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# The cost-of-illness for invasive meningococcal disease caused by serogroup B *Neisseria meningitidis* (MenB) in Germany

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ABSTRACT

*Introduction:* Invasive meningococcal disease (IMD) is a severe disease mainly affecting infants and young children. The most common serogroup causing IMD in Germany is the serogroup type B *Neisseria meningitidis* (MenB). The aim of the present study is to estimate the economic burden of MenB-related IMD in Germany.

*Method:* A bottom-up, model-based costing approach has been used to calculate the diagnose- and age-specific yearly lifetime costs of a hypothetical cohort of MenB-related IMD cases. Direct costs contain the treatment cost for the acute phase of the disease, long-term sequelae, costs for rehabilitation, and public health response. Indirect costs are calculated for the human-capital approach and the friction-cost approach considering productivity losses of patients or parents for the acute phase and long-term sequelae. Publicly available databases from the Federal Statistical Office, the SOEP panel data set, literature, and expert opinion were used as data sources. All future costs beyond the reference year of 2015 were discounted at 3%.

*Results:* The total costs for the hypothetical cohort (343 patients) from a societal perspective are €19.6 million (€57,100/IMD case) using the friction-cost approach and €58.8 million (€171,000/IMD case) using the human-capital approach. Direct costs amount to €18.6 million or €54,300 €/case. Sequelae are responsible for 81% of the direct costs/case.

*Discussion:* The elevated costs/MenB-related IMD case reflect the severity of the disease. The total costs are sensitive to the productivity-loss estimation approach applied. MenB is an uncommon but severe disease; The costs/case reflect the severity of the disease and is within the same magnitude as for human papilloma virus infections. The available literature on sequelae is due to the uncommonness limited and heterogeneous.



## 1. Introduction

Invasive meningococcal disease (IMD) is caused by the bacteria *Neisseria meningitidis* and manifests itself in acute meningitis or sepsis [1]. Further, IMD is characterized by a high case-fatality and by partly serious long-term sequelae [2]. The overall incidence of cases of IMD in Germany was decreasing from 0.95 in 2001 to 0.44/100,000 persons in 2012, but has been stabilizing since then, reaching 0.35 cases/100,000 persons in 2017 [3]. Over all observed years the incidence is highly age-dependent: especially infants (<1 year of age (yoa)) but also children (1–4 yoa) and young adolescents (15–19 yoa) show particularly high incidence rates with 4.6, 1.8 and 0.73/100,000 persons between 2013 and 2016 [4]. The lethality of an IMD also seems to be age-dependent with a higher lethality in children <5 yoa (9.5%) and adults (up to 12.3%) [1].

In Germany as in Europe the serogroup type B *Neisseria meningitidis* (MenB) is the most common and accounted for between 2013 and 2016 with 58.0% of IMD cases in Germany (i.e., 0.27/100,000 persons) [4,5]. MenB-related IMD mortality (9.4%) is

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almost as high as for the second most common serogroup type C (MenC; (13.6%; incidence = 0.07/100,000 persons) [1]. Further, there is no significant difference with MenB regarding the manifestation of the disease (sepsis and/or meningitis) [1]. Due to the low case numbers, significant differences in the probability of occurrence of possible sequelae between particular serogroups of *Neisseria meningitidis* or IMD are rarely seen [6]. However, evidence on general bacterial meningitis and on MenB specifically reports a variety of persistent physical (e.g., amputations), neurological (e.g., seizures) and psychological (e.g., separation anxiety) sequelae [7,2].

Regarding the economic burden of disease (i.e., cost-of-illness (CoI) of IMD), a recent systematic review identified 14 studies and found IMD resulting in substantial costs from the healthcare payer perspective [8]. No study conducted in Germany was included and the authors also found a lack of evidence for the costs of long-term consequences as they are provided [9] for the United Kingdom (UK), and indirect costs of IMD. The objective of this study is to systematically estimate the CoI caused by IMD (MenB-disease) from a societal perspective in Germany.

## 2. Methods

### 2.1. Study design

We used a "Sum Diagnosis Specific"-CoI study design [10]. Costs were calculated from a societal perspective and have been inflated – if necessary – to the reference year of 2015 using the harmonized Consumer Price Index (CPI) for Germany published by the Federal Statistical Office [11] as recommended for Germany [12]. The reported direct costs correspond to the perspective of the statutory health insurance community, including direct costs for the third payer (i.e. statutory sickness funds) as well as direct costs of the patients (e.g. co-payments) as recommended for cost-effectiveness analyses in Germany [12]. If not stated otherwise, the age groups were split as "<1 year", "1–4 years", "5–9 years" and then 5-year age groups until the age group "80 years and older".

The costs are calculated for a hypothetical cohort using a model-based incidence approach for each age group, (i.e., we followed each age-group until the end of their life). The cohort has been constructed based on the mandatorily reported number of IMD cases, that has been drawn from the web-database (SurvStat) of cases of notifiable diseases maintained by the SurvStat-database of the Robert Koch Institute (RKI), the German national public health institute in Germany, [3], for all available years (2001–2016) including the age of a case and the serogroup. Cases of unknown serogroup or unknown age have been re-distributed by year based on the serogroup distribution of cases with full information of the respective year. The number of deaths for the 3-digit International Classification of Diseases (ICD)-code A39 has been retrieved from the deaths statistics from the Federal Statistical Office [13]. Thus, lethality rates had to be calculated for IMD cases without serogroup distribution. However, to calculate the deaths caused by MenB exclusively, the overall IMD-fatality was multiplied with MenB case proportions. The cohort used for the cost calculations is displayed in appendix I. Fig. 1 shows the underlying model used for the cost calculations described in the following sections.

