Disease Burden of Invasive Meningococcal Disease in the Netherlands Between June 1999 and June 2011: A Subjective Role for Serogroup and Clonal Complex

Susanne P. Stoof,1,2 Gerwin D. Rodenburg,2 Mirjam J. Knol,1 Lidewij W. Rümke,2 Sandra Bovenkerk,3 Guy A. M. Berbers,1 Lodewijk Spanjaard,3,4 Arie van der Ende,3,4 and Elisabeth A. M. Sanders1,2

1Centre for Infectious Disease Control (Cib), National Institute for Public Health and the Environment (RIVM), Bilthoven, 2Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children’s Hospital, University Medical Center, Utrecht, 3Department of Medical Microbiology, and 4Netherlands Reference Laboratory for Bacterial Meningitis, Center for Infection and Immunity Amsterdam, Academic Medical Center, The Netherlands

Background. Several countries consider the implementation of a meningococcal serogroup B vaccine for young children and/or serogroup C or ACWY conjugate vaccine for adolescents. Representative information on clinical course of invasive meningococcal disease (IMD) is useful to evaluate cost-effectiveness of vaccination. Information on the relation between infecting meningococcal clonal complex (CC), disease course and outcome of IMD is scarce.

Methods. A retrospective study using Dutch surveillance data on IMD from June 1999 to June 2011. Clinical information was retrieved from hospital records. The effect of age, comorbidity, clinical manifestation, serogroup, and CC on disease course and outcome was assessed in multivariable analyses. Meningococcal CCs were assessed by multilocus sequence typing.

Results. Clinical information was retrieved for 879 IMD cases: 48% of patients presented with meningitis, 17% with septic shock, and 22% with septic shock plus meningitis. Development of septic shock was not related to CC or serogroup. Median (interquartile range) duration of hospital admission was 10 (8–13) days. Intensive care unit admittance (38%) was higher for patients aged ≥10 years and patients with septic shock (P-values ≤.001). Case-fatality rate (8%) and development of sequelae (29%) was dependent on age and clinical manifestation (P-values ≤.001) and not affected by comorbidity, CC, or serogroup.

Conclusions. IMD still coincides with a considerable disease burden and mortality. Disease course and outcome depend mainly on age and clinical manifestation and less on meningococcal CC or serogroup.

Keywords. invasive meningococcal disease; clonal complex; septic shock; case-fatality; sequelae.

Invasive infection due to Neisseria meningitidis or meningococcus is highly feared because of its rapid progression into severe disease like septic shock and meningitis. Despite antibiotic treatment, invasive meningococcal disease (IMD) can be fatal within 24 hours and patients who survive can suffer from serious sequelae [1]. IMD is almost exclusively caused by encapsulated meningococci, in particular those with serogroup A, B, C, W and Y, with striking geographical differences in their incidence. In industrialized countries IMD is mainly caused by serogroup B (MenB) followed by C and Y [2].

Vaccination is the best preventive strategy against IMD. Consequently, various effective polysaccharide (conjugate) vaccines against serogroups A, C, W, and...
Y meningococci have become available. In response to an increase in the incidence of serogroup C (MenC) IMD in the late 1990s, caused by isolates of the hyperinvasive sequence type 11 (ST-11) clonal complex (CC11), several countries implemented a monovalent MenC conjugate (MenCC) vaccine into their national immunization program (NIP) for infants, toddlers, or both [3]. The Netherlands implemented a MenCC vaccine into the NIP in 2002 as a single vaccination for children aged 14 months. Like the United Kingdom, this implementation was accompanied by a catch-up campaign for all children aged 1–18 years which led to a marked reduction in the total incidence of MenC IMD [4]. Adolescents have the highest carriage levels and are considered as the main transmitters of meningococci [5]. Hence, high vaccination coverage in this age group reduced transmission and induced herd protection [6, 7]. Because MenC specific antibody levels wane rapidly after MenCC vaccinations in young children [8, 9] and adolescents also have an increased risk of IMD, implementation of an adolescent MenCC booster vaccination is considered in several European countries [3, 10, 11]. Based on the increase in serogroup Y (MenY) IMD in Europe in the last decade [12, 13] and the more recent increase in serogroup W (MenW) IMD in the United Kingdom due to rapid endemic expansion of a single clone belonging to CC11 [14], a MenACWY conjugate vaccine could be considered instead.

Conjugate serogroup B (MenB) vaccines are not applicable due to poor immunogenicity of the capsular polysaccharide of MenB. Previous MenB vaccines consisted of outer membrane vesicles containing immunogenic outer membrane proteins (OMP) made of an epidemic causing strain. Because the immunodominant OMPs are highly antigenic variable, the use of these vaccines was restricted to strain-specific outbreaks [15]. Recently, a 4-component MenB vaccine (4CMenB, Bexsero, Novartis) with potentially broader coverage was licensed in Europe, Canada, Australia, and the United States. Another MenB vaccine (LP2086, Trumenba, Pfizer) containing 2 variants of the meningococcal factor H binding protein was recently licensed in the United States. Consequently, implementation of a MenB vaccine is currently considered in several countries [16–18].

