Bacterial meningitis: epidemiology, herd protection, clinical characteristics, and risk assessment
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Citation for published version (APA):

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A decade of herd protection after introduction of meningococcal serogroup c conjugate vaccination

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Clinical Infectious Diseases 2014; 59: 1216-21
Abstract

Vaccination with meningococcal serogroup C (MenC) conjugate (MCC) polysaccharide vaccines led to a substantial decline in MenC disease in the vaccinated and the unvaccinated population. The decline in the unvaccinated population can be explained by herd protection by reduced colonization of meningococci expressing the MenC capsule. The duration of such herd protection is unknown. In a nationwide study from the Netherlands, we compared MenC invasive disease between 1998 and the introduction of MCC vaccination (2002) with that from 2002 to 2012, in age groups eligible and not eligible for vaccination. The proportion of isolates from clonal complexes with high serogroup C capsule expression rates during carriage (sequence type [ST] 11 and ST-8 complex) was compared between the pre- and post-vaccination periods. A total of 814 patients with invasive MenC disease were included for analysis. There was a 99% decline in MenC disease in patients eligible for vaccination and a 93% decline in those not eligible. Thirty-six percent of the overall MenC reduction between the first and last 4 years of the observation period occurred in the unvaccinated population. Clonal complex was determined in 350 (43%) isolates. The proportion of cases caused by clonal complex ST-11 and ST-8 serogroup C meningococci decreased from 251 of 268 (94%) before, to 46 of 57 (81%) after MCC vaccine introduction (P = .004). Our findings provide further evidence that herd protection results from reduced carriage of virulent meningococci. Herd protection was responsible for >36% of MCC vaccine impact and lasted for ≥10 years.

Introduction

The introduction of meningococcal serogroup C (MenC) conjugate (MCC) polysaccharide vaccines has greatly contributed to invasive meningococcal disease control.1 In the Netherlands, in response to a sharp increase in MenC cases that started in the fall of 1998, children aged 1–18 years were offered a single MCC vaccination in 2002.2 Routine vaccination at 14 months was subsequently introduced.3 Vaccine coverage of the target population has been estimated at 94%.4 After MCC vaccine introduction there was a large decline in the MenC incidence rate in the unvaccinated population.3-5 Indirect protection is thought to be the result of herd protection, whereby MCC vaccination protects the unvaccinated population by reducing carriage and transmission of virulent meningococci in the vaccinated population.6,7 Reduced carriage in the vaccinated population results in reduced transmission to the unvaccinated population. A computer simulation study in the United Kingdom has suggested that protection against carriage might last 3–10 years.8 It is unknown how long herd protection after MCC vaccination will last. Herd protection is especially relevant for countries that opted for routine MCC vaccination of infants only, because it has become clear that protective antibody titres do not last for more than a few years after infant immunization.9,10
The majority of meningococcal invasive cases are caused by a limited number of hyperinvasive bacterial lineages. Multilocus sequence typing can identify genetically related meningococcal isolates, based on similarities in 7 conserved housekeeping genes. A sequence type (ST) is defined as a combination of unique sequences of the 7 loci. Genetically similar isolates can be grouped into clonal complexes. During nasopharyngeal carriage, meningococci of different clonal complexes vary in their propensity to express their polysaccharide capsule, which is the main virulence factor of the meningococcus. Carriage studies in the United Kingdom and Germany have shown that between 78% and 88% of the clonal complexes ST-11 and ST-8 serogroup C meningococci expressed their polysaccharide capsule compared with <28% of serogroup C meningococci of other clonal complexes combined.

In a nationwide surveillance study, we determined the long-term effect of MCC vaccination on the incidence rate of MenC disease in both the vaccinated and unvaccinated population. To evaluate the proposed mechanism of herd protection, we studied the impact of MCC vaccination on the occurrence of invasive MenC disease due to isolates from clonal complexes that are known to have a high expression rate of their polysaccharide capsule during nasopharyngeal carriage.