A lower and upper bound was estimated for each parameter. If available from the sources, 95% confidence intervals (CI) or one standard deviation in each direction of the base-case estimate were used alternatively. In the case there was no information available for the variance of an estimate, a 20% decrease or increase were used as the lower and upper bound in uncertainty analyses, respectively. All costs have been included from the onset of the disease until the end-of-life using the further life-expectancy for each age group. As recommended for Germany, future costs were discounted annually with 3% (0% and 5%) in the base-case and additional scenario analyses (uncertainty analyses) [12]. All analyses have been conducted in Microsoft Excel 2013 and R version 3.4.4. The final input parameters can be found in the appendix I of this article. Detailed results can be found in appendix II.

### 2.2. Costs related to the acute IMD phase

Direct costs during the acute phase of IMD cases are comprised of inpatient costs, rehabilitation costs and costs related to public health responses to an IMD outbreak by local health authorities (LHA). An overview on all cost components considered can be found in Table 1. Due to the severity of the IMD, it was assumed that patients were directly hospitalized without previous outpatient treatment as done elsewhere in Germany [14]. For inpatient cost calculations, all IMD-related cases stratified by 4-digit ICD-codes (A39.0 to A39.9), age-groups and length-of-stay (LOS), were taken from the statistics from the Federal Statistical Office for the years 2001 to 2015 [15]. For aggregated LOS categories, the mean LOS was derived from the interval limits (e.g., 8.5 days for the category "8–9 days"). Afterwards, an age-specific German Diagnosis-Related Group (G-DRG) has been identified for each ICD-code via the "Webgrouper" [16], giving the relative economic cost weight of the respective diagnoses. The mapping of ICDs to G-DRGs can be found in appendix III. Finally, the age-specific hospitalization costs were calculated by taking the weighted average of the relative cost weights over all ICDs and LOS-categories and multiplying them with the German Federal base rate of 3231.20€ (reference year 2015). Co-payments of 10€/hospital day (up to a maximum of 28 days) for patients >18 years have also been considered for a societal perspective. The number of reported IMD-hospitalizations exceeded the number of reported IMD-cases to the RKI by an average factor of 1.22 between 2003 and 2015. We assumed the excess hospitalizations to be reimbursable readmissions. Thus, we multiplied the inpatient costs (including co-payments from a societal perspective) and productivity losses (during hospital stay, societal perspective) by this factor.

For inpatient rehabilitation costs, age-specific LOS-data for the years 2003 to 2015 have also been retrieved from the corresponding statistic of the Federal Statistical Office [17] for all patients with a 3-digit A39-ICD. The reimbursement scheme of rehabilitation pays a fixed amount/day independent from ICDs. The price/-day has been taken from the literature [18] and complemented by patient co-payments. The CPI-adjusted costs of public health management/IMD case, including staff costs of LHA and post-exposure prophylaxis for an average of 16.39 persons/case, were €824 [19].

### 2.3. Costs related to sequelae

The probabilities of the different sequelae have been extracted from the results of a systematic literature review on IMD-sequelae [20] and can be found in Table 2. The relevant direct cost components of the different sequelae included in the analyses were inpatient and outpatient care, rehabilitation, special education and long-term care.

For each sequelae, a literature search was conducted and German CoI studies could be found for blindness [21], attention deficit/hyperactivity disorder (ADHD) [22,23], social anxiety [24], hearing loss [25], depression [26] and epilepsy [27]. Data were extracted for direct costs during the first year and the following years, separately where possible, to account for special training or medical devices at the onset of the sequelae, as well as indirect

