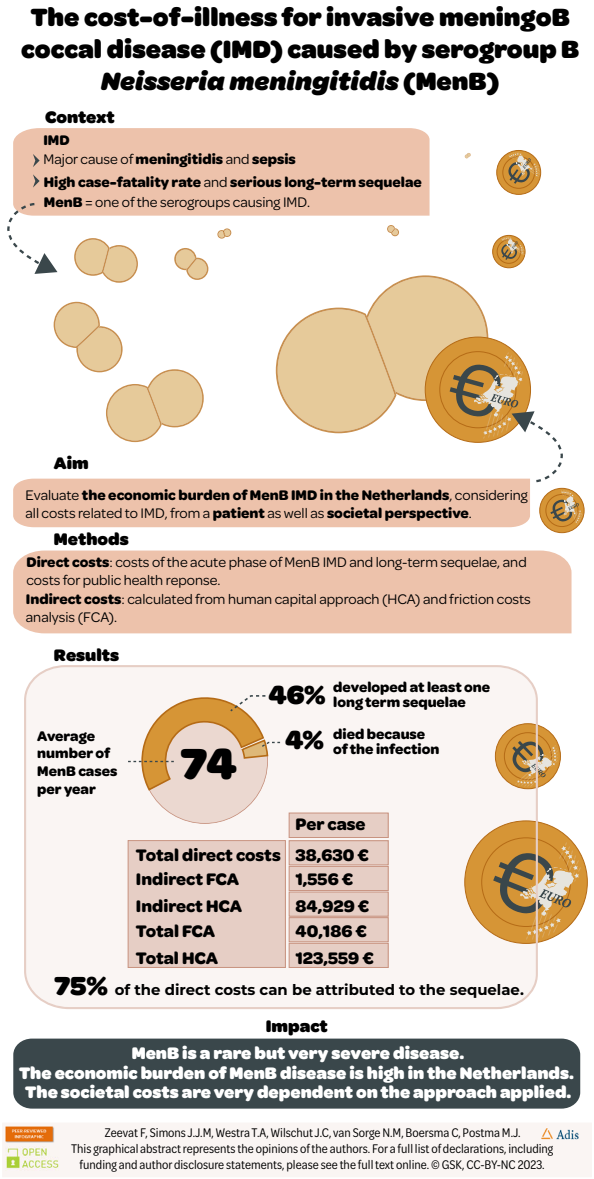
year in the study period 2015–2019. Case-fatality rate (3.8%) and percentage of patients discharged with sequelae (46%) were derived from literature. Direct costs included treatment costs of the acute phase, long-term sequelae, and public health response. Indirect costs were calculated using the human capital (HCA) and friction costs (FCA) approaches, in which productivity losses were estimated for patients and parents during the acute and sequelae phases. Costs were discounted by 4% yearly.

Results: Estimated costs due to MenB IMD in an annual cohort were €3,094,199 with FCA and €9,480,764 with HCA. Direct costs amounted to €2,974,996, of which 75.2% were related to sequelae. Indirect costs related to sequelae were €52,532 with FCA and €5,220,398 with HCA.

Conclusion: Our analysis reflects the high economic burden of MenB-related IMD in the Netherlands. Sequelae costs represent a high proportion of the total costs. Societal costs were dependent on the applied approach (FCA or HCA).

Graphical Plain Language Summary:



Keywords: Cost of illness; Direct and indirect costs; Economic burden; Invasive meningococcal disease; Netherlands; Serogroup B meningococcal disease; Short- and long-term sequelae

Key Summary Points

Why carry out this study?

Invasive meningococcal disease (IMD) caused by serogroup B (MenB-related IMD) is a serious disease that may cause long-term sequelae and has a high economic burden.

Previous studies often considered a small set of sequelae only, which could lead to underestimation of the actual IMD-related health impact and costs.

This study estimates MenB-related IMD costs in the Netherlands between 2015 and 2019, including all sequelae costs.

What was learned from the study?

In the Netherlands, almost half of patients with MenB IMD will experience sequelae, ranging from scars, hearing and/or vision loss, limb amputation, to neurological and mental disorders.

Costs due to sequelae, including long-term therapy, represent more than two-thirds of total costs.

Indirect costs, including productivity losses, are highly dependent on the applied approach, i.e., human-capital versus friction-cost approach.

DIGITAL FEATURES

This article is published with digital features, including a graphical plain language summary, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24746118.

INTRODUCTION

Invasive meningococcal disease (IMD), caused by the bacterium *Neisseria meningitidis*, often presents as acute meningitis or sepsis, which are both characterized by a high mortality rate or serious long-term sequelae [1, 2]. IMD incidence is highly age-specific, with peaks among infants and children aged 5 years or younger, adolescents, and adults 65 years or older [1, 3].

As shown in the last surveillance report of the European Centre for Disease Prevention and Control (ECDC), the incidence of IMD in the Netherlands increased from approximately 108 cases (0.6 cases per 100,000 inhabitants) in 2013 to 198 cases (1.2 cases per 100,000 inhabitants) in 2017 [4, 5], due to an epidemic outbreak of almost exclusively *Neisseria meningitidis* serogroup W. Therefore, in 2018, the Dutch Ministry of Health incorporated vaccination against the serogroups A, C, W, and Y in the National Immunization Program (NIP) for both young children and adolescents, replacing the existing vaccine against serogroup C. However, during the same period, the majority of IMD-confirmed cases were attributable to serogroup B (MenB) (75% in 2013 and 40.5% in 2017) [6].