Healthcare authorities’ decision to implement a vaccine into the NIP will take into account cost-effectiveness analyses [19]. Accurate statistics on disease course and outcome contribute to the estimation of direct effects of vaccination. Previous studies have suggested more severe disease caused by CC11 isolates [20–23]. These conclusions were based on higher mortality rates, whereas data on differences between CCs in clinical course and development of sequelae is scarce. The aims of the current study are (1) to provide updated and representative information on the burden of IMD in a Western European country and (2) to assess the relation between clonal complex of the infecting strain and clinical manifestation, disease course and outcome. We also analyzed the effect of age, comorbidity, clinical manifestation, and serogroup on the disease course and outcome. The clinical information was retrospectively collected from hospitalized IMD cases between June 1999 and June 2011 in a representative sample of the Dutch population.

METHODS

Study Design

We performed a retrospective chart review. The medical ethics committee of the University Medical Center Utrecht concluded that this surveillance study did not fall within the ambit of the Dutch Medical Research Involving Human Subject Act (WMO). Informed consent might cause substantial bias and missing data that would hamper representative estimates on national burden of IMD. Approval for data collection from hospital records was obtained from all executive boards of the participating hospitals. This study was carried out in accordance with the Dutch privacy legislation.

Meningococcal Surveillance Data

Since 1959, the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) collects meningococcal isolates from blood, cerebrospinal fluid, and other sterile body fluids from patients with IMD throughout the Netherlands. For the current study, information on the clinical course of IMD was collected for isolates that were received by the NRLBM between June 1999 and June 2011 and originated from 9 sentinel microbiology laboratories spread across the Netherlands. Together, these 9 laboratories are considered representative for approximately 25% of the Dutch population [24]. Serogroup of the isolates was obtained by ouchterlony gel diffusion [25]. CCs were assessed by multilocus sequence typing as described by Maiden and colleagues [26].

Clinical Characteristics

Information on comorbidity, clinical manifestation, disease course (duration of hospitalization and intensive care unit [ICU] admittance) and outcome (case-fatality rate [CFR] and sequelae) was retrospectively extracted from hospital records by trained medical students using a standard anonymized data collection form.

Comorbidities were subdivided into immunocompromising comorbidities and nonimmunocompromising comorbidities as previously described [24].

Clinical manifestation of IMD was subdivided into (1) septic shock, (2) septic shock and meningitis, (3) meningitis, and (4) mild meningococcaemia [27]. “Septic shock” was defined as ≥2 systemic inflammatory response syndrome criteria together with extensive hemorrhagic skin lesions and/or organ dysfunction and/or haemodynamic instability requiring immediate
fluid suppletion and/or treatment with vasopressors and/or artificial ventilation [27, 28]. “Meningitis” was defined as a cerebrospinal fluid (CSF) culture positive for Neisseria meningitidis, a positive CSF polymerase chain reaction, or a clinical diagnosis of meningitis together with a positive blood culture. “Mild meningococcaemia” was defined as meningococcaemia without septic shock or meningitis but with mild and slowly progressive disease or with another main focus (eg, arthritis or pneumonia) [27].

Case-fatality was defined as in-hospital death or death within 30 days after the first reported blood/CSF culture positive for N. meningitidis. Sequelae at discharge or in the year afterward were subdivided into severe (vegetative state, admission to nursing home/rehabilitation clinic, mental retardation, necrosis requiring skin transplantation or amputation, deafness requiring cochlear implant(s), renal insufficiency, adrenal gland insufficiency, epilepsy, or peripheral paralysis/paresis) and mild (all other sequelae, including all other forms of objectified and subjective hearing loss).

Statistical Analysis
The independent variables age, clinical manifestation, serogroup and CC were divided into categories: 7 age groups, 4 clinical manifestations, 4 serogroups, 6 CCs, 3 comorbidity groups (none, immunocompromising, nonimmunocompromising). Crude differences between categories were determined using χ²-test (and additional z-tests with Bonferroni correction for multiple testing) or Kruskal–Wallis test were appropriate. Subsequently, we used generalized linear models and performed logistic regression analyses to evaluate the overall influence of the independent variables on binary outcomes (ICU admittance, mortality, sequelae). Differences between categories in their effect on the outcome measure were assessed by using one of the categories within each variable as reference. We performed linear regression analysis to evaluate the effect of the independent variables on duration of hospital admission. The number of days in the hospital was log transformed (natural logarithm) to obtain a normal distribution of values. Log transformation of the number of days on the ICU did not induce a normal distribution. The effect of the independent variables on duration of ICU admittance was therefore not assessed in a multivariable linear regression analysis. Data were analyzed using Excel 2010 software (Microsoft Office) and SPSS statistics 22 (IBM). Analyses were performed on all available data. A P-value < .05 was considered significant.

RESULTS

Age and Comorbidity
Between June 1999 and June 2011 the NRLBM received 939 isolates from the nine sentinel laboratories. Hospital records were retrieved from 879 (94%) of these IMD cases. Information on comorbidities as obtained from the medical records is provided in Table 1 and Supplementary Table 1. In the multivariable models, presence of (immunocompromising) comorbidity had no effect on disease course or outcome (data not shown).