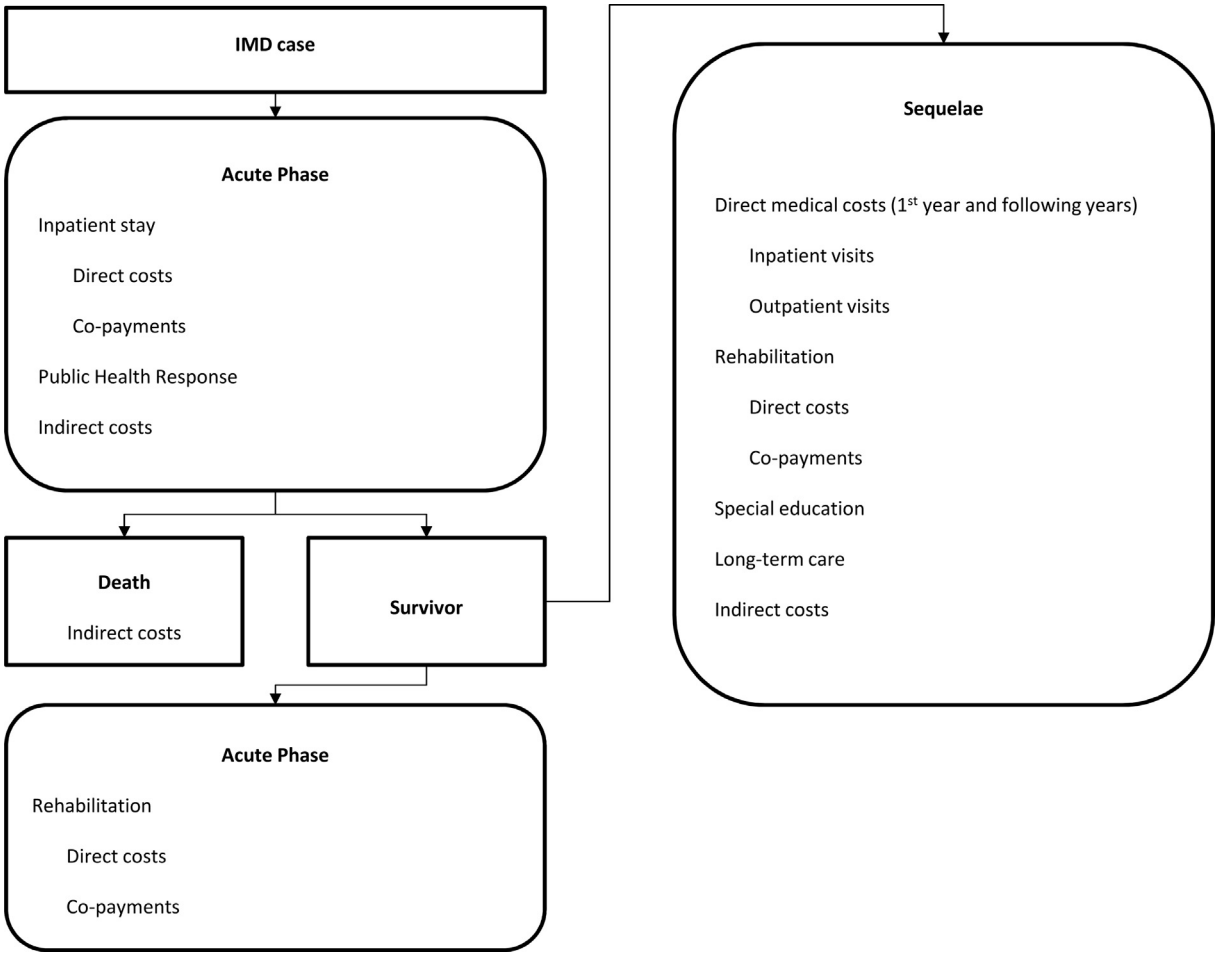


**Fig. 1.** Schematic flow-chart of the cost calculation for each IMD case of the cohort. IMD, invasive meningococcal disease.

**Table 1**
Cost components considered in the calculation of direct costs.

| Acute IMD phase | Sequelae |
|---|---|
| – Inpatient cost (LOS/prices)* | – Inpatient costs (visits, price) |
| – Inpatient co-payments* | • 1st year |
| – Inpatient re-admission factor* | • Following years |
| – Inpatient-related outpatient care (visits to hospital after discharge) | – Inpatient-related outpatient care (visits, price) |
| – Rehabilitation probability* | • 1st year |
| – Rehabilitation costs* | • Following years |
| – Rehabilitation co-payments* | – Following Following-years medical costs |
| – Other acute care cost (Public health outbreak management) | – Outpatient costs (visits, price) |
| | – Rehabilitation (days, price) |
| | – Special Education |
| | – Long-term care |
| | • Professional care |
| | • Benefits for informal care |

IMD, invasive meningococcal disease; LOS, length-of-stay.
* Are age-dependent.

**Table 2**
Included sequelae with their corresponding probabilities and ICD-codes.

| Sequelae | ICD-10 codes | Probability of occurrence in survivors of acute IMD (%) | Source |
|---|---|---|---|
| Hearing loss | | | |
| With Cochlear | H91.2 – 0.9 | 2.45 | [7] |
| Moderate bilateral | H93.3 – 0.9 | 3.80 | [7] |
| Moderate unilateral | H94.0/0.8 | 5.21 | [7] |
| Neurological disability | | | |
| Severe neurological | | 1.79 | [50] |
| Mental retardation | | 0.50 | [14] |
| Speech problems | | 3.56 | [7] |
| Motor deficits | | 0.77 | [50] |
| Limp amputation | Not applicable | 1.26 | [7] |
| Seizures/Epilepsy | G40.0 – 0.9; G41.0 – 0.9; R56.8 | 1.78 | [7] |
| Skin scarring | L90.5; L91.0 | 1.53 | [6] |
| Renal disease | N17.0 – 0.9 | 1.92 | [6] |
| Blindness | | 0.42 | [7] |
| Attention deficit hyperactivity disorder (ADHD) | | 9.66 | [7] |
| Anxiety | | 2.25 | [7] |
| Separation anxiety | | 5.96 | [7] |

ICD, international classification of diseases; IMD, invasive meningococcal disease.

costs. Additionally, expert opinions of two clinicians working as heads of their departments (paediatrics and infectiology) in university hospitals were used for missing cost items. The experts were selected based on their engagement in the medical scientific community and by the size of their departments to maximise the experience of the experts with regard to IMD cases. The questionnaire for the experts asked for their personal experience and included the number of hospitalizations, follow-up visits to the

hospital after the inpatient IMD phase, outpatient visits in the 1st year as well as the following years, respectively, and visits to special education institutions. To validate the expert opinion we compared their answers with results from the literature for those sequelae for which studies were available. For inpatient and rehabilitation visits, costs have been calculated for neurological sequelae, limp amputation and renal disease, using the same approach as for acute IMD-cases described above. As there are no data available linking sequelae exclusively to IMD-cases, an un-weighted mean over all possible ICD-codes/sequelae was calculated to estimate inpatient costs. For all other items of resource use, the average of both expert estimates has been taken and multiplied with the corresponding inflated prices for follow-up visits [28,29], outpatient visits [18,30] and pediatric centers for special education [31]. Following a previous study [32], it was assumed that 10% of all IMD patients needed a life-long care giver for which payments from the statutory long-term care insurance were considered [33]. This long-term care also includes payments from the German long-term care insurance [33]. As these are not transfer costs they were included in the direct costs.

### 2.4. Indirect costs due to productivity losses

Indirect costs were calculated separately for (I) productivity losses due to the acute phase of IMD, (II) IMD-attributable premature mortality, and (III) reduced productivity due to long-term consequences of sequelae in IMD survivors. Table 3 contains a detailed description of the components considered for indirect costs. For all three aspects of indirect costs, age-stratified values on the labour-force participation rate and the average, sex-independent wage/person was multiplied to calculate the future earnings from the time of impairment or death. Following the guidelines [34,12], a friction-cost approach (FCA; employer perspective) was applied in the base-case analysis and a human-capital approach (HCA; employee perspective) was presented as an additional scenario-analysis. The average duration of job vacancy (i.e., friction period) was available for 2015 from the Federal Employment Agency [35] and amounted to 92 days, assuming 1.0 as the elasticity for labor time vs. labor productivity. An elasticity of 0.8 as recommended by Dutch guidelines [36] was explored in a sensitivity analysis.