Despite the severity of MenB IMD, the Dutch Health Council advised the Dutch Ministry of Health to not implement MenB vaccination in the NIP in two subsequent advices, the latest dating from 2022 [7, 8]. The main reasons for this advice were (i) uncertainty on MenB vaccine effectiveness and the duration of vaccine-induced protection, (ii) concerns about the risk of high fever following concomitant administration of MenB vaccine with other vaccines, (iii) estimated unfavorable cost-effectiveness of MenB vaccination, driven by the relatively low incidence and high price of the vaccine, and (iv) uncertainty about the ability of the vaccine to induce herd protection [7, 8]. However, the Health Council also indicated to reconsider MenB vaccination when more data on vaccine effectiveness would become available [7].

With newly published real-world data from Quebec, South Australia, Portugal, the United Kingdom (UK), and Italy, it is expected that the efficacy and safety concerns of the Dutch

Health Council will be adequately covered [9–11]. However, an updated cost-effectiveness analysis is thus far not available. To update the existing economical model, additional data are required on epidemiology, costs, and health impact of MenB-related IMD. The economical evaluation of the MenB vaccine performed in 2018 was based on a Dutch cost-effectiveness model published almost a decade ago [12]. This model did not include all costs related to long-term sequelae, thereby underestimating the real economic burden. Recent investigations in the Netherlands have provided more insights into the long-term sequelae of IMD [13].

Here, we aim to estimate the economic burden, or cost of illness (CoI), of MenB-related IMD in the Netherlands, considering direct and indirect medical costs related to short- and long-term sequelae from a societal perspective.

METHODS

A CoI model was used to calculate the total economic burden of MenB-related IMD in the Netherlands for a single annual cohort over a life-time horizon. The model included both short- and long-term sequelae and considered direct and indirect costs. Average costs incurred by one MenB IMD case over a lifetime horizon were also estimated. An existing model, previously used to estimate the economic burden of MenB-related IMD in Germany [14], was adapted to the Dutch setting. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Cost data were retrieved from a literature search. When Dutch data were not available, studies from other countries were used and adapted using transferability methods (i.e., purchasing power parity) [9]. Moreover, experts validated and further completed the overview of medical costs for MenB-related IMD and sequelae. Costs were assessed from a third-party payer (TPP) perspective, which includes direct medical costs and a broader societal perspective including productivity losses. Costs were adjusted to the reference year 2021, using the harmonized Consumer Price Index (CPI) for the Netherlands published by Statistics Netherlands (see Appendix I, Table S1) [15]. As recommended for the Netherlands, future costs were discounted annually with 4% [16].

Population data for 2019 were collected from the Statistics Netherlands by age (0–100 years) [17]. MenB-related IMD incidence data were obtained from the Netherlands Reference Laboratory for Bacterial Meningitis for individuals 0–100 years of age (see Table 1) for the years 2015–2019. The number of MenB-related IMD cases was expressed as incidence per 100,000 inhabitants by age. The case-fatality rate for the MenB serogroup was extracted from a recent publication by Loenenbach et al. [18], and derived per age group. Sequelae probabilities in IMD survivors were obtained from the previously published model in Germany, in which the probabilities were derived from a systematic literature review [13, 14]. Costs and health impacts were calculated for the following age groups: " < 1 year", "1–4 years", "5–9 years", until the age group "90 years and older".

Model Structure

Figure 1 shows the model structure. It includes costs of the IMD acute phase (i.e., costs for inpatient stay, productivity losses, and public health response), costs for the survivors with sequelae (i.e., costs for direct medical care, rehabilitation, special education, long-term care), and productivity losses. Co-payments of inpatient and outpatient visits were not included.

Cost Related to the IMD Acute Phase

Direct medical costs of the acute phase of MenB-related IMD are presented in the Appendix, Table S2 with the associated parameters in Appendix I, Table S3. Every patient with IMD was assumed to visit a general practitioner (GP) before being hospitalized. Direct medical costs related to GP visit and hospitalization were collected from the Dutch Costing Manual [16]. The median duration of hospitalization and admission to the intensive care unit (ICU) was

Table 1 Incidence and fatality rate of MenB-related invasive meningococcal disease per age group and probability of sequelae in survivors

Parameter	Base case	Range/SD	Distribution	Source
Incidence (per 100,000 cases)				
Age group (years)				
< 1	5.699	3.015–7.750	Poisson	National Reference Laboratory for Bacterial Meningitis [22]
1–4	2.283	1.302–3.488	Poisson	
5–9	0.397	0.000–0.993	Poisson	
10–14	0.270	0.000–0.818	Poisson	
15–19	1.210	0.288–2.271	Poisson	
20–29	0.393	0.000–0.963	Poisson	
30–49	0.101	0.000–0.366	Poisson	
50–64	0.209	0.028–0.571	Poisson	
Above 65	0.325	0.000–1.191	Poisson	
Case fatality rate				
Age group (years)				
0–19	3.80%	0.008	β	Loenenbach et al. [18]
20–64	4.20%	0.008	β	
≥ 65	2.90%	0.006	β	
Sequelae probability				
Physical sequelae				
Amputation with severe disability	1.26%	0.012	β	Viner et al. [41]
Skin scarring	6.39%	0.060	β	Bettinger et al. [42]
Renal disease	2.05%	0.020	β	
Neurological sequelae				
Blindness/severe visual impairment	0.42%	0.004	β	Viner et al. [41]
Hearing loss—severe/profound bilateral/ deafness (cochlear implant)	2.45%	0.024	β	
Hearing loss—moderate bilateral	3.80%	0.037	β	
Hearing loss—unilateral/ hearing impairment	5.21%	0.049	β	
Epilepsy/seizures	1.78%	0.017	β	
Severe neurological disorders	1.02%	0.010	β	Bettinger et al. [42]
Speech or communication problems	3.56%	0.034	β	Viner et al. [41]
Mental retardation/low IQ	0.50%	0.005	β	