Methods

The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) started a nationwide surveillance on meningococcal disease in the Netherlands in 1958. Clinical microbiology laboratories throughout the country send patient characteristics and meningococcal isolates to the NRLBM. Studies have estimated that isolates and clinical information on >85% of patients with meningococcal disease in the Netherlands is reported to the NRLBM. For this study, patients were included if the NRLBM received a MenC isolate cultured from blood, skin biopsy, and/or cerebrospinal fluid (CSF), or if polymerase chain reaction findings were positive for MenC in CSF from 1 June 1998 to 1 June 2012. Serogrouping was performed by Ouchterlony gel diffusion. Multilocus sequence typing was performed as described by Maiden et al. Statistics about the Dutch population were obtained from the Dutch Central Bureau of Statistics (available at: http://www.cbs.nl).

Patients were categorized as eligible or ineligible for MCC vaccination based on the earliest recorded date of the illness and the patient’s age at that time. Incidence rates were calculated per 100,000 inhabitants of the same age group, both per 3 months and per 12 months, starting 1 June 1998. Based on previous carriage studies, MenC isolates from ST-11 and ST-8 complexes were considered to express their polysaccharide capsule frequently during nasopharyngeal carriage, and MenC isolates from other clonal complexes were considered to express their capsule infrequently. The proportion of sequence typed isolates from ST-11 and ST-8 complexes before the start of MCC vaccination (1 June 1998 to 1 June 2002) was compared with that from ST-11 and
ST-8 after completion of MCC catch-up campaign (1 December 2002 to 1 June 2012). Differences between proportions were tested with the Fisher exact test. Differences were considered statistically significant at $P < .05$, and statistical tests were 2 tailed.

**Results**

In total 900 MenC episodes were identified; 86 episodes (10%) were excluded (52 were identified as double entries, and 34 were excluded because the source of isolation was not blood, skin biopsy, or CSF or was not reported; figure 1), leaving 814 patients. Age, date of illness, and date of birth were available for all 814 included cases; sex was available for 788 of 814 patients (97%). *Neisseria meningitidis* was detected in both CSF and blood in 218 patients (27%), in CSF only in 212 (26%), and in blood only in 384 (47%).

![Flowchart of case inclusion](image)

**Figure 1.** Flowchart of case inclusion.

Abbreviations:
CSF, cerebrospinal fluid;
*N. meningitidis, Neisseria meningitidis*.

The median age was 16 years (interquartile range, 5–29 years; figure 2) and 51% of patients were male. The seasonal distribution showed that the most cases occurred in January (12%) and the fewest in September (5%). The incidence rate per 100 000 persons per 12 months increased from
Herd protection after MenC conjugate vaccination

0.48 in 1998 to 1.99 in 2001 and declined after the introduction of the MCC vaccine to 0.006 in 2011. The epidemic did not affect age groups equally. Peak incidence in 2001 was 7.4 per 100,000 infants and children aged 0–5 years, 5.3 per 100,000 children and adolescents aged 6–18 years, and 1.8 per 100,000 young adults aged 19–28 years. The relative increase of the incidence rate was highest for young adults. Compared with the start of the epidemic (1998), the incidence rates increased 10-, 5-, and 3-fold, respectively, for those aged 19–28, 6–18, or 0–5 years. The median age increased, from 15 years before the introduction of MCC vaccination, to 35 years after the catch-up campaign.

In June and July 2002 children aged 1–5 years and 15–18 years received the MCC vaccination. Children aged 6–14 years were vaccinated in September, October and November 2002. During the first 3 months of the vaccination campaign, the incidence rates per 3 months for all age groups decreased (table 1). Compared with the same period in the previous year, the incidence rate decreased 65% in patients aged 15–18 years and 23% in those aged 1–5 years (table 2). Interestingly, in the same period the incidence rate for age groups that were not (yet) eligible for vaccination also decreased; this decrease was 49% in infants <1 year old, 41% in 6–14-year-olds, 24% in 19–28-year-olds, and 50% in 29–99-year-olds. The decrease tended to occur later in infants <1 year old, but numbers were small.