Aspect I: Productivity losses due to the acute phase have been calculated by multiplying the age-specific average LOS with the corresponding age-specific, employment adjusted wage/day. For children <15 yoa, it was assumed that one parent stayed absent from work for the duration of the child's hospitalization. Two additional scenarios have been explored in the sensitivity analyses: one scenario with no parent being absent from work (e.g. grandparents taking care of the child [37]) and another scenario with both parents being absent from work. As the wage is age-specific, the parent's age is of relevance for the calculation of the productivity losses due to parents caring for their children. The average age of mothers at the birth of their first child was 30.99 years in 2015 [38] and was used as a proxy for the age of parents, where the weighted mean age of the children was added to calculate the wage loss of the parents. E.g. for children "1–4 years" the wage of persons aged 33.47 years (30.99 + 2.48) was used. As all average LOS estimates of the acute phase were below the friction-cost duration of 92 days, there is no difference between the HCA and the FCA in aspect I (Table 3).

Aspect II: The indirect costs due to IMD-related mortality were calculated by multiplying the friction period with the age-specific wage/day. Consequentially, the deaths of patients aged <15 years causes no indirect costs under the FCA as they do not belong to the labour force. When applying the HCA, the age-specific life expectancy at the time of death has been derived from the German life-table of 2015 [39] and future years in the workforce have been determined. Thereafter, the future, discounted age-related wages [40] were computed to calculate the discounted productivity loss/IMD-related death by age.

Aspect III: For the calculation of indirect costs due to productivity losses caused by sequelae, a multi-step approach was applied:

1. The degree of disability (Grad der Behinderung; GdB) ranging from 0 (no disability) to 100 (fully disabled) for each sequela has been determined from German regulation of health care provision (Versorgungsmedizin-Verordnung) [41] (see Appendix IV).
2. The average income of persons with a disability has been estimated from the socio-economic panel dataset (Sozio-ökonomisches Panel; SOEP), a large longitudinal survey for social sciences and economics in Germany [42].
3. The incomes for people with disability and without disability were compared for intervals of 10 points on the GdB-scale. For each person with a GdB-score, 3 controls have been matched without replacement using the Matching package [43] in R Version 3.4.4 [44] with age and sex as exact matching variables.
4. The differences and ratios were then calculated for each 10-degree interval of the GdB-score (see Table 4).

For the FCA, the resulting percentage of productivity has been multiplied with the age-specific earnings during the friction period used for the indirect costs for IMD-mortality described above. For instance, the FCA assumed that a 50% productivity loss of an IMD patient would be captured by a new employee covering the remaining 50%. Applying the HCA, the indirect costs were calculated as the reduction of the future earnings of an IMD patient with sequelae by the percentage of productivity loss.

**Table 3**
Cost components considered under the different indirect costing approaches, stratified for the different scenarios of patients with IMD.

| Aspect | Indirect cost components | |
|---|---|---|
| | Friction-cost approach | Human-capital approach |
| I. Surviving acute phase without sequelae | – Productivity loss of patient or one parent during hospitalization | |
| II. Death during acute phase | Productivity loss of patient or one parent during hospitalization<br>– Productivity loss due to foregone future productivity (max. 92 days (friction period)) | – Productivity loss due to foregone future productivity of the deceased (≥15 yoa) |
| III. Surviving acute phase with sequelae | Productivity loss of patient or one parent during hospitalization<br>– Productivity loss due to reduced future productivity of the patient (>15 yoa) until the end of the friction period.<br>– Productivity loss until the end of the friction period due to parents leaving work force to care for children. | – Productivity loss due to reduced future productivity of the patient.<br>– Productivity loss due to parents leaving work force to care for children. |

IMD, invasive meningococcal disease; yoa, years of age.

**Table 4**
Reduced income in percent by the [a]degree of disability, estimated from the SOEP-dataset for the year 2009 not inflated to reference year [40].

| GdB-category[a] | N | Monthly labour income disabled | Monthly labour income controls | Labour income percentage/decrement | 95% CI |
|---|---|---|---|---|---|
| (0,10] | 14 | 1558.14 € | 2183.24 € | 71.4/28.6 | [45.3–97.5]/[2.5–54.7] |
| (10,20] | 125 | 1668.09 € | 1985.19 € | 84.0/16.0 | [77.5–90.5]/[9.5–22.5] |
| (20,30] | 332 | 1255.55 € | 1719.34 € | 73.0/27.0 | [68.2–77.8]/[22.2–31.8] |
| (30,40] | 253 | 1004.13 € | 1608.33 € | 62.4/37.6 | [56.4–68.4]/[31.6–43.6] |
| (40,50] | 656 | 807.33 € | 1341.56 € | 60.2/39.8 | [56.4–63.9]/[36.1–43.6] |
| (50,60] | 324 | 519.63 € | 1080.41 € | 48.1/51.9 | [42.6–53.6]/[46.4–57.4] |
| (60,70] | 231 | 366.66 € | 1077.09 € | 34.0/66.0 | [27.9–40.2]/[59.8–72.1] |
| (70,80] | 230 | 389.32 € | 1011.62 € | 38.5/61.5 | [32.2–44.8]/[55.2–67.8] |
| (80,90] | 65 | 346.22 € | 962.22 € | 36.0/64.0 | [24.1–47.9]/[52.1–75.9] |
| (90,100] | 356 | 280.14 € | 1077.13 € | 26.0/74.0 | [21.4–30.6]/[69.4–78.6] |

CI, confidence interval; GdB, Grad der Behinderung [degree of disability]; N, number of observations; SOEP, Sozio-ökonomisches Panel [socio-economic panel dataset].