Most patients (48%) had developed distinct meningitis. Septic shock (with and without meningitis) was more prevalent among children with a significant difference between children aged 2–4 years and adults aged 20–64 years (P < .05) (Table 1).

Duration of hospital admission was longer for adults compared to children aged between 6 months and 19 years. The proportion of patients admitted to the ICU was higher among patients aged ≥10 years compared to patients aged <10 years (Table 2). The overall CFR throughout the study was 8%. Of the surviving patients, 29% had 1 or more sequelae. The CFR

Table 1. Case Characteristics and Clinical Manifestation of Invasive Meningococcal Disease by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Total mo</th>
<th>0–6 mo</th>
<th>6–24 mo</th>
<th>2–4 y</th>
<th>5–9 y</th>
<th>10–19 y</th>
<th>20–64 y</th>
<th>≥65 y</th>
<th>All Ages</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (% of total)</td>
<td>939</td>
<td>64 (7)</td>
<td>171 (18)</td>
<td>178 (19)</td>
<td>94 (10)</td>
<td>186 (20)</td>
<td>170 (18)</td>
<td>76 (8)</td>
<td>939 (100)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>28 (44)</td>
<td>73 (43)</td>
<td>74 (42)</td>
<td>42 (45)</td>
<td>99 (53)</td>
<td>87 (51)</td>
<td>52 (51)</td>
<td>40 (63)</td>
<td>181 (21)</td>
<td>.002</td>
</tr>
<tr>
<td>Comorbidity, n (%)</td>
<td>853</td>
<td>16 (28)</td>
<td>30 (19)</td>
<td>23 (15)</td>
<td>14 (16)</td>
<td>23 (14)</td>
<td>59 (37)</td>
<td>50 (79)</td>
<td>215 (25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Immunocompromising, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>7 (4)</td>
<td>13 (8)</td>
<td>10 (16)</td>
<td>34 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonimmunocompromising, n (%)</td>
<td>16 (28)</td>
<td>30 (19)</td>
<td>20 (13)</td>
<td>13 (15)</td>
<td>16 (10)</td>
<td>46 (29)</td>
<td>40 (63)</td>
<td>181 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical manifestation:</td>
<td>879</td>
<td>6 (10)</td>
<td>25 (15)</td>
<td>40 (24)</td>
<td>16 (18)</td>
<td>26 (15)</td>
<td>22 (14)</td>
<td>13 (20)</td>
<td>148 (17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Septic shock, n (%)</td>
<td>10 (6)</td>
<td>25 (15)</td>
<td>40 (24)</td>
<td>16 (18)</td>
<td>26 (15)</td>
<td>22 (14)</td>
<td>13 (20)</td>
<td>148 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock + meningitis, n (%)</td>
<td>17 (29)</td>
<td>39 (24)</td>
<td>52 (31)</td>
<td>22 (25)</td>
<td>37 (21)</td>
<td>18 (11)</td>
<td>12 (19)</td>
<td>197 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis, n (%)</td>
<td>33 (56)</td>
<td>89 (54)</td>
<td>64 (38)</td>
<td>40 (46)</td>
<td>82 (47)</td>
<td>90 (56)</td>
<td>22 (34)</td>
<td>420 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild meningococcaemia, n (%)</td>
<td>3 (5)</td>
<td>12 (7)</td>
<td>13 (8)</td>
<td>10 (11)</td>
<td>28 (16)</td>
<td>31 (19)</td>
<td>17 (27)</td>
<td>114 (13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Total number with information available.
*b χ²-test; significant differences are outlined in italic.
### Table 2. Disease Course and Outcome of Invasive Meningococcal Disease by Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. Cases (%)</th>
<th>No. Days in Hospital</th>
<th>ICU Admittance</th>
<th>No. Days in ICU</th>
<th>Case-fatality</th>
<th>Sequelae</th>
<th>Total, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>β^a [95% CI]</td>
<td>n (%)</td>
<td>Median (IQR)</td>
<td>aOR^b [95% CI]</td>
<td>aOR^b [95% CI]</td>
<td>&gt;1 Mild, n (%)</td>
</tr>
<tr>
<td>0–6 mo</td>
<td>849 (97)</td>
<td>819 (93)</td>
<td>861 (99)</td>
<td>836 (95)</td>
<td>307 (93)</td>
<td>NA</td>
<td>874 (99)</td>
</tr>
<tr>
<td>6–24 mo</td>
<td>8 (8–15)</td>
<td>−0.1 [−0.4–0.1]</td>
<td>15 (25)</td>
<td>4 (2–6.3)</td>
<td>NP</td>
<td>1 (2)</td>
<td>1.0</td>
</tr>
<tr>
<td>2–4 y</td>
<td>9 (8–11)</td>
<td>−0.4 [−0.6–0.2]</td>
<td>49 (30)</td>
<td>1.6 [0.7–3.6]</td>
<td>3 (1.5–7)</td>
<td>NP</td>
<td>11 (7)</td>
</tr>
<tr>
<td>5–9 y</td>
<td>8 (8–10)</td>
<td>−0.5 [−0.7–0.2]</td>
<td>55 (33)</td>
<td>1.4 [0.6–3.0]</td>
<td>3.5 (2–6)</td>
<td>NP</td>
<td>8 (5)</td>
</tr>
<tr>
<td>10–19 y</td>
<td>9 (8–12)</td>
<td>−0.4 [−0.6–0.1]</td>
<td>77 (45)</td>
<td>4.8 [2.1–10.8]</td>
<td>3 (2–5)</td>
<td>NP</td>
<td>7 (4)</td>
</tr>
<tr>
<td>20–64 y</td>
<td>13 (10–16)</td>
<td>−0.2 [−0.4–0.04]</td>
<td>77 (49)</td>
<td>8.0 [3.5–18.2]</td>
<td>3 (2–5)</td>
<td>NP</td>
<td>13 (8)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>15 (6.5–23.5)</td>
<td>0</td>
<td>32 (53)</td>
<td>7.0 [2.6–19.0]</td>
<td>7 (2–10)</td>
<td>NP</td>
<td>26 (39)</td>
</tr>
<tr>
<td>All ages</td>
<td>10 (8–13)</td>
<td>NA</td>
<td>331 (38)</td>
<td>3 (2–5)</td>
<td>NA</td>
<td>69 (8)</td>
<td>175 (22.9)</td>
</tr>
</tbody>
</table>

