

# Comparative Long-term Adverse Effects Elicited by Invasive Group B and C Meningococcal Infections

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**Background.** Given the identity between *Neisseria meningitidis* serogroup B (MenB) capsular polysaccharide (polysialic acid; PSA) and PSA found on neural cell adhesion molecules, it has been proposed that infection with MenB or vaccination with PSA may be associated with subsequent autoimmune or neurological disease.

**Methods.** We conducted 2 studies. The first was a retrospective nationwide study of invasive meningococcal disease (IMD) in Iceland (with 541 subjects) during the period 1975–2004, and we cross referenced this cohort with databases with respect to subsequent diagnosis of autoimmune disorders. A follow-up study involving 120 survivors of IMD was performed. The study included 70 patients with a history of MenB and 50 patients with *N. meningitidis* serogroup C (MenC) infection, who served as control subjects. Participants answered standardized questionnaires (Beck's Depression Inventory [BDI] II, Depression Anxiety Stress Scales [DASS], and Patient Health Questionnaire [PHQ]), and serum levels of immunoglobulin (Ig) G against MenB and MenC capsular polysaccharides were measured.

**Results.** The nationwide cohort had 9166 patient-years of follow up. No evidence of increased autoimmunity was found to be associated with MenB, compared with MenC. In the follow-up study, patients were evaluated 16.6 years after the infection, representing 2022 patient-years of observation. Comparable rates of most complications were recorded, but MenC infections were associated with arthritis ( $P = .008$ ) and migraine headaches ( $P = .01$ ) more frequently than were MenB infections. No difference was observed with respect to scores on BDI-II, DASS, or PHQ. IgG anti-MenB and anti-MenC capsular polysaccharide levels were not related to patient complaints.

**Conclusions.** This study does not support the hypothesis that MenB infection may predispose to autoimmunity. MenC infections are associated with a higher prevalence of arthritis and migraine headaches. No evidence of antibody-associated pathology was detected at long-term follow-up.

Invasive meningococcal disease (IMD) represents a worldwide health problem [1]. The recent incidence of meningococcal disease is 0.35–1.01 cases per 100 000 inhabitants in most western countries [2]. In Iceland,

however, the incidence has been 2–3 times higher [3]. In the meningitis belt of sub-Saharan Africa, the incidence of IMD can approach a staggering 1000 cases per 100 000 inhabitants during epidemics; most of these cases are caused by group A meningococci [2]. The prognosis of and case fatality rate among patients affected by IMD have not changed significantly over the past 3 decades, and the infection carries a rate of postinfectious complications of 4.3%–12% [4, 5]. These long-term complications can be neurological, psychological, or physical in nature and do not seem to be associated with each other [6]. *Neisseria meningitidis* serogroup B (MenB) is the serogroup that is most commonly found in Icelandic patients, followed by *N. meningitidis* serogroup C (MenC) [3]. Since 2002, all Icelandic children are vaccinated against MenC, which

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has resulted in a significant decrease in the number of cases, but a universal vaccine against MenB is unavailable [7]. MenB capsular polysaccharide is composed of a linear homopolymer of  $\alpha(2 \rightarrow 8)$  *N*-acetyl-neuraminic acid (polysialic acid; PSA). PSA is a potential vaccine candidate, but it is poorly immunogenic, which is a property attributed to immunologic tolerance induced by polysialylated glycoproteins that include neural cell adhesion molecules (PSA-NCAM), which can be found in several molecular forms. The embryonic form, especially expressed in neural tissue during development, possesses an unusually large amount of PSA [8]. Antigenic identity between the carbohydrate component of this form and MenB PSA has been reported [9, 10]. Antibodies have been detected in patients with MenB meningitis that bind to embryonic NCAM in mouse embryonic brain cultures [11]. Because of a theoretical risk of autoimmune reactivity against neural tissue, most vaccine researchers have therefore focused on antigens other than PSA for MenB [12]. Conversely, MenC are not known to possess any surface antigens that share a similarity with surface molecules in human tissues. Therefore, one way to test the hypothesis of increased autoimmune or neurological morbidity following PSA exposure is to study individuals who have been infected with MenB and to use patients with MenC infection as control subjects. MenC has a capsular polysaccharide that differs from that of MenB only by its anomeric linkage; MenB is  $\alpha(2 \rightarrow 8)$  and MenC is  $\alpha(2 \rightarrow 9)$  linked. However, studies on late complications from IMD are challenging, because the number of patients required for such studies is difficult to estimate and a cause and effect relationship is hard to establish. A population-based study of patients with a history of IMD in Denmark found no evidence of increased autoimmunity in patients [13] or adverse birth outcomes in offspring of mothers following MenB infection [14]. We addressed this problem in 3 ways. First, the incidence of autoimmune disorders was studied in a population-based cohort with IMD in Iceland with long-term follow-up. Second, a subset of patients who survived the infection was recruited for clinical examination and to answer questionnaires regarding physical and mental well-being. Third, immunoglobulin (Ig) G anti MenB and MenC capsular polysaccharides were assayed in this patient subset. Iceland is ideally suited for studies of this nature, because meningococcal infections are relatively common in the country; a nationwide registry of all invasive cases has been kept since 1975, and clinical records are available for review and cross-referencing with hospital diagnoses.