Indirect costs also include the productivity loss of parents to care for a child with sequelae. Analogously to the approach by Gasparini et al. (2016) [32] we assumed that children were dependent on their parents' care until they reached 18 yoa.

## 3. Results

### 3.1. Total costs

The total MenB-related costs, as measured by direct and indirect costs (societal perspective) of acute phase and sequelae for a hypothetical, average (years 2001–2015) cohort consisting of 343 patients, are €19.6 million using the FCA and €58.8 million using the HCA. These cost estimates correspond to €57,100 and €171,000/MenB-disease case, respectively, in Euros of the reference year 2015.

The estimate on the indirect costs depends strongly on the chosen method to measure productivity loss. Using the HCA results in indirect costs of €40.2million while the FCA results in €941,000. When looking at the indirect costs/case, the estimates for the HCA increase with age from €110,000 for under <1 year-olds to €202,000 in the age group "30–34 years" before they monotonically decrease to €10 for IMD patients ≥80 years. The differences across age groups reveal the strong influence of discounting on the forgone productivity. Applying the FCA shows a different pattern, as only the lost productivity of the parents is incorporated in the age groups <15 years. Hence, until patients are old enough to enter the workforce themselves, the indirect costs due to productivity loss increase with age as their parents' income increases. After a sharp drop in the age group "20–24 years" to €480, the indirect costs peak at "45–49 years" with €5580 and decrease to under €30 in the age groups older than the legal retirement age of 65 years.

### 3.2. Cost due to the acute phase

The direct, discounted costs of the acute phase for the hypothetical, average cohort from IMD patients between 2001 and 2015 amount to €3.19 million or €9300/patient. As can be seen in Table 5, the costs decrease with increasing age until the age group of 30–34 yoa and afterwards increase in the older age groups with up to €16,100 for the 75–79 yoa. In this context, the re-admission factor plays an influential role. Assuming no re-admission, costs are €7390 per IMD case. The indirect costs due to the acute phase sum up to €453,000 for the cohort or €1320 per case, with 71.7% due to productivity loss of parents and 28.3% due to patients' productivity loss.

The forgone productivity due to pre-mature mortality is estimated to be €73,000 for the complete cohort or €213/IMD case using the FCA (note: children <15 yoa do not cause any productivity loss as they are not part of the labour force). Changing the denominator to IMD cases >15 yoa yields indirect costs of €437 for IMD-related mortality. Indirect costs due to IMD-related pre-mature mortality calculated using the HCA amount to €12.6million, corresponding to €36,600/IMD case or €355,000/death.

**Table 5**
Direct and indirect costs across age groups associated with the acute phase of IMD.

| | Cohort | | | | Per patient | | | |
|---|---|---|---|---|---|---|---|---|
| | Direct | Indirect | | | Direct | Indirect | | |
| Age group | Acute phase | Patients | Parents | Indirect total | Acute phase | Patients | Parents | Total |
| <1 | 557.986 € | 0 € | 79.861 € | 79.861 € | 10.255 € | 0 € | 1.468 € | 1.468 € |
| 1–4 | 711.541 € | 0 € | 93.098 € | 93.098 € | 9.022 € | 0 € | 1.180 € | 1.180 € |
| 5–9 | 227.666 € | 0 € | 32.716 € | 32.716 € | 9.915 € | 0 € | 1.425 € | 1.425 € |
| 10–14 | 188.623 € | 0 € | 30.158 € | 30.158 € | 9.439 € | 0 € | 1.509 € | 1.509 € |
| 15–19 | 532.156 € | 17.964 € | 89.424 € | 107.388 € | 7.837 € | 265 € | 1.317 € | 1.582 € |
| 20–24 | 187.522 € | 7.646 € | 0 € | 7.646 € | 7.374 € | 301 € | 0 € | 301 € |
| 25–29 | 81.396 € | 12.614 € | 0 € | 12.614 € | 8.468 € | 1.312 € | 0 € | 1.312 € |
| 30–34 | 48.849 € | 8.602 € | 0 € | 8.602 € | 8.010 € | 1.411 € | 0 € | 1.411 € |
| 35–39 | 51.157 € | 10.914 € | 0 € | 10.914 € | 8.806 € | 1.879 € | 0 € | 1.879 € |
| 40–44 | 60.343 € | 13.960 € | 0 € | 13.960 € | 10.253 € | 2.372 € | 0 € | 2.372 € |
| 45–49 | 76.178 € | 17.981 € | 0 € | 17.981 € | 10.145 € | 2.395 € | 0 € | 2.395 € |
| 50–54 | 61.718 € | 15.087 € | 0 € | 15.087 € | 10.321 € | 2.523 € | 0 € | 2.523 € |
| 55–59 | 70.278 € | 11.332 € | 0 € | 11.332 € | 10.890 € | 1.756 € | 0 € | 1.756 € |
| 60–64 | 76.078 € | 11.841 € | 0 € | 11.841 € | 12.702 € | 1.977 € | 0 € | 1.977 € |
| 65–69 | 53.966 € | 88 € | 0 € | 88 € | 10.585 € | 17 € | 0 € | 17 € |
| 70–74 | 64.767 € | 108 € | 0 € | 108 € | 11.823 € | 20 € | 0 € | 20 € |
| 75–79 | 60.781 € | 103 € | 0 € | 103 € | 16.132 € | 27 € | 0 € | 27 € |
| ≥80 | 81.591 € | 138 € | 0 € | 138 € | 13.558 € | 23 € | 0 € | 23 € |
| Total | 3.192.596 € | 128.378 € | 325.256 € | 453.634 € | 9.301 € | 374 € | 948 € | 1.322 € |