Table 1 continued

Parameter	Base case	Range/SD	Distribution	Source
Motor deficits	1.53%	0.015	β	Bettinger et al. [42]
Psychological and behavioral sequelae				
Depression	0.00%	–	β	Viner et al. [41]
Anxiety	2.25%	0.022	β	
Separation anxiety	5.96%	0.056	β	
ADHD	9.66%	0.087	β	

Abbreviations: *ADHD* attention deficit hyperactivity disorder, *IQ* intelligence quotient, *MenB Neisseria meningitidis* serogroup B, *SD* standard deviation

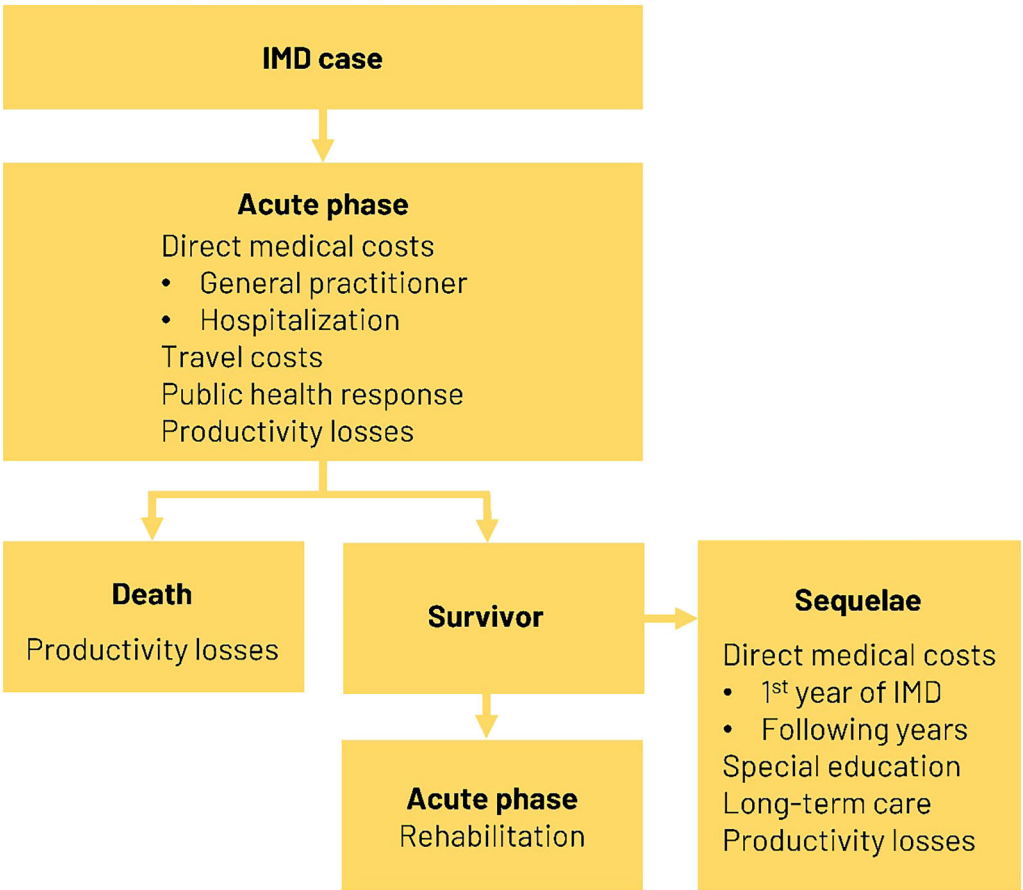


Fig. 1 Schematic flowchart of the cost calculation for each case of invasive meningococcal disease. Abbreviation: *IMD* invasive meningococcal disease

Table 2 Epidemiology and costs (direct and indirect) of the acute phase and sequelae of invasive meningococcal disease per age group

Age group	Epidemiology		IMD acute phase					Combined Sequelae					
	Cases	Deaths	Direct costs	Indirect costs				Cases	Direct costs	Indirect costs			
				Productivity loss						Productivity loss†			
				Acute phase		Premature deaths				Patients		Parents	
				HCA	*FCA*	*HCA*	*FCA*			HCA	FCA	HCA	FCA
< 1	10	0.4	€107,148	€9340	€9340	€119,728	€–	4.42	€369,879	€373,196	€–	€504,810	€7551
1–4	16	0.6	€141,580	€12,578	€12,578	€212,664	€–	7.27	€609,186	€662,881	€–	€786,723	€12,429
5–9	4	0.1	€29,752	€3225	€3225	€58,021	€–	1.66	€148,480	€180,855	€–	€146,999	€3,585
10–14	3	0.1	€23,294	€2620	€2620	€53,096	€–	1.20	€96,096	€165,501	€–	€55,910	€2512
15–19	13	0.5	€114,663	€9218	€9218	€305,014	€920	5.89	€415,794	€950,739	€2868	€46,352	€6218
20–24	6	0.2	€55,475	€1676	€1676	€171,785	€461	2.66	€90,424	€482,450	€1294	€–	€–
25–29	3	0.1	€26,781	€3220	€3220	€90,473	€886	1.28	€82,777	€254,089	€2489	€–	€–
30–34	1	0.0	€5739	€690	€690	€18,804	€190	0.27	€17,121	€52,809	€533	€–	€–
35–39	1	0.0	€9565	€1456	€1456	€30,121	€400	0.46	€27,981	€84,595	€1123	€–	€–
40–44	1	0.1	€13,391	€2038	€2038	€37,134	€559	0.64	€37,520	€104,290	€1569	€–	€–
45–49	1	0.1	€13,391	€2171	€2171	€32,219	€596	0.64	€35,998	€90,486	€1673	€–	€–
50–54	2	0.1	€22,955	€3722	€3722	€40,726	€1024	1.10	€57,846	€114,378	€2877	€–	€–
55–59	4	0.2	€36,346	€4623	€4623	€43,308	€1270	1.74	€85,584	€121,629	€3567	€–	€–
60–64	1	0.1	€13,391	€1703	€1703	€7808	€467	0.64	€28,813	€21,929	€1310	€–	€–
65–69	3	0.1	€36,021	€696	€696	€3328	€114	1.21	€48,711	€13,720	€469	€–	€–
70–74	3	0.1	€36,021	€696	€696	€1469	€113	1.21	€42,974	€6058	€465	€–	€–
75–79	1	0.0	€19,396	€–	€–	€–	€–	0.65	€18,355	€–	€–	€–	€–
80–84	1	0.0	€13,854	€–	€–	€–	€–	0.46	€11,611	€–	€–	€–	€–
85–89	1	0.0	€11,083	€–	€–	€–	€–	0.37	€7324	€–	€–	€–	€–