Significant differences are outlined in italic.

Abbreviations: aOR, adjusted odds ratio; CC, clonal complex; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; NA, not applicable; NP, not performed.

^a β = regression coefficient of linear regression analysis with adjustment for clinical manifestation, CC, and comorbidity. β represents the difference in log transformed (ln) number of days in the hospital compared to the reference category (0).

^b aOR = adjusted odds ratio compared to reference category (1.0) in logistic regression analysis with adjustment for clinical manifestation, CC and comorbidity.

^c Per outcome measure, the no. of cases represent the total no. with information available (left) and the no. with information available for all variables included in the adjusted analysis (right). Percentages represent the proportion of cases in relation to the total no. of retrieved hospital records (n = 879).

^d No. of cases related to no. of total cases admitted to ICU (n = 331).

^e No. of cases related to no. of known survivors (n = 805).

^f Overall P-values of the effect of age on the outcome measure in the crude (left) and adjusted (right) analysis.

^g The outcome “sequelae” was included as categorical outcome (none vs >1 mild vs >1 severe) in the crude analyses and as a binary outcome (present vs absent) in the adjusted analyses.
Table 3. Disease Course and Outcome of Invasive Meningococcal Disease by Clinical Manifestation

<table>
<thead>
<tr>
<th></th>
<th>No. Days in Hospital Median (IQR)</th>
<th>β&lt;sup&gt;a&lt;/sup&gt; [95% CI]</th>
<th>ICU Admittance n (%)</th>
<th>aOR&lt;sup&gt;b&lt;/sup&gt; [95% CI]</th>
<th>No. Days in ICU Median (IQR)</th>
<th>aOR&lt;sup&gt;b&lt;/sup&gt; [95% CI]</th>
<th>Case-fatality n (%)</th>
<th>aOR&lt;sup&gt;b&lt;/sup&gt; [95% CI]</th>
<th>Sequelae ≥1 Mild, n (%)</th>
<th>aOR&lt;sup&gt;c&lt;/sup&gt; [95% CI]</th>
<th>Total n (%)</th>
<th>aOR&lt;sup&gt;b&lt;/sup&gt; [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases (%)</td>
<td>842 (96)</td>
<td>819 (93)</td>
<td>860 (97)</td>
<td>836 (95)</td>
<td>307 (93)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>865 (98)</td>
<td>840 (96)</td>
<td>763 (95)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>746 (93)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>9 (7–13.75)</td>
<td>0</td>
<td>92 (63)</td>
<td>40.5 [17.6–93.0]</td>
<td>4 (2–7)</td>
<td>NP</td>
<td>27 (19)</td>
<td>16.3 [4.7–56.9]</td>
<td>28 (25)</td>
<td>9 (8)</td>
<td>37 (33)</td>
<td>3.3 [1.6–6.7]</td>
</tr>
<tr>
<td>Septic shock + meningitis</td>
<td>10 (8–14)</td>
<td>0.2 [1–4]</td>
<td>130 (67)</td>
<td>55.8 [24.4–127.7]</td>
<td>3 (2–7)</td>
<td>NP</td>
<td>27 (14)</td>
<td>9.6 [2.7–34.1]</td>
<td>36 (23)</td>
<td>23 (14)</td>
<td>59 (37)</td>
<td>4.2 [2.1–8.3]</td>
</tr>
<tr>
<td>Meningitis</td>
<td>10 (8–13)</td>
<td>0.3 [1–4]</td>
<td>100 (24)</td>
<td>5.4 [2.5–11.5]</td>
<td>3 (2–4)</td>
<td>NP</td>
<td>9 (2)</td>
<td>1.1 [0.3–4.1]</td>
<td>98 (25)</td>
<td>12 (3)</td>
<td>110 (28)</td>
<td>2.5 [1.4–4.6]</td>
</tr>
<tr>
<td>Mild meningococcaemia</td>
<td>9 (8–12)</td>
<td>0.1 [0.04–3]</td>
<td>9 (8)</td>
<td>1.0</td>
<td>2 (1–6)</td>
<td>NP</td>
<td>4 (4)</td>
<td>1.0</td>
<td>13 (13)</td>
<td>3 (3)</td>
<td>16 (16)</td>
<td>1.0</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;f&lt;/sup&gt;</td>
<td>.024</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001&lt;sup&gt;g&lt;/sup&gt;</td>
<td>&lt;.001&lt;sup&gt;g&lt;/sup&gt;</td>
<td>&lt;.001&lt;sup&gt;g&lt;/sup&gt;</td>
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</tbody>
</table>

Significant differences are outlined in italic.