### 3.3. Cost due to sequelae

The costs of single sequelae/IMD case are determined by the probability of the specific sequelae (Table 2) and the costs/sequelae case. Overall, direct costs of sequelae account for €15.5million for the cohort or €50,200 for the average IMD survivor. The costliest sequelae regarding the average costs/IMD case is hearing loss. Over all age groups, €7.41 million (€24,100/IMD survivor) are spent on direct costs for all cases with this sequela. Psychological impairments are the second costliest sequelae with €3.05 million in total costs and €9900/IMD survivor. Skin scarring and blindness or visual impairment cause the least amount of direct costs up to €500 per IMD survivor. The direct costs decrease monotonically with increasing age. Direct costs of the acute phase and sequelae are displayed in Fig. 2 and the composition of direct costs caused by all sequelae is displayed in Fig. 3.

The indirect costs related to the sequelae (i.e., reduced productivity of patients or parents caring for their child) are estimated to be €414,000 for the cohort or €1210/patient. Again, using the HCA increases sequelae-related, indirect costs to €27.1 million for the cohort which corresponds to €88,200/IMD survivor.

### 3.4. Sensitivity analyses

A variety of sensitivity analyses have been performed to analyse the impact of certain assumptions on the overall cost-estimate. Fig. 4 summarises the results in two tornado plots with blue bars representing the lower input value and red bars representing the higher value. Assuming no time preference (i.e., a discount rate of zero), direct costs nearly doubles compared to the base case. As most of the indirect costs occur in the future, the effect of the lower discount rate is even higher for this cost component.

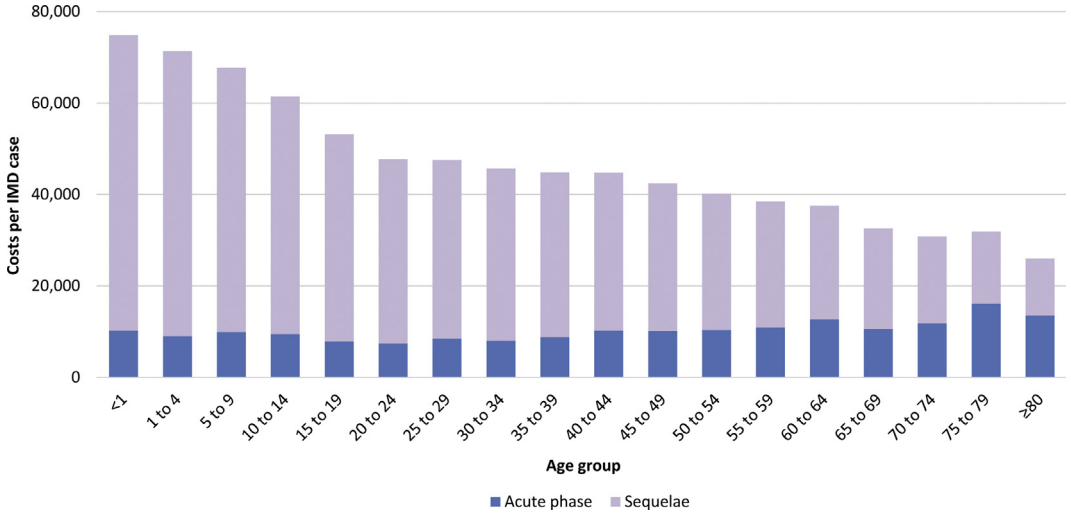


**Fig. 2.** Direct costs per IMD case, stratified by age group and by cost component (blue: costs for the acute IMD phase, red: costs for long-term sequelae). IMD, invasive meningococcal disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