## MATERIALS AND METHODS

### Setting and Description of the Invasive Meningococcal Disease Registry

Iceland is a 103,000 km<sup>2</sup> island in the North Atlantic where Invasive meningococcal disease (IMD) is a notifiable disease, and a nationwide registry of cases has been kept since 1975. The

country had 216,695 inhabitants in 1975 and 293,577 at the end of 2004 [15]. During this time, there were 14 hospitals in the country that provided inpatient services, and all blood cultures were processed at 2 sites. Cases were classified as IMD if they fulfilled 1 of the following 2 criteria: a positive culture of *N. meningitidis* in blood, cerebrospinal fluid (CSF), or synovial fluid specimens; or clinical signs of meningococcal infection and either a positive culture from a throat specimen or a positive Gram stain result, latex agglutination test result, or PCR result (since 2002) for meningococci from a normally sterile site.

### Retrospective Population-Based Study

Medical records of all patients with IMD in the country during 1975–2004 were reviewed. Information on clinical characteristics of the patients and their hospital course was registered, in addition to the serogroup of the meningococcal isolate. To evaluate the severity of illness, the Glasgow Meningococcal Septicemia Prognostic Score (GMSPS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring systems were used for children and adults, respectively [16, 17]. Missing values were assumed to be within normal limits. Postinfectious complications were defined as short-term or long-term complications on the basis of time of onset and duration. Short-term complications began while the patients were hospitalized and subsided within 2 weeks of onset. Long-term complications began while the patient was still hospitalized and had not subsided within 2 weeks or began after discharge from the hospital. The medical records were searched for subsequent diagnoses of rheumatic and/or immunological diseases, both manually and by computerized cross-referencing the patient identifiers with a broad range of *International Classification of Diseases, Ninth Revision* and *Tenth Revision* codes from hospital registries using codes similar to those used by Howitz et al [13]. The study was approved by the National Bioethics Committee of Iceland.

### Selection of Subjects for Follow-up Study

From the patient registry described above, 20 patients who survived the infection but were alive at the time of the study (January 2007–April 2008) and were considered to have long-term sequelae were invited to participate in a follow-up study. In addition, a random sample of 150 survivors of documented IMD caused by either MenB or MenC infection were initially informed about the study by mail. They were subsequently contacted by telephone and invited to participate. This study was approved by the National Bioethics Committee and Data Protection Agency of Iceland.

### Patient Evaluation During Follow-up

After provision of written informed consent, the participants were interviewed, and a medical history was obtained. If a child was included in the study, informed consent was obtained from the parents or legal guardians. Participants were unaware of the

serogroup of the infecting isolate. They were asked specifically about symptoms or conditions that could be attributed to sequelae from IMD, neurological, psychological, or autoimmune process (for example, seizures, cognitive dysfunction, mental problems, muscle weakness, paralysis, numbness, hearing impairment, rheumatologic diseases, skin diseases, migraine, and arthritis). They also answered 3 questionnaires regarding their mental and physical symptoms, Patient Health Questionnaire (PHQ), measuring somatoform disorder, major depressive syndrome, other depressive syndrome, panic syndrome, other anxiety syndrome, bulimia nervosa, binge eating disorder, and alcohol abuse; Beck's Depression Inventory II (BDI-II), measuring symptoms of depression; and Depression Anxiety Stress Scales (DASS), measuring symptoms of depression, anxiety, and stress, all of which have been validated in Iceland [18–20]. Finally, a physical examination was performed, and blood samples were collected.