Abbreviations: aOR, adjusted odds ratio; CC, clonal complex; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; NP, not performed.

<sup>a</sup> β = regression coefficient of linear regression analysis with adjustment for age, CC, and comorbidity. β represents the difference in log transformed (ln) number of days in the hospital compared to the reference category (0).

<sup>b</sup> aOR = adjusted odds ratio compared to reference category (1.0) in logistic regression analysis with adjustment for age, CC, and comorbidity.

<sup>c</sup> Per outcome measure, the no. of cases represent the total no. with information available (left) and the no. with information available for all variables included in the adjusted analysis (right). Percentages represent the proportion of cases in relation to the total no. of retrieved hospital records (n = 879).

<sup>d</sup> No. of cases related to no. of total cases admitted to ICU (n = 331).

<sup>e</sup> No. of cases related to no. of known survivors (n = 805).

<sup>f</sup> Overall P-values of the effect of clinical manifestation on the outcome measure in the crude (left) and adjusted (right) analysis.

<sup>g</sup> The outcome “sequelae” was included as categorical outcome (none vs ≥1 mild vs ≥1 severe) in the crude analyses and as a binary outcome (present vs absent) in the adjusted analyses.
and proportion of patients with sequelae was higher in adult patients, particularly in patients aged ≥65 years, compared to children (Table 2). An overview of all noted sequelae is provided in Supplementary Table 2.

Clinical Manifestation
Duration of hospital admission was slightly longer for patients with meningitis compared to patients without meningitis (Table 3). The proportion of patients admitted to the ICU was highest among patients with septic shock (Table 3). The CFR was higher in patients with septic shock compared to patients without septic shock (Table 3). In addition, (severe) sequelae developed most frequently after septic shock (Table 3).

Clonal Complex
Information on CC was available for 900 patients (96%) and categorized into 6 groups based on prevalence of the different CCs. Most prevalent was CC1/44 (n = 427, 47%) followed by CC32 (n = 148, 16%), CC11 (n = 144, 16%), CC213 (n = 38, 4%), CC269 (n = 26, 3%). The remainder (n = 117, 13%) was categorized as “other CCs.” The distribution of age and clinical manifestation per CC is outlined in Figures 1A and 2A, respectively. CC11 was less prevalent among patients aged 0–4 years compared to patients aged 10–64 years (Figure 1A) (P < .05). The proportion of cases with septic shock (with and without meningitis) did not differ between CCs.

The number of days in the hospital was significantly higher for patients infected with CC11 meningococci compared to

![Diagram A](image1.png)

![Diagram B](image2.png)

Figure 1. Distribution of meningococcal clonal complex (CC) (A) and serogroup (B) by age. Differences between categories were tested using χ²-tests and additional z-tests with Bonferroni correction for multiple testing. The overall P-values for differences between age groups in proportions of infecting CCs and serogroups were P < .001 and P < .001, respectively. CC41/44 was more prevalent among patients aged 6 months to 4 years compared to patients aged >10 years (P < .05), whereas CC11 was significantly less prevalent among patients aged 0–4 years compared to patients aged 10–64 years (P < .05). The proportion of MenB cases was higher in children aged 0–4 years compared to patients aged ≥10 years (P < .05), whereas the proportion of MenC cases was higher in patients aged 10–64 years compared to patients aged 0–4 years (P < .05). 94% (18/19) of MenY cases were aged ≥15 years with 53% (10/19) aged ≥65 years. MenW cases were equally distributed across the age groups. Abbreviations: IMD, invasive meningococcal disease; MenB, serogroup B; MenC, serogroup C; MenW, serogroup W; MenY, serogroup Y.
CC41/44, CC32, and “other CCs.” The proportion of patients admitted to the ICU appeared slightly higher for patients infected with CC11 meningococci compared to patients infected with meningococci of CC32, CC213, and CC269 (Table 4). The CC of the infecting strain had no significant effect on CFR or development of sequelae (Table 4).

Serogroup
The meningococcal serogroup was determined in 928 (99%) of the isolates. Serogroup B was most prevalent (n = 711, 77%), followed by serogroup C (n = 180, 19%), serogroup Y (n = 19, 2%), and serogroup W (n = 16, 2%). Serogroups Z (n = 1) and E (n = 1) were excluded from the analyses. The majority of MenC cases (88%) had occurred between June 1999 and December 2002, that is, prior to the implementation of the MenCC vaccine into the Dutch NIP, whereas the majority (94%) of MenY cases originated from the period after June 2006. Results on distribution of age and clinical manifestation per serogroup are outlined in Figures 1B and 2B, respectively.