Table 2 continued

Age group	Epidemiology		IMD acute phase						Combined Sequelae					
	Cases	Deaths	Direct costs	Indirect costs					Cases	Direct costs	Indirect costs			
				Productivity loss							Productivity loss†			
				Acute phase		Premature deaths					Patients		Parents	
				HCA	*FCA*	*HCA*	*FCA*				HCA	FCA	HCA	FCA
90–100	1	0.0	€8312	€–	€–	€–	€–		0.28	€4365	€–	€–	€–	€–
Total	**74**	**2.8**	**€738,156**	**€59,671**	**€57,644**	**€1,225,699**	**€6999**		**34.1**	**€2,236,841**	**€3,679,604**	**€20,238**	**€1,540,794**	**€32,295**

Abbreviations: *IMD* invasive meningococcal disease, *FCA* friction-cost approach, *HCA* human-capital approach
†Total indirect costs due to productivity loss for patients and parents together were €5,043,056 for HCA and €50,748 for FCA

derived from Stoof et al. [13]. It was assumed that 36.1% of the MenB-related IMD cases needed care in ICU [18]. The probability of developing sequelae after the acute IMD phase is reported in Table 1. For IMD survivors without sequelae, only one pediatrician/neurologist check-up visit was assumed.

Public health response costs following an IMD case were included as part of the direct costs of the acute phase and were based on Welte et al. [19]. They comprised costs for post-exposure prophylaxis treatment of close contacts (on average two children and three adults) with rifampicin or ceftriaxone, as well as pharmacy and GP visits and reports to other public parties [16]. No costs for local public health authorities were included.

Travel costs were only included in the costs of acute IMD. Travel costs to the GP and hospital were estimated using the travel distance and travel cost per kilometer following the Dutch Costing Manual [16].

Direct Medical Costs Related to Sequelae

Direct medical costs of the sequelae were estimated as the costs for the first year (i.e., the year of occurrence of the sequelae) plus the costs for the second year onwards (i.e., the following years after occurrence of the sequelae) of an IMD case (see Appendix, Table S3). Direct medical treatment costs were estimated for each sequelae using published cost estimates and costing approaches validated by Dutch clinical and medical experts. The direct medical cost estimates per sequela are described in the Appendix I, Table S4. As mentioned, travel costs were not considered for sequelae.

Education Costs

IMD survivors who develop long-term sequelae may also have special educational needs because of their physical and neurological conditions. Special education costs were taken into account at 50% for IMD survivors with severe hearing loss (i.e., with cochlear implant), severe neurological disorders, mental retardation/low intelligence quotient (IQ), motor deficits, limb

Table 3 Number of cases and costs (direct and indirect) by sequelae type.

	Number of cases	Direct cost	Indirect costs			
			Patients		Parents	
			HCA	FCA	HCA	FCA
Hearing loss						
Cochlear implant	1.74	€634,513	€340,463	€1873	€348,020	€7373
Moderate bilateral	2.71	€19,939	€306,618	€1686	€53,979	€1144
Moderate unilateral	3.71	€15,211	€451,529	€2483	€74,007	€1568
Neurological disability						
Severe neurological	0.73	€200,851	€141,744	€780	€144,890	€3070
Mental retardation/low IQ	0.36	€153,001	€27,942	€154	€71,024	€1505
Speech problems	2.53	€10,013	€287,253	€1580	€50,569	€1071
Motor deficits	1.09	€302,351	€212,615	€1169	€217,335	€4605
Limb amputation	0.90	€595,745	€175,095	€963	€178,981	€3792
Epilepsy/seizures	1.27	€816	–	–		–
Skin scarring	4.55	€5713	€305,542	€1680	€90,769	€1923
Renal disease	1.46	€4298	€19,911	€110	€1820	€39
Blindness	0.30	€91,372	€58,365	€321	€59,660	€1264
Psychological impairments						
ADHD	6.88	€195,402	€1,097,011	€6034	€137,219	€2907
Anxiety	1.60	€6459	€255,515	€1405	€31,961	€677
Separation anxiety	4.24	€1157	–	–	€80,556	€1357
Total	**34.07**	**€2,236,841**	**€3,679,604**	**€20,238**	**€1,540,794**	**€32,295**