**Figure 2.** Age distribution.

Light grey: number of cases per year of age.

Dark grey: incidence rate per 100,000 population of same year of age.

**Herd Protection**

The reduction in MenC cases was most pronounced in patients eligible for MCC vaccination, but the incidence declined in all age groups (figure 3). During the 48 months before the introduction of MCC vaccination (June 1 1998 to June 1 2002) there were 413 cases in patients eligible for vaccination and 249 cases in patients not eligible for vaccination. During the last 48 months of
the observation period (June 1, 2008 to June 1, 2012) only four cases occurred in vaccinated age groups and 18 cases in the unvaccinated age groups; a reduction of respectively 99% and 93%. Thirty-six percent of the reduction of cases between these 2 periods occurred in the unvaccinated age groups.

**Multilocus Sequence Typing**

Multilocus sequence typing was performed in 350 of 814 isolates (43%). Fifty-three STs were identified; the median number of cases per ST was 1, and the maximum was 234. Six STs had not yet been assigned to a clonal complex at the time of writing. The most common clonal complex was ST-11 complex with 264 of 350 isolates (77%), followed by ST-8 complex with 51 of 350 (15%). Although the MenC incidence rate declined in all clonal complexes after the introduction of MCC vaccination, the decline was most pronounced among ST-11 and ST-8 complex serogroup C meningococci, which frequently express their capsule during nasopharyngeal carriage. The proportion of ST-8 and ST-11 isolates decreased from 251 of 268 isolates (94%) before the start of MCC vaccination to 46 of 57 (81%) after completion of the MCC catch-up campaign ($P = .004$; table 3). A similar pattern was observed in unvaccinated patients: the proportion of ST-11 and ST-8 complex isolates decreased from 103 of 111 cases (93%) before to 42 of 52 (81%) after completion of the MCC catch-up campaign ($P = .03$; table 3).

| Table 1. Serogroup C meningococcal disease incidence rates in different age groups, before and after the introduction of MCC vaccination. |
|-----------------|---|---|---|---|---|---|
| **Age group (years)** | **<1** | **1-5** | **6-14** | **15-18** | **19-28** | **29-99** |
| **Quarter** | **Jun - Aug 01** | **Sep - Nov 01** | **Dec - Feb 02** | **Mar - May 02** | **Jun - Aug 02** | **Sep - Nov 02** | **Dec - Feb 03** | **Mar - May 03** | **Jun - Aug 03** | **Sep - Nov 03** | **Dec - Feb 04** | **Mar - May 04** |
| **Incidence rate per 3 months per 100,000 of the same age** | | | | | | | | | | | | |
| **Jun - Aug 01** | 1.95 | .90 | .95 | 1.81 | .40 | .12 |
| **Sep - Nov 01** | 1.95 | 1.20 | .67 | 2.19 | .35 | .11 |
| **Dec - Feb 02** | 3.43 | 2.49 | 1.12 | 2.95 | .60 | .23 |
| **Mar - May 02** | 2.46 | 2.28 | 1.06 | 1.79 | .45 | .13 |
| **Jun - Aug 02** | .98 | .69 | .56 | .64 | .30 | .06 |
| **Sep - Nov 02** | .49 | .10 | .06 | .13 | .10 | .03 |
| **Dec - Feb 03** | 1.00 | .20 | 0 | .13 | .20 | .05 |
| **Mar - May 03** | 2.48 | .29 | 0 | 0 | .05 | .07 |
| **Jun - Aug 03** | .50 | 0 | 0 | 0 | .05 | .04 |
| **Sep - Nov 03** | 0 | .10 | 0 | 0 | .05 | 0 |
| **Dec - Feb 04** | 1.00 | .10 | 0 | 0 | .10 | .09 |
| **Mar - May 04** | 0 | 0 | 0 | 0 | 0 | .01 |