Mild meningococcaemia was more prevalent among MenW cases compared to MenB and MenC cases (Figure 2B) (P < .05).

The number of days in the hospital was significantly lower for MenB cases compared to MenC cases. The proportion of patients admitted to the ICU was lowest for MenY cases (Table 5). Serogroup had no significant effect of on CFR. More severe sequelae were found for MenY (23%) compared to MenB (5%) in the crude analysis (P < .05), whereas no effect of serogroup on development of sequelae was found in the adjusted analysis (Table 5).

DISCUSSION
IMD mainly affects young and—more importantly—healthy individuals, and morbidity and mortality rates remain high. Disease course and outcome are mainly affected by age and clinical manifestation and much less by meningococcal clonal complex or serogroup. Underlying comorbidity, whether immunocompromising or not, has no effect on disease course or outcome.
### Table 4. Disease Course and Outcome of Invasive Meningococcal Disease by Clonal Complex

<table>
<thead>
<tr>
<th>Clonal Complex</th>
<th>No. Days in Hospital Median (IQR)</th>
<th>ICU Admittance</th>
<th>aOR[^a] [95% CI]</th>
<th>No. Days in ICU Median (IQR)</th>
<th>aOR[^b] [95% CI]</th>
<th>Case-fatality n (%)</th>
<th>aOR[^b] [95% CI]</th>
<th>Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[Per outcome measure, the no. of cases represent the total no. with information available (left) and the no. with information available for all variables included in the adjusted analysis (right). Percentages represent the proportion of cases in relation to the total no. of retrieved hospital records (n = 879).]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[≥1 Mild, n (%)]</td>
</tr>
<tr>
<td>No. cases (%)[^c]</td>
<td>849 (96)</td>
<td>819 (93)</td>
<td>861 (98)</td>
<td>836 (95)</td>
<td>307 (93)</td>
<td>874 (99)</td>
<td>840 (860)</td>
<td>763 (95)^d</td>
</tr>
<tr>
<td>CC11</td>
<td>12 (8–17)</td>
<td>0</td>
<td>70 (54)</td>
<td>1.0</td>
<td>4 (2–7)</td>
<td>NP</td>
<td>11 (9)</td>
<td>1.0</td>
</tr>
<tr>
<td>CC41/44</td>
<td>9 (8–12)</td>
<td>−0.3 [−.4−.1]</td>
<td>150 (38)</td>
<td>0.7 [0.4–1.2]</td>
<td>3 (2–5)</td>
<td>NP</td>
<td>36 (9)</td>
<td>2.1 [0.8–5.0]</td>
</tr>
<tr>
<td>CC32</td>
<td>9 (8–12)</td>
<td>−0.2 [−.4−.1]</td>
<td>45 (32)</td>
<td>0.5 [0.3–0.9]</td>
<td>3 (2–6)</td>
<td>NP</td>
<td>8 (6)</td>
<td>1.7 [0.6–4.6]</td>
</tr>
<tr>
<td>CC213</td>
<td>9 (8–12)</td>
<td>−0.2 [−.5−.02]</td>
<td>8 (22)</td>
<td>0.3 [−.1−.08]</td>
<td>6.5 (3.5–11)</td>
<td>NP</td>
<td>1 (3)</td>
<td>0.2 [0.02–2.5]</td>
</tr>
<tr>
<td>CC269</td>
<td>10 (7.5–16)</td>
<td>−0.2 [−.5–.1]</td>
<td>7 (28)</td>
<td>0.3 [−.1−.08]</td>
<td>6 (4–18)</td>
<td>NP</td>
<td>1 (4)</td>
<td>0.4 [0.03–5.6]</td>
</tr>
<tr>
<td>Other CCs</td>
<td>10 (8–14)</td>
<td>−0.2 [−.4−.02]</td>
<td>51 (37)</td>
<td>0.6 [0.3–1.2]</td>
<td>3 (2–6)</td>
<td>NP</td>
<td>11 (8)</td>
<td>0.6 [0.2–1.9]</td>
</tr>
<tr>
<td>P-value[^f]</td>
<td>.001</td>
<td>.026</td>
<td>.001</td>
<td>.065</td>
<td>.037</td>
<td>NP</td>
<td>.574[^g]</td>
<td>.092</td>
</tr>
</tbody>
</table>

Significant differences are outlined in italic.

Abbreviations: aOR, adjusted odds ratio; CC, clonal complex; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; NP, not performed.

[^a]: β = regression coefficient of linear regression analysis with adjustment for age, clinical manifestation and comorbidity. β represents the difference in log transformed (ln) number of days in the hospital compared to the reference category (0).

[^b]: aOR = adjusted odds ratio compared to reference category (1.0) in logistic regression analysis with adjustment for age, clinical manifestation and comorbidity.

[^c]: Per outcome measure, the no. of cases represent the total no. with information available (left) and the no. with information available for all variables included in the adjusted analysis (right). Percentages represent the proportion of cases in relation to the total no. of retrieved hospital records (n = 879).

[^d]: No. of cases related to no. of total cases admitted to ICU (n = 331).

[^e]: No. of cases related to no. of known survivors (n = 805).