#### Measurement of Antibodies to MenB and MenC

Enzyme-linked immunosorbent assay for MenB and MenC antibodies was performed as previously described [21–23].

#### Statistical Analysis

##### Retrospective Study

The Mann–Whitney *U* test was used to compare the GMSPS and APACHE II scores of individuals who survived with the scores of patients with fatal infection. Fisher's exact test was used to compare the mean severity score of patients who received a diagnosis with serogroup B infection with that of patients who received a diagnosis of serogroup C infection. Statistical comparison was performed using SPSS software, version 11.0 (SPSS).

##### Follow-up Study

Data are reported as mean values  $\pm$  standard deviations (SDs). Unpaired *t* test with Welch correction, paired *t* test, analysis of variance, and Fisher's exact tests were used for comparisons as

appropriate. The Mann–Whitney *U* test was used to compare IgG titers in the 2 patient groups. All *P* values were 2-tailed.

## RESULTS

#### Retrospective Cohort

Overall, 562 patients received a diagnosis of IMD during the period 1975–2004 in Iceland. Of these, the medical records of 541 (96%) were available for review. The 30-day case fatality rate in this group was 7.9% (43 of 541 patients died). Of the meningococcal isolates, MenB was most commonly identified (in 261 patients; 48.2%), followed by MenC (154; 28.5%), serogroup A (20; 3.7%), and serogroups Y and W-135 (3 each; 0.6%). Information about the serogroup was not available for 100 cases (18.5%). As reported previously, the most common sequence types (ST) in Iceland during the period 1977–2004 were ST 32, ST 11, ST 10, and ST 3492 (part of the ST41/44 complex) [3].

An overview of complications in the retrospective cohort is shown in Table 1. As shown, these were most commonly arthritis, acute renal failure, and hearing loss. Arthritis was diagnosed more often in patients with MenC than in patients with MenB infections ( $P < .001$ ), but the prevalence of other complications was not statistically different between the 2 groups. Other less common long-term health problems were epilepsy (3 patients; 0.6%), migraine headaches (3), and pericarditis (3). The following diagnoses were made in 1 patient each: adrenal insufficiency, psoriasis, strabismus, Henoch–Schönlein purpura, impaired coordination, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). The patient with SLE had IMD caused by MenC and subsequently received a diagnosis of C2 complement deficiency that was believed to be preexisting and that predisposed him to both IMD and SLE. The patient registry was cross-referenced with hospital discharge diagnoses to detect potential associations with autoimmune diseases following the

**Table 1. Retrospective Study**

Serogroup	Complication							No. of patients
	Hemorrhage	Arthritis	Renal failure	Skin necrosis	Hearing loss	Cognitive dysfunction	Other long-term complication	
A								20
B	7	6 <sup>a</sup>	5	4	8	4	10	261
C	3	21 <sup>a</sup>	7	6	4	2	5	154
Y								3
W-135								3
Unknown	3	4	3	3	2	2	1	100
Total	13	31	15	13	14	8	16	541

Acute and long-term complications by meningococcal serogroups in a cohort of 541 patients in Iceland. The far right column shows the number of infections caused by individual serogroups in the cohort.

<sup>a</sup>  $P < .001$  for B versus C.