*a* Bold-faced incidence rates indicate vaccinated groups. Abbreviation: MCC, meningococcal serogroup C conjugate.
Table 2. Serogroup C meningococcal disease incidence rate per age group compared to the same period in the peak year 2001-2002.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>&lt;1</th>
<th>1-5</th>
<th>6-14</th>
<th>15-18</th>
<th>19-28</th>
<th>29-99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jun - Aug 02</td>
<td>51</td>
<td>77</td>
<td>59</td>
<td>35</td>
<td>76</td>
<td>50</td>
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<tr>
<td>Sep - Nov 02</td>
<td>25</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Dec - Feb 03</td>
<td>29</td>
<td>8</td>
<td>0</td>
<td>4</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Mar - May 03</td>
<td>101</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>11</td>
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<td>33</td>
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<tr>
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<td>8</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dec - Feb 04</td>
<td>29</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>Mar - May 04</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

*a Bold-faced incidence rates indicate vaccinated groups.

Figure 3. Number of serogroup C cases per 3 months in patients eligible and not eligible for meningococcal serogroup C conjugate vaccination.

Table 3. Proportion of isolates from clonal complexes with frequent capsule expression during nasopharyngeal carriage (ST-11 and ST-8 complex) before and after the introduction of MCC vaccination.

<table>
<thead>
<tr>
<th>ST-11 and ST-8 Isolates/All Isolates, No. (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>All age groups</td>
<td></td>
</tr>
<tr>
<td>251/268 (94%)</td>
<td>46/57 (81%)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td></td>
</tr>
<tr>
<td>103/111 (93%)</td>
<td>42/52 (81%)</td>
</tr>
</tbody>
</table>

Abbreviations:
MCC, meningococcal serogroup C conjugate;
ST, sequence type.
*a Fisher exact test.
Discussion

Our data show that a decade after MCC vaccine introduction, MenC disease has been reduced by >93%. These results are in accordance with previous findings. The United Kingdom, Spain, Ireland, Iceland, and Belgium experienced a substantial decline in MenC disease after the introduction of routine MCC vaccination between 1999 and 2002.

Our findings provide further evidence for the conclusion that herd protection is an important part of MCC vaccine effectiveness. We found that at least a third of the reduction of cases occurred in unvaccinated age groups. Herd protection was probably responsible for more than the 36% decrease in serogroup C cases because reduced transmission will also have prevented serogroup C cases in the vaccinated age groups. Previous work has demonstrated that MCC vaccination has a disproportionate impact on the carriage of serogroup C meningococci belonging to the ST-11 complex, which showed a high frequency of capsule expression during nasopharyngeal colonization. We now show that MCC mass vaccination also has the highest impact on reducing disease caused by clonal complexes with a high capsule expression rate, both in all patients and in the subgroup of unvaccinated patients. This finding supports the proposed mechanism of herd protection in meningococcal disease whereby reduced nasopharyngeal carriage in immunized individuals leads to less disease transmission to the unvaccinated population. The magnitude of the herd effects after MCC vaccination was largely unanticipated. Reliable estimates of the impact and duration of herd protection are important for policy deliberations about vaccine cost-effectiveness and the design of future immunization strategies.

It is unknown how long this herd protection after MCC vaccination will last. Computer models that were developed based on data from the United Kingdom have predicted stabilization of low levels of MenC disease for >15 years after mass vaccination. Our national surveillance data together with postlicensure surveillance studies from the United Kingdom have now confirmed that herd protection has persisted for at least a decade. National surveillance studies are crucial to estimate MCC vaccine effectiveness and herd protection.