Abbreviations: *ADHD* attention deficit hyperactivity disorder, *FCA* friction-cost approach, *HCA* human-capital approach, *IQ* intelligence quotient

Table 4 Economic burden (direct and indirect costs) from a societal perspective over a lifetime horizon

	Total IMD (annual) cases ($n = 74$)			Per IMD case		
	Base case	Lower bound[a]	Upper bound[a]	Base case	Lower bound[a]	Upper bound[a]
Direct costs	€2,974,996	€1,559,593	€5,291,834	€40,203	€21,076	€71,551
Indirect costs						
FCA	€119,202	€90,836	€162,563	€1611	€1228	€2197
HCA	€6,505,768	€3,554,964	€11,829,715	€87,916	€48,040	€159,861
Total costs						
FCA	€3,094,199	€1,660,649	€5,460,473	€41,813	€22,441	€73,790
HCA	€9,480,764	€5,355,859	€15,998,842	€128,118	€72,376	€216,201

Abbreviations: *IMD* invasive meningococcal disease, *FCA* friction-cost approach, *HCA* human-capital approach
[a]Lower and upper bounds based on 2.5% and 97.5% probabilistic sensitivity outcomes

amputation, blindness/severe visual impairment, and attention deficit hyperactivity disorder (ADHD) [12, 20].

Special education costs were assumed annually until the end of schooling age (i.e., 18 years) (detailed in Appendix I, Table S5). Education costs were dependent on age (primary or secondary education) and category of special education needs (i.e., children with a physical or intellectual disability, or serious learning difficulties) [21, 22]. Costs for deafness were assumed to be the same as costs for blindness [23]. Educational costs for ADHD were derived from Van der Kolk et al. [24]. Costs for issuing and review of the special education needs assessment statement were not considered in this analysis.

Long-Term Care Costs

An overview and description of the long-term sequelae are presented in Table S4. Long-term care costs were only considered for IMD survivors with severe long-term sequelae (i.e., hearing loss with a cochlear implant, severe neurological disorders, motor deficits, mental retardation/low IQ, limb amputation with severe disability, and blindness/severe visual impairment). Based on previous studies, it was assumed that 25% of patients with severe sequelae need lifetime care in institutes for mentally and physically disabled [20, 25].

Productivity Losses

Productivity losses due to the IMD acute phase were calculated for (i) the patient or his/her parents during hospitalization, (ii) premature patient mortality, and (iii) survivors with sequelae.

Productivity losses were calculated using the friction-costs approach (FCA) and the human-capital approach (HCA) [26–28]. FCA assumes that a person will be replaced by another member of the active workforce, limiting productivity loss to the time required to hire and train his/her replacement, i.e., the friction period. On the other hand, HCA values the entire productivity loss incurred by an individual's premature death or morbidity due to long-term sequelae. The average yearly income was age-dependent and derived from Statistics Netherlands [29]. The friction period was derived from the Dutch Costing Manual and amounted to 85 days [16].

For hospitalized patients under 15 years of age, productivity losses were calculated for one of the parents. Costs were estimated by multiplying the age-dependent length of stay in the hospital with the age-specific employment wage per day [13, 29]. The average age of mothers at the birth of their first child (i.e., 29.9 years) was used to estimate the age-specific wage per day of the parent(s) [30]. There was no difference in

costs using the HCA or the FCA as the duration of the acute phase was below the friction period.

Costs related to premature mortality were calculated using friction period, duration of job, age-specific wage per day, and life expectancy at the time of death. The numbers of days of productivity lost are presented in Appendix I, Table S6 [16, 29]. No productivity losses have been included for children who die under the age of 15 years.

Costs for reduced productivity among patients and their parents were estimated for each survivor with sequelae. Productivity losses due to epilepsy and separation anxiety were not included, as separation anxiety is seen up to 12 years of age and epilepsy recovery was assumed after 2 years of treatment. For patients under 18 years of age with severe sequelae, one of the parents was assumed to stay at home to take care of their disabled child [14, 31], for the other sequelae, a productivity loss of 10% for one of the parents was assumed. Patients were assumed to have reduced labor participation throughout life, because of their severe disability (detailed in Appendix I, Table S7). The degree of work impairment (absenteeism) was used to calculate the indirect costs. Productivity losses for mental disorders, hearing, vision, and mobility disabilities were obtained from Dutch specific public health data [32]. Due to the lack of data, productivity losses for the other sequelae were taken from a previous German study [14]. For FCA, the percentage of productivity loss was multiplied with the age-specific wage per day [29, 31].

Sensitivity and Scenario Analysis

A probabilistic sensitivity analysis was conducted to assess the impact of uncertainty in the input parameters of the total costs from a TPP perspective. The distribution was dependent on the relevant parameters (see Table 1, and Appendix I, Tables S2 and S8) and the availability of underlying data. The analysis was performed using 1000 Monte Carlo simulations, independently and randomly varying all input variables over their range at the same time.

A deterministic analysis to test the robustness of the model and identify major drivers of the outcomes was performed, and included the following parameters: IMD cases, case-fatality rate, age at first child, percentage long-term care, and the percentage special education need (see Appendix I, Table S8).