[^f]: Overall P-values of the effect of CC on the outcome measure in the crude (left) and adjusted (right) analysis.

[^g]: The outcome “sequelae” was included as categorical outcome (none vs ≥1 mild vs ≥1 severe) in the crude analyses and as a binary outcome (present vs absent) in the adjusted analyses.
<table>
<thead>
<tr>
<th>Serogroup</th>
<th>No. cases (%)</th>
<th>ICU Admittance (n (%))</th>
<th>aORβ [95% CI]</th>
<th>No. Days in ICU Median (IQR)</th>
<th>aORβ [95% CI]</th>
<th>Case-fatality n (%)</th>
<th>aORβ [95% CI]</th>
<th>No. Days in ICU Median (IQR)</th>
<th>aORβ [95% CI]</th>
<th>Sequeleae ≥1 Mild, n (%)</th>
<th>aORβ [95% CI]</th>
<th>Sequeleae ≥1 Severe, n (%)</th>
<th>aORβ [95% CI]</th>
<th>Sequeleae ≥1 Total, n (%)</th>
<th>aORβ [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serogroup B</td>
<td>9 (8–12)</td>
<td>0</td>
<td>232 (25)</td>
<td>3.9 [1.0–16.3]</td>
<td>NP</td>
<td>50 (8)</td>
<td>1.0</td>
<td>133 (23)</td>
<td>29 (5)</td>
<td>162 (28)</td>
<td>0.4 [0.1–1.4]</td>
<td>753 (94)</td>
<td>736 (91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serogroup C</td>
<td>11 (8–17)</td>
<td>0.2 [0.1–0.3]</td>
<td>83 (50)</td>
<td>5.6 [1.3–23.6]</td>
<td>NP</td>
<td>15 (9)</td>
<td>0.5 [0.2–1.2]</td>
<td>34 (24)</td>
<td>15 (10)</td>
<td>49 (34)</td>
<td>0.5 [0.1–1.6]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serogroup W</td>
<td>11 (10–16)</td>
<td>0.3 [-1.7]</td>
<td>5 (33)</td>
<td>10.0 [1.4–69.7]</td>
<td>NP</td>
<td>2 (13)</td>
<td>1.4 [0.2–11.8]</td>
<td>2 (15)</td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>0.3 [0.04–1.7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serogroup Y</td>
<td>12 (8.5–15.8)</td>
<td>0.1 [-3.4]</td>
<td>4 (27)</td>
<td>1.0</td>
<td>9 (2.8–13.8)</td>
<td>NP</td>
<td>2 (13)</td>
<td>0.3 [0.04–1.8]</td>
<td>4 (31)</td>
<td>3 (23)</td>
<td>7 (54)</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-value<sup>4</sup> <.001 | .002 | .004 | .045 | .178 | NP | .722 | .251 | .020<sup>g</sup> | .463<sup>g</sup> |

Significant differences are outlined in italic.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; NP, not performed.

<sup>a</sup> β = regression coefficient of linear regression analysis with adjustment for age, clinical manifestation and comorbidity. β represents the difference in log transformed (ln) number of days in the hospital compared to the reference category (0). For serogroup C, the case fatality rate (CFR) after 2002 (10.0%) was not different from the CFR prior to the implementation of the MenC conjugate vaccine (8.6%) (P = .836).

<sup>b</sup> aOR = adjusted odds ratio compared to the reference category (1.0) in logistic regression analysis with adjustment for age, clinical manifestation and comorbidity.

<sup>c</sup> Per outcome measure, the no. of cases represent the total no. with information available (left) and the no. with information available for all variables included in the adjusted analysis (right). Percentages represent the proportion of cases in relation to the total no. of retrieved hospital records (n = 879).

<sup>d</sup> No. of cases related to no. of total cases admitted to ICU (n = 331).

<sup>e</sup> No. of cases related to no. of known survivors (n = 805).

<sup>f</sup> Overall P-values of the effect of serogroup on the outcome measure in the crude (left) and adjusted (right) analysis.

<sup>g</sup> The outcome “sequelae” was included as categorical outcome (none vs ≥1 mild vs ≥1 severe) in the crude analyses and as a binary outcome (present vs absent) in the adjusted analyses.
Our results underline that septic shock is the main determinant of the burden of IMD with higher percentages of ICU admittance, mortality, and (severe) sequelae compared to meningitis or mild meningococcaemia. We found that approximately one third of IMD patients develops septic shock, which corresponds with results from previous studies [27, 29]. The mechanism underlying differences in disease severity is not fully understood and considered as an interplay between host and virulence factors [30, 31]. We found more septic shock among patients aged 2–4 years compared to patients aged 20–64 years, indicating that maturity of the immune system plays a role. In addition, several host genetic polymorphisms have been associated with differences in disease severity [31]. As to bacterial factors, we found that patients infected with MenW more frequently developed mild meningococcaemia, which includes atypical presentations like arthritis and pneumonia. This corresponds with several previously reported clinical manifestations of MenW [1, 14]. Results from previous studies suggested more severe disease caused by MenC isolates of CC11 [20–23]. Of note, these conclusions were based on increased CFRs rather than clinical manifestation. We found no significantly higher risk for septic shock for any of the serogroups or CCs, even after stratification by age (data not shown). Presumably, CC independent virulence factors contribute to development of septic shock. Large prospective whole-genome association studies are required to provide more insight into associations between host genetic factors, meningococcal virulence factors, and severity of IMD [31]. Meanwhile, it remains unpredictable whether or not a patient will develop septic shock.