**Table 2. Autoimmunity in Retrospective Cohort**

Age, years, at time of infection	Sex	Serogroup	Clinical manifestation	Diagnosis, ICD-10 code	Years after infection
14.7	M	C	Meningitis	Rheumatoid arthritis, unspecified, M06.9	0
12.7	M	Unknown	Meningitis	Insulin-dependent diabetes mellitus, E10.0	18
3.3	M	B	Sepsis	Non-insulin-dependent diabetes mellitus, E11.8	21

The total observation time was 9166 person-years. Three patients subsequently received a diagnosis of autoimmune disease. ICD-10, *International Classification of Diseases, Tenth Revision*.

diagnosis of IMD during 9166 person-years of observation. Only 3 patients were found; the results are shown in Table 2. The patient with RA had already been identified, but 2 additional patients received a diagnosis of diabetes mellitus 18–21 years after IMD.

### Follow-up Study of Survivors

Of the 170 patients that were offered the opportunity to participate in the study, 120 (70.6%) accepted. Of the remaining patients, 8 (4.7%) declined to participate, 14 (8.2%) could not be contacted, 22 (12.9%) could not participate for geographical reasons, and 6 (3.5%) agreed to participate but repeatedly missed appointments. Characteristics of participants are shown in Table 3. The total follow-up period was 2022 years for the entire cohort. Patients infected with MenB had longer follow-up than did those infected with MenC ( $P < .001$ ). As shown, patients infected with MenB were, on average, infected at a younger age, and children with MenB had significantly less severe disease, compared with children with MenC ( $P = .02$ ). Although average APACHE II scores for adults were higher among patients with MenC, the difference did not reach statistical significance.

### Evaluation During Follow-up

The patients were questioned about their health following the meningococcal infection (Table 4). Patients with MenC disease reported migraine headaches and previous or current arthritis ( $P < .01$  and  $P = .008$ , respectively) more frequently than did

patients with MenB disease. One patient with MenC disease, also identified in the retrospective study, had received a diagnosis of SLE. Other autoimmune disorders were not reported. The results of a physical examination, including vital signs and neurological examination findings, are shown in Table 5. The results were similar, with no significant statistical difference in any of the categories between the 2 groups.

### Questionnaires on Physical and Mental Health

Results from the 2 questionnaires measuring symptoms of depression, anxiety, and stress (BDI-II; DASS) are shown in Table 6. No difference was observed between patients infected with MenB or MenC with reference to self-reported depressive symptoms, anxiety, and stress-related symptoms. Table 6 also lists mean scores from the general public for reference. No difference was observed between the patient groups and the general public with respect to depressive scores and stress-related symptoms. However, both MenB [ $t(55) = -2.93$ ;  $P < .05$ ] and MenC patients [ $t(42) = -2.24$ ;  $P < .05$ ] had lower scores than did the reference group with respect to anxiety (table 6). According to the PHQ, 27.9% of participants with MenB diseases and 26.1% of participants with MenC disease had screening results that were positive for any of the 8 mental symptoms that the questionnaire measures ( $P = .83$ ). In a sample of outpatients in primary care in Iceland [24], 26.3% had screening results that were positive for any of the 8 mental symptoms using the same

**Table 3. Follow-up Study of Survivors**

Variable	MenB (n = 70)	MenC (n = 50)	Total (n = 120)	P
Age at time of infection, mean years ( $\pm$ SD)	9.3 $\pm$ 11.7	17.6 $\pm$ 16.8	12.7 $\pm$ 14.6	<.002 <sup>a</sup>
Current age, mean years ( $\pm$ SD)	29.1 $\pm$ 13.3	30.0 $\pm$ 16.3	29.5 $\pm$ 14.6	.72
Cumulated years of observation	1404.5	617.9	2022.4	<.001 <sup>a</sup>
Male sex, proportion (%)	32/70 (46)	22/50 (44)	54/120 (45)	
APACHE II <sup>b</sup> ( $\pm$ SD)	7.6 $\pm$ 5.2	9.2 $\pm$ 6.9	8.5 $\pm$ 6.2	.37
GMSPS <sup>c</sup> mean ( $\pm$ SD)	1.9 $\pm$ 2.2	2.7 $\pm$ 2.3	2.2 $\pm$ 2.3	.02 <sup>a</sup>

At the time of evaluation, the cohort had accrued a total of 2022 years of follow-up. One patient had 2 separate infection episodes due to MenB.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; GMSPS, Glasgow Meningococcal Septicemia Prognostic Score; SD, standard deviation.