To further explore the variation in the base case, nine scenario analyses were performed: (1)

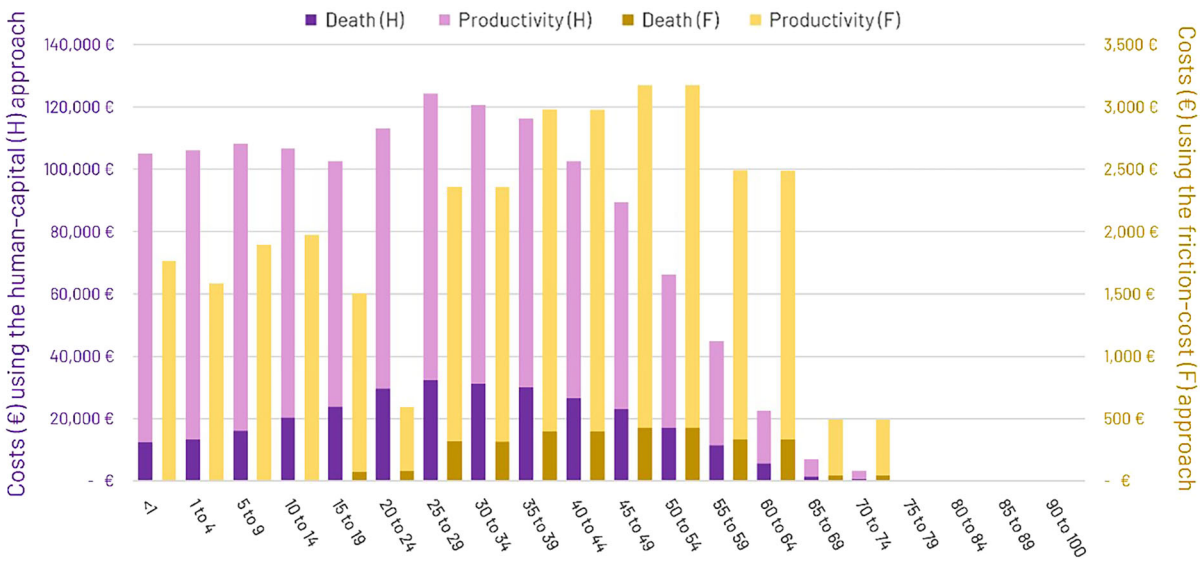


Fig. 2 Comparison of human-capital approach (H) and friction-cost approach (F), with discounted productivity losses per work loss or premature death

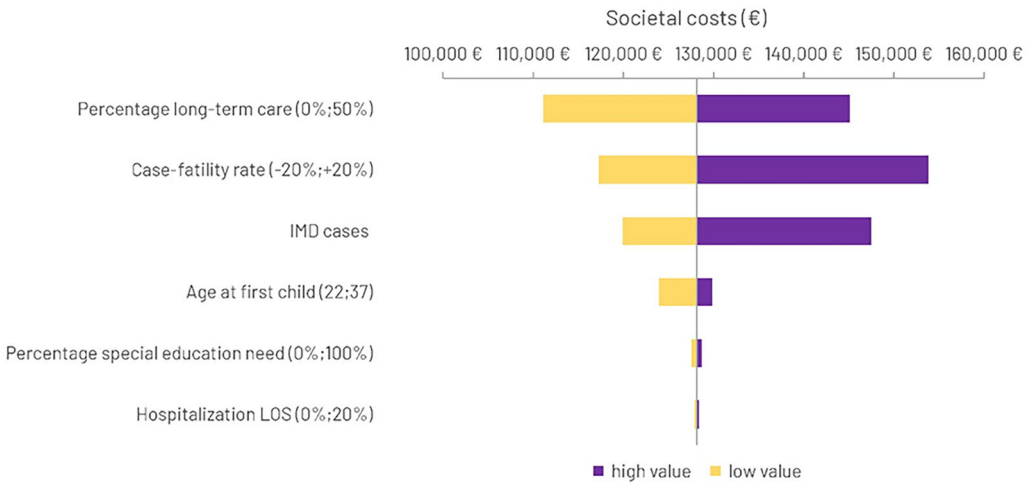


Fig. 3 Tornado diagram of the societal cost per case of invasive meningococcal disease, using the human-capital approach. Notes: The HCA was used for the indirect cost. Lower and upper parameters values are presented in parentheses. Abbreviations: *HCA* human-capital approach, *IMD* invasive meningococcal disease, *LOS* length of stay

Direct medical costs of the sequelae from Scholz et al. [14], (2) direct medical costs of the sequelae from Beck et al. [31]; (3) public health response and outbreak management costs from Scholz et al. [14], (4) productivity losses during hospitalization of the acute phase based on Welte et al. [19], (5) patients with severe sequelae requiring long-term informal care (changing 25% institutional care to 10% informal care), (6) all patients requiring long-term informal care instead of only patients with severe sequelae needing institutional care, (7) exclusion of psychological impairments, (8) no discounting applied, and (9) discounting costs with 1.5%. Detailed scenario analyses are shown in the Appendix I, Tables S9 and S10.

RESULTS

Our model estimated that among 74 MenB-related IMD cases in the Netherlands per year (average of reported cases between 2015 and 2019), 2.8 patients died and 34.1 patients developed sequelae. Thirty-five percent of cases were registered among children below the age of 4 years and 18% among adolescents 15–19 years old (Tables 2, 3, Fig. S1).

As presented in Table 4, the total costs due to MenB-related IMD from a societal perspective amounted to €3,094,199 and €9,480,764 using the FCA and the HCA, respectively (Tables 2, 4).

The estimated direct costs from a TPP perspective were € 2,974,996, of which 75.2% were attributable to sequelae (Table 3, Fig. S2). Direct costs accounted for 96.1% and 31.4% of total costs in the FCA and HCA, respectively.