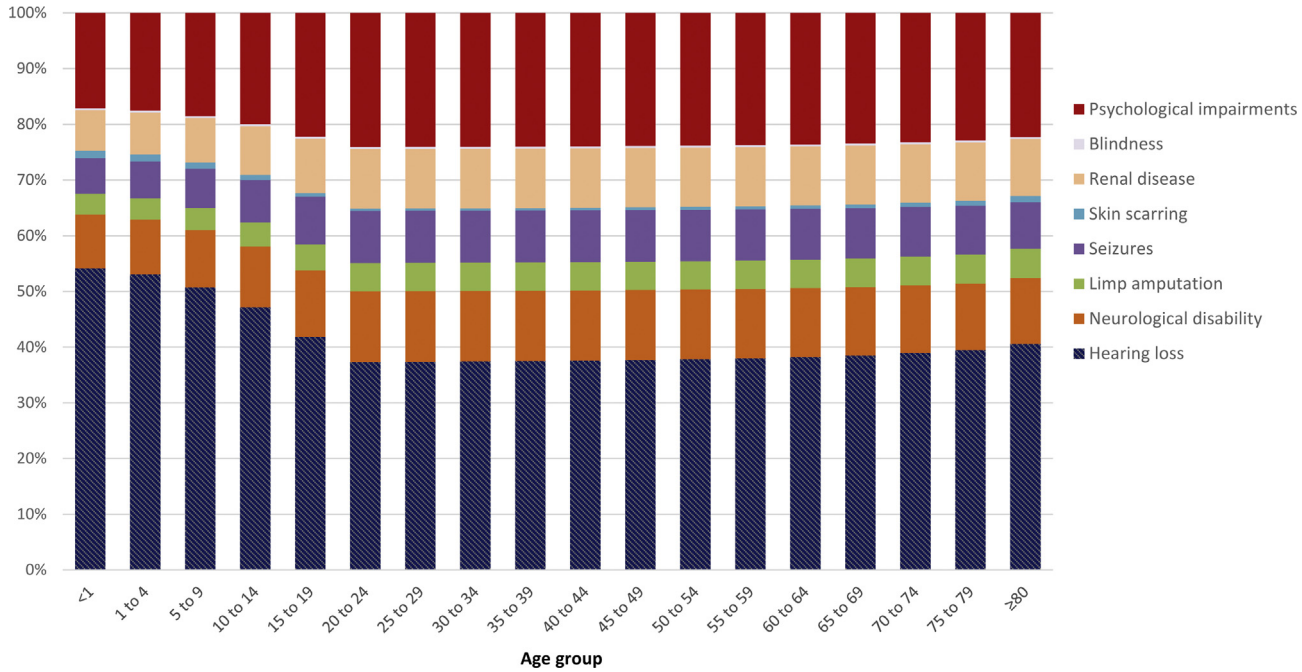


**Fig. 3.** Percentage of direct costs per average IMD survivor caused by the different sequelae on a population level, i.e. the values present the combination of the costs and the probability of the sequelae. IMD, invasive meningococcal disease.

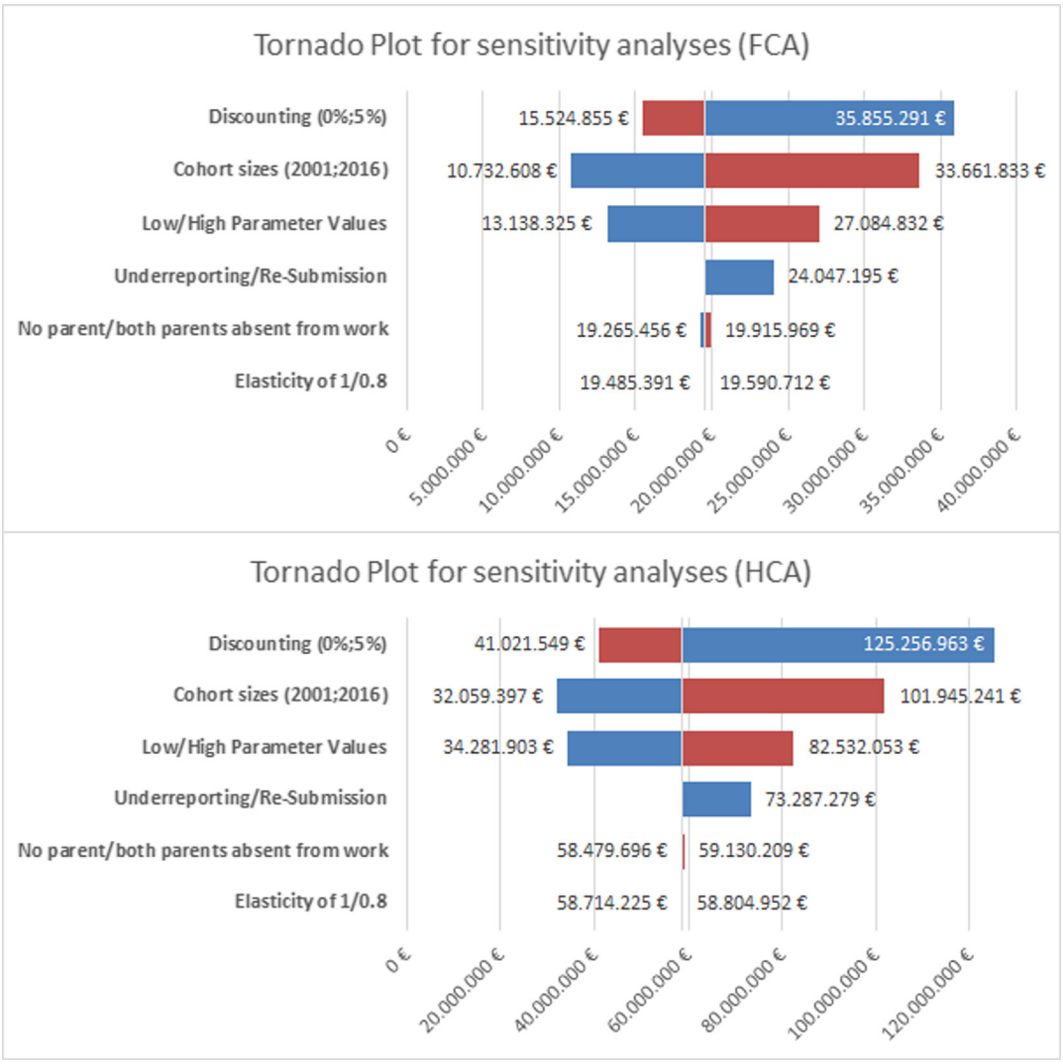


**Fig. 4.** Tornado plots for Human Capital and Friction Cost Approach depicting the change in the total costs for IMD in Germany for the different scenarios of the sensitivity analysis. IMD, invasive meningococcal disease.

However, as the friction period is shorter than one year, indirect costs calculated via the FCA are not affected by the discount rate. Increasing the discount rate to 5%, leads to lower total costs accordingly. A low- and a high-cost scenario were also explored in the sensitivity analyses with the discount rate held at 3%. The effect of the changes on the total costs were similar to the changes in the discount rate, but the low-cost scenario led to even lower total costs than the scenario with 5% discount rate. The high-cost scenario did not reach the scenario with 0% discounting. Naturally, the cohort size shows also a large effect on the total costs. The cohort from 2001 would have caused almost three times the costs of the cohort from 2016. Assuming that the difference between reported cases and cases from the hospital admissions indicates underreporting instead of re-submission results in increased overall costs of a lower magnitude than in the high cost scenario. Lastly, assuming that no parent stays at home vs. both parents stay at home, or varying the elasticity of work time vs. productivity had only minor impact on the total costs. Detailed results on these analyses can be found in the appendix II.