The overall CFR in this study was 8% and higher for adults compared to children with a clear peak in patients aged ≥65 years, which corresponds with results from several previous studies [20, 29, 30, 32–35]. The presence of comorbidity increased with age but did not affect the CFR. The increased CFR might therefore be due to a more general deteriorating physical condition with age, particularly in the oldest patients. No significant effect of serogroup or CC on CFR was found, which to some extent corresponds with the absence of an association between CC or serogroup and development of septic shock in this study. Although some previous studies also reported no relation between CFR and serogroup [29, 30, 36, 37], several others found a higher CFR for MenC and CC11 [20–22, 32]. A study from the United Kingdom that included >16 000 cases between 1993 and 2000 attributed the higher CFR for MenC of CC11 to the hypervirulent 2a serotype [21]. However, 73% of MenC cases in the current study were also subtype 2a, and we found no relation between the presence of serotype 2a and CFR (data not shown). The current study may have lacked power, but the numbers for MenC and CC11 were fairly high. Improvements of care for pediatric patients with septic shock [37] together with increased awareness among the Dutch population during the MenC outbreak around 2000 may have also affected the CFR in this study.

The overall proportion of patients with sequelae was 29% without a significant effect of CC, serogroup, or comorbidity. Recent studies on IMD from other countries show a marked variation in the reported percentages of sequelae, ranging from 3% to 57% [32, 33, 38]. Differences in the population under study, quality of follow-up and definition of sequelae are likely causes of the wide variation. Most studies record the notorious sequelae of IMD like scarring, amputations, hearing loss, and neurological deficits. In the current study we recorded all sequelae mentioned in the chart, including milder cognitive dysfunction and general complaints like fatigue and headache. Because we did not question patients, the prevalence of these milder sequelae is likely underestimated. Nevertheless, recording of these sequelae is relevant because they can be rather disabling in daily life and might cause additional (healthcare) expenditures. It should also be acknowledged that the impact of IMD is not restricted to the patient but also affects the family. In a follow-up study among pediatric survivors of meningococcal septic shock, 17% of the mothers reported emotional problems requiring professional help [39]. Efforts to establish accurate recording of all short- and long-term health effects of IMD will improve the accuracy of cost-effectiveness analyses.

Crucial in the judgment of cost-effectiveness of vaccination is the incidence of IMD. The incidence of IMD in the Netherlands—including MenB—peaked around 2000 (4.5/100.000 population in 2001) and subsequently dropped to the lowest level since decades (currently 0.7/100.000 population) [40]. A similar pattern of IMD incidence occurred in other countries [41–43]. Consequently, recent cost-effectiveness analyses indicated that implementation of a MenB vaccine or an adolescent MenACWY booster will only be cost-effective if the incidence of the particular serogroups increases [17, 18, 44]. The epidemiology of IMD is characterized by cyclical fluctuations and disease incidence due to one or several serogroups will likely increase at some point [45]. The United Kingdom recently implemented an adolescent MenC booster vaccination into the NIP, and the MenB vaccine is on the verge of being implemented into the UK NIP as well. Enhanced post-implementation surveillance will establish the true cost-effectiveness of these measures.

Our study has some important strengths like the detailed clinical information acquired from a large number of cases and the use of a nationally representative sample. Distribution of age and serogroup in the study population was comparable to the nation-wide distribution as well as the distribution throughout Europe [43, 46], indicating that our findings are representative for other countries with similar medical facilities. An important limitation is the retrospective study design, which might have led to over- or underestimation of values. However,
we consider it unlikely that the missing cases differed extremely from the included cases in (average) disease course or outcome.

To conclude, IMD remains a disease with high morbidity and mortality for all ages though mainly affecting young and healthy individuals. Disease course and outcome differ by age and clinical manifestation and remain unpredictable, even when the serogroup or CC is known. Because of its rapid progression and unpredictability, prevention through vaccination remains the most effective strategy against IMD. The results of this study can contribute to the accuracy of cost-effectiveness analyses.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. The authors thank the medical students for their help in data collection and the participating hospitals and sentinel laboratories for their cooperation. Furthermore, the authors acknowledge the expert laboratory assistance of Agaath Arends, Wendy Keijzers, and Ilse Schuurman. Financial support. This work was supported by the Dutch Ministry of Health, Welfare and Sports. The Netherlands Reference Laboratory received financial support from the National Institute of Public Health and the Environment (RIVM).

Potential conflicts of interest. A. v. d. E. declares to have received research support from Pfizer for vaccine studies, fees paid to the institution for consultancy services for GlaxoSmithKline (GSK) and participated in Scientific Advisory Boards of Pfizer. E. A. M. S. declares to have received unrestricted research support from Pfizer, grant support for vaccine studies from Pfizer and GSK and fees paid to the institution for advisory boards or participation in independent data monitoring committees for Pfizer and GSK. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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