Total indirect costs were strongly dependent on the chosen approach (see Fig. 2), being estimated at €6,505,768 using the HCA and €119,202 using the FCA. The indirect costs due to the IMD acute phase (which comprised costs due to the acute phase itself plus costs due to premature death) amounted to €1,285,370 using the HCA and to €66,670 using the FCA. This difference is mostly determined by premature death, which had a huge impact when using the HCA, especially amongst patients below the age of 4 years (€332,392), and between 15 and 19 years (€305,014). The indirect costs due to sequelae (which comprised costs for patients and parents) were estimated at €52,532 when using the FCA, and €5,220,398 when using the HCA (a detailed description can be found in Tables 2 and 3 and in Appendix I, Tables S2, S3).

Table 5 Scenario analysis per IMD case

	Total direct costs	Difference base case (%)	Total costs (HCA)	Difference base case (%)
Base case	€40,203		€128,118	
Scenario 1: Scholz et al. [14] direct medical costs	€37,282	− 7%	€125,198	− 2%
Scenario 2: Beck et al. [31] direct medical costs	€37,787	−6%	€125,702	−2%
Scenario 3: public health response and outbreak management costs Scholz et al. [14]	€40,842	2%	€128,758	0%
Scenario 4: productivity losses Welte et al. [19]	€40,203	0%	€127,958	0%
Scenario 5: include long-term informal care (10%) instead of institutionalized care (25%) for patients with severe sequelae	€24,302	−40%	€112,218	−12%
Scenario 6: include long-term informal care instead of institutionalized care for all patient	€28,540	−29%	€116,456	−9%
Scenario 7: exclusion of psychological impairments	€37,478	−7%	€103,742	−19%
Scenario 8: no discounting	€86,778	116%	€315,034	146%
Scenario 9: 1.5% discounting	€59,925	49%	€210,845	65%

Abbreviations: *IMD* invasive meningococcal disease, *HCA* human-capital approach

Sensitivity and Scenario Analysis

Figure 3 summarizes the results of the deterministic sensitivity analysis, while the impact of the nine possible scenarios on the base case is presented in Table 5. Cost estimates remained similar or decreased except for scenarios 8 and 9, where the discount rate was changed to 0% and 1.5%, respectively. Total cost increased by 146% and 65%, respectively, compared with the base case scenario. Scenarios 5 and 6, that include only informal long-term care instead of formal institutional care, reduced the total cost outcomes by up to 12%.

DISCUSSION

MenB-related IMD is relatively rare in the Netherlands; however, it may result in severe long-term sequelae associated with substantial costs. Our model estimated that over the 2015–2019 period, 74 MenB-related IMD cases occurred annually; among these cases, approximately 34 (46%) patients developed sequelae and approximately 3 (3.8%) died. This translated to total costs of €3,094,199 over a lifetime horizon using the FCA, of which 96.1% were direct costs and 3.9% were productivity losses. Total costs amounted to €9,480,764 using the HCA, of which 31.4% were direct costs and 68.6% were productivity losses.

The study period between 2015 and 2019 may not be representative for the past 3 years (2020–2022), as the incidence of MenB decreased by almost 70% due to the national COVID-19 restrictions [33]. Fewer cases obviously lead to lower costs. Nevertheless, the withdrawal of the COVID-19 measurements may well result in an increased number of MenB cases, as was seen in adolescents and young adults in England [34, 35]. While an increase in MenB cases has been observed in the Netherlands after lifting COVID-19 restrictions, numbers are not yet higher than in the pre-COVID-19 period.

The significant difference between the HCA and FCA costs is attributable to the friction period of the FCA, which assumes that patients can be replaced in their jobs after 85 days. Moreover, the FCA assumes no productivity losses for children under 15 years, while the HCA assumes lifelong productivity losses. There is an ongoing discussion about these methods and which method should be used for health economic analyses [26]. The FCA method is more widely accepted since it is more conservative and has been used in a previous cost-effectiveness analysis for vaccines against serogroups A, C, W, and Y [28, 36]. However, with the current unemployment rate, it is not granted that after 85 days a worker can always be replaced. Currently, around 340,000 people are unemployed in the Netherlands, but over 450,000 job offers exist; hence, FCA might underestimate the actual productivity losses meaning that HCA could potentially show more realistic estimates [37, 38].

In our analysis, the total percentage of IMD patients who developed sequelae was 46%, whereas in a Dutch surveillance study a percentage of 29% was reported [13]. However, the surveillance study did not include psychological impairments (i.e., ADHD, anxiety and separation anxiety); therefore, discrepancies between our study and the Dutch surveillance study might be due to methodological differences. This is further supported by a recent systematic literature review focusing on IMD sequelae, which found that more recent studies reported an increased number of sequelae cases and a wider variety of sequelae types compared with older studies [2]. Assuming a sequelae rate of 29% (excluding psychological impairments), costs decreased from €128,118 to €103,742 per IMD case, corresponding to a 19% cost reduction. This difference is due to the high probability of developing ADHD (9.66%) in our base case analysis [14], combined with direct medical costs of ADHD per year (€5113), as well as productivity losses of 38% of a patient with ADHD.

This is the first CoI study in the Netherlands that includes all sequelae caused by MenB-related IMD. Previous analyses only included direct medical costs for severe hearing loss (with a cochlear implant), treatment of scars and amputation, and indirect costs for special education and institutional care [12, 19, 20], clearly representing an underestimation of the impact of IMD in the Netherlands by not taking into account the full burden of physical, psychological, and mental sequelae. The current analysis improves the validity and robustness of these previous studies and may further help decision-makers in future economic evaluations of MenB vaccination in the Netherlands.