## 4. Discussion

This study presents findings on the economic burden of IMD for an average cohort on the last 15 years from a societal perspective using a bottom-up, model-based costing approach to sum diagnosis specific costs for Germany. The total discounted direct costs amount to €54,300/case and the additional discounted indirect costs vary from €2740 using the FCA to €117,000 applying the HCA. The results suggest that direct and indirect costs show age-specific differences, with higher costs occurring in younger age groups. This can be explained by two major factors. Firstly, the medical costs and the costs of caregiving of long-term sequelae accumulate over a longer life-span in young patients suffering from IMD compared to elderly IMD patients. Secondly, IMD cases in young age groups cause not only productivity losses in future earnings of young patients, but also losses in the current earnings of their parents.

Our study results are subject to some limitations. First, our estimates are not derived from a database analysis (e.g., case control study with claims data), but are model-based. We chose this study design for the availability of secondary data sources, the small number of expected cases in claims data and the better reflection of long-term costs. Also, our calculations assume that the mortality of MenB does not differ from all *Neisseria meningitidis* cases as there is no serogroup-specific data available. This assumption on mortality might over- or underestimate the real burden. Further, the extent of underreporting of MenB cases in Germany is unknown and might underestimate the burden. In this context,

we found the number of IMD-related hospitalizations exceeding the number of reported cases by the factor 1.2. This factor may indicate the existence of underreporting but may also be due to reimbursable readmissions. We decided for the latter interpretation in the base case to be conservative but used this factor also for underreporting in a sensitivity analysis. Therefore, only the inpatient costs during the acute phase were adjusted accordingly. Furthermore, we used a relatively detailed approach by estimating the reduction in productivity for persons with sequelae using the degree of disability in the SOEP dataset. Unfortunately, the degree of disability dataset does not allow differentiating between mental and physical disability which might bias the participation in this panel dataset. However, the German regulation of health care provision (Versorgungsmedizin-Verordnung) [41] is designed to measure different disabilities on the same scale, making them comparable. Another limitation is the use of expert opinion which represents a lower level of evidence [45]. Comparing the values derived from expert opinion for sequelae for which also values from the literature were available revealed a high concordance of both data sources. To take these limitations into account we explored the uncertainty of all input parameters by estimating the costs using a lower and an upper scenario in the uncertainty analysis.

As the present study is one of the first to analyze the costs of MenB-related IMD from a societal perspective in Germany, a comparison to previously published results, however, is hardly possible. A cost-effectiveness model on MenB vaccination, published by Christensen et al. (2016) [14], provided some cost estimates which were lower than our estimates (i.e., direct costs of €11,400, inflated to 2015). The lower estimates by Christensen et al. can to some extent be explained by the fewer sequelae with lower probabilities being incorporated in this estimate (neurological disabilities, renal disease, blindness and psychological impairments are omitted). Applying the cost components of Christensen et al. of the acute phase of IMD to our cohort results in costs of €6370/case compared to €9300. The difference between the studies may be attributed to using a no-re-admission rate as well as to a longer duration of rehabilitation and the respective patient copayments. However, many details of their calculation remain unclear and a proper comparison seems not possible.

In an international context, our results lie within the range of given estimates. While a modelling study by Gasparini et al. (2016) for Italy [32] lacks to provide overall cost estimates, the values of the input parameters are fairly similar to the values resulting from our study. For example, direct costs of the acute phase amount to €11,100/IMD case for medical care and public health responses, compared to the value of €9300 of the corresponding findings in our study. Wright et al. (2013) [9] calculated the costs of two specific, severe cases of meningococcal disease in the United Kingdom. Their total estimates of £590,000 to £1,090,000 (€679,000 to €1,254,000) for a further life-span of 70 years are far above the corresponding value of €476,000 for the undiscounted lifetime costs of a patient younger than one year. However, the two hypothetical cases considered in their study represent severe cases suffering from renal failure, amputation and other minor sequelae. According to a recent review of Wang et al. (2018) [8] on cost-of-illness studies on IMD for all serogroups, there is no study available that calculated indirect costs against which our results could be compared.

As most of the costs occur in the years following the onset of the disease and are related to productivity losses, the choice of the method for calculating indirect costs has a crucial impact on the results. Furthermore, the natural course of IMD, including the low probability of a single sequelae but the high number of different sequelae, makes the costing of the disease challenging. While MenB-related IMD is a rare disease as measured by the population prevalence [46], the elevated costs/case reflect the severity of the disease for the single patient and the caregivers. Compared to costs of illness in Germany other diseases such as Rotavirus infection (up to €2100/case [47–49]), seasonal Influenza (€105/child case [50]), and Varicella (up to €1300/case [51]) the (economic) severity of MenB-disease is higher, and within the same magnitude as for human papilloma virus infections (up to €66,600/case). While for these indications a universal mass vaccination (UMV) is in place in Germany, this is not the case for MenB, yet. However, the success of the MenB vaccination program implemented in the UK might support decision-making in Germany towards UMV to protect infants and children from MenB.

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## Conflict of interest

KM, RF, BU, and RW are employees of the GSK group of companies. KM, BU and RW hold shares in the GSK group of companies. During the conduct of this analysis and abstract/poster development, FK was an employee of the GSK group of companies and hold limited amounts of shares of GSK. SS received a grant from the GSK group of companies for the conduct of this analysis. WG has nothing to disclose.

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## Authors' contributions

BU, RW, KM, WG, FK, RMS and SS conceived and designed the study; SS developed the model; BU, KM, WG, FK, RMS and SS acquired and analysed the data; SS drafted the manuscript; SS and KM conducted the literature review.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.01.013.

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