The MCC vaccines became available at a time of increased MenC incidence in Europe. Because large randomized controlled trials were considered to be unattainable, MCC vaccines were licensed on the basis of safety and immunogenicity studies only. Even if randomized controlled trials had been performed, they would have been of limited use to investigate herd protection. The relatively small numbers of study participants in randomized controlled trials are unlikely to confer herd protection. Even if herd protection is elicited, the traditional calculation of vaccine efficacy is insufficient. Vaccine efficacy is calculated as [(Iu − Iv)/Iu] × 100%, where Iu and Iv represent for disease incidence in the unvaccinated and vaccinated study arms, respectively. Herd protection can affect both Iu and Iv. If disease frequency is equally reduced in both groups, the herd protection effect is cancelled out. Bias is introduced if the protective effect is unevenly distributed between the vaccinated and unvaccinated study arm. Methodological advances in the
design and analysis of cluster randomized trials have been proposed that would make it possible to assess herd protection before introducing a vaccine into public health programs.\textsuperscript{23}

Lasting herd protection is especially relevant, because it has become clear in recent years that children who are vaccinated before the age of 5 years lose their serological protective antibody levels within a few years.\textsuperscript{9} However, most countries that have implemented MCC vaccination opted for a vaccination schedules with either 2 doses in the first year of life and a booster in the second year or a single dose in the second year of life.\textsuperscript{4} As the catch-up cohort ages, protection against carriage and disease in the adolescent population will diminish in the coming years. Meningococcal carriage is age dependent, with the highest prevalence in teenagers and young adults.\textsuperscript{24} Furthermore, natural immunity in the population has declined because MCC vaccination has reduced MenC circulation.\textsuperscript{25} Dutch children <14 months of age and nonimmunized adults have lower serogroup C specific immunoglobulin G levels at present compared with the prevaccination era.\textsuperscript{9} This might actually put these individuals at high risk for invasive meningococcal disease if MenC circulation were to increase again.

Our data suggest a delay of herd protection in infants <1 year of age but offer no clear explanation for this finding. Seasonal variation may be more important in this age group, perhaps owing to a higher incidence of respiratory infections.\textsuperscript{26}

In case of re-emergence of MenC, additional vaccination of children between age 5 years (adequate immunological response) and adolescence (high carriage rate) should be considered. Because of age-dependent carriage, an additional booster vaccination in teenagers and young adults would probably improve herd protection.

The capability of meningococci to switch to a different polysaccharide capsule poses another potentially limiting factor for long-term effectiveness of MCC mass vaccination.\textsuperscript{27} Capsular switching under the selective pressure of MCC vaccination could in theory explain part of the reduction of serogroup C disease in our study. However, in that case one would expect a concurrent increase in the occurrence of other serogroup disease. Since the introduction of MCC mass vaccination, the incidence rates of all serogroups except serogroup Y have declined in the Netherlands. Clonal complexes responsible for the rise in serogroup Y disease did not previously express the serogroup C capsule.\textsuperscript{28}

A limitation of our study is its observational design. The observed decrease in MenC may have been caused by other factors than MCC vaccination. However, the consistent high coverage of the reference laboratory, the temporal relationship between the mass vaccination campaign, and the decline in the MenC incidence rate, as well as the consistency with the experience in other countries, make a causal effect likely.\textsuperscript{1}

Our findings provide further evidence that herd protection results mostly from reduced carriage of meningococci with a high capsule expression rate and that it is responsible for >36\% of MCC vaccine impact. The observed herd protection lasted for ≥10 years.
References


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Herd protection after MenC conjugate vaccination


Supplementary material

Acknowledgements. This work was supported by the National Institute of Public Health and the Environment, the European Union’s Seventh Framework program (EC-GA grant 279185 [EUCLIDS] to D. v. d. B.), the Netherlands Organization for Health Research and Development (NWO-Vidi grant 2010 to D. v. d. B.), the Academic Medical Center (AMC fellowship 2008 to D. v. d. B.), and the European Research Council (ERC starting grant 2011 to D. v. d. B.).