At an international level, a similar approach was applied in CoI studies in the UK and in Germany [14, 31]. Direct costs per IMD case were estimated at €54,300 in the German study (using 2015 price levels), compared with €40,203 in the current study (using 2021 price levels). Applying the same incidence and direct medical costs for the sequelae as in the German study (see Scenario 1 of the sensitivity analyses), reduced costs in our study by 7% to €37,282. This difference can be explained by the following conservative assumptions applied to the direct costs estimated per sequelae in the current study: (1) speech problems, communication and occupational therapy consults were assumed to occur only in the first year; (2) epilepsy treatment (i.e., medication and biannual monitoring) was taken into account only for the first 2 years; (3) no costs were assumed for renal disease during the first year, as they were already included in the IMD acute phase costs, only costs involved in chronic kidney disease (assumed to represent 6%) were included; and (4) separation anxiety treatment was only included until the age of 12 years. Although most sequelae costs per case were lower in the Netherlands than in Germany, direct medical costs were higher for neurological disability, limb amputation, blindness, and ADHD due to higher costs per treatment.

The outbreak management cost of Scholz et al. [14] (see Scenario 3 of the sensitivity analyses) slightly increased the direct costs per case (1.6%), reaching €40,842. Compared with the German study, our study used a more conservative approach for the long-term and education costs, because we only included costs for survivors with severe sequelae. As shown in the sensitivity analysis, the costs used per year for

both special education and long-term care were higher (by 29%) in the current analysis.

Our study has several limitations. First, there is a lack of data on the specific costs and use of medical resources for the treatment of IMD sequelae in the Netherlands. The costs of the sequelae that were estimated in this study were not specific costs for an IMD population. Moreover, for some sequelae, Dutch cost data were not available. For these costs, the average of similar studies in Germany and the UK (Scholz et al. [14] and Beck et al. [31], respectively) were used (e.g., severe neurologic disorders and blindness). Based on the sensitivity analyses (scenarios 1 and 2), we considered that these data were not overestimated for the Dutch situation. Potential travel costs were not included for the sequelae, which results in more conservative estimates. The percentage of patients requiring long-term care and special education were retrieved from previous published studies [12, 14, 20, 31]. Data of Scholz et al. [14] were included in the sensitivity analysis (scenario 5), where it was assumed that 10% of all patients with severe sequelae receive informal care instead of 25% (base case) needing long-term institutional care, and this analysis demonstrated a significant impact on the base-case results (40% decrease on direct costs and 12% decrease on indirect costs using the HCA). Regarding special education, no costs could be identified for cases with deafness, and therefore these costs were assumed to be the same as for cases with blindness. Since blind children generally need more guidance and materials for their education, these costs might be overestimated for deaf children. However, our deterministic analysis showed only a small impact on the societal costs per case. In addition, because of the construction of the model, the survivor could experience multiple sequelae, and therefore, special education and long-term costs can be overestimated. This potential overestimation is reduced by applying a 50% and 25% rate for long-term care and special education needs, respectively. Additionally, as a conservative assumption, absenteeism was not included in this study, although the mean number of days of absence is higher among disabled employees (i.e., 31 days per year) than in the general population (i.e., 14 days per year) [39]. Furthermore, the incidence of MenB-related IMD was based on data prior to the COVID-19 pandemic and associated social distancing measures. However, because COVID-19 related restrictions have since been terminated, the impact of these extraordinary measures were not considered in our analysis. Finally, results should be updated in the future as new estimates for disease outcomes become available, such as those published by Middeldorp et al., which were not yet taken into account in the present analysis [40].

Future research should focus on further exploration of the exact costs per sequela related to IMD in the Netherlands. An ongoing trial in the Netherlands, which follows IMD survivors for over 15 years, is likely to provide data for a further improved cost analysis and reveal the entire economic ramifications of the disease [28].

CONCLUSIONS

The current study reflects the high economic burden of MenB-related IMD in the Netherlands. For the first time, all costs related to sequelae were included in the analysis. These costs represent a high proportion of direct and indirect costs. The overall economic burden due to MenB-related IMD leads to important costs to the society, regardless of the method used.

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Data Availability. GSK makes available, the anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

Declarations

Conflict of Interest. Joost J. M. Simons and Tjalke A. Westra are employed by and hold shares in GSK. Florian Zeevat reports grants from GSK for the conduct of the study via her institution (UMCG/RUG). Florian Zeevat also reports a grant from Health-Ecore and travel fees from GSK, outside the submitted work. Jan C. Wilschut reports consulting fees for advisory boards from Sanofi Pasteur and Janssen and payment from GSK for report writing outside the submitted work. Jan C. Wilschut also holds shares in Arbutus Corporation, Mymetics Corporation and ViciniVax Holding. Nina M. van Sorge declares consulting fees for service directly paid to her institution from MSD, outside the submitted work. Nina M. van Sorge also declares grants from Dutch Health Counsel, NIH and Amsterdam UMC and holds patent related to development of a vaccine against *Streptococcus pyogenes*, and for advisory board with the ItsME foundation (no honorarium) and the Rapua te me ngaro ka tau (honorarium paid to her institution), outside the submitted work. Nina M. van Sorge also holds share in Genmab BV. Cornelis Boersma reports funding from GSK to complete the work disclosed in this manuscript. Cornelis Boersma also receives consulting fees, payment and travel fees paid to his institution from various medical and pharmaceutical companies and has board membership with Netherlands Antibiotic Development Platform, ParkinsonNL, Veroz, Sustainable Health Accelerator and WAAH! Accelerator. Cornelis Boersma also holds shares in Health-Ecore, Digital Health Link, SensUR Health and Pitts. Maarten J. Postma holds shares in Health-Ecore and Pharmacoeconomics Advice Groningen Ltd. The authors declare no other financial and non-financial relationships and activities.

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