<sup>a</sup> Two-tailed independent *t* test.

<sup>b</sup> n = 20 for MenB (only the first episode was counted in a single patient with recurrent infection), n = 22 for MenC.

<sup>c</sup> n = 50 for MenB, n = 28 for MenC.

**Table 4. Follow-up Study of Survivors Self-Reported Health During Structured Interview With a Study Physician**

Health problems and complaints	Serogroup B (n = 70)	Serogroup C (n = 50)	Total	P
Seizures/seizure disorder	4	0	4	.14
Cognitive problems	17	16	33	.41
Mental problems	14	9	23	.82
Depression	4	3	7	>.99
Anxiety	5	2	7	.70
Depression/anxiety	2	0	2	.51
NOS	5	3	8	>.99
Muscle weakness	3	4	7	.45
Paralysis	0	1	1	.42
Numbness	3	3	6	>.99
Hearing impairment	9	7	16	.92
Autoimmune disease	0	1	1	.42
Skin disease	15	7	22	.42
Eczema	3	2	5	>.99
Psoriasis	3	0	3	.26
NOS	9	5	14	.78
Migraine	7	15	22	.01
Arthritis	2	9	11	.008

Abbreviation: NOS, other diagnoses or not otherwise specified.

criteria. The difference between the 2 samples was not significant ( $P = .80$  and  $P = .97$  for MenB and MenC, respectively). In patients with MenB, 21.3% fulfilled the PHQ criteria for alcohol abuse, and in patients with MenC, 17.4% fulfilled these criteria. This difference was not significant ( $P = .61$ ).

#### Antibody Measurements

IgG levels against MenB capsular polysaccharide were similar in the 2 groups (MenB [median IgG, 6.0 EU/mL] and MenC [6.6 EU/mL];  $P = .345$ ). In contrast, patients with a history of MenC disease had significantly higher IgG to MenC capsular polysaccharide (median IgG, 5.9 EU/mL) than did patients with MenB (median, 2.3 EU/mL;  $P = .009$ ). No difference was noted between the MenB IgG levels in persons with arthritis and in those without arthritis ( $P = .592$ ). Similarly, no significant differences were detected between MenB IgG levels in subjects with migraine headaches and in those without migraine headaches ( $P = .207$ ), and no significant differences were detected between IgG to MenC capsular polysaccharide levels in subjects with arthritis and in those without arthritis ( $P = .414$ ) or in those with migraine and in those without migraine ( $P = .687$ ).

**Table 5. Follow-up Study of Survivors Results of Physical Examination**

Health problem	Serogroup B (n = 70)	Serogroup C (n = 50)	Total
General examination			
Skin scarring	1	1	2
Vital signs			
Systolic blood pressure, mean mm Hg ( $\pm$ SD)	124 $\pm$ 17	122 $\pm$ 15	
Diastolic blood pressure, mean mm Hg ( $\pm$ SD)	79 $\pm$ 10	77 $\pm$ 10	
Heart rate, mean beats/min ( $\pm$ SD)	70 $\pm$ 12	74 $\pm$ 11	
Arterial pressure, mean mm Hg ( $\pm$ SD)	94 $\pm$ 11	92 $\pm$ 11	
Neurological abnormalities			
Cranial nerves			
Smell and taste	1	1	2
Esotropia	1	0	1
Hearing impairment	6 <sup>a</sup>	9 <sup>e</sup>	15
Facial sensorium	5 <sup>b</sup>	0	5
Touch/pain	3 <sup>c</sup>	4 <sup>f</sup>	7
Vibration <sup>d</sup>	2	3	5
Strength	1	2	3
Reflexes	5	5	10
Proprioception	1	2	3

No statistical difference was observed between the 2 groups in any of the categories.

<sup>a</sup> Of the 6 patients with MenB and hearing impairment, 1 developed hearing impairment following acute otitis and 1 developed hearing impairment following an explosion.

<sup>b</sup> At least 2 due to causes other than invasive meningococcal disease.

<sup>c</sup> One secondary to surgery.

<sup>d</sup> Defined as  $<6/8$ .

<sup>e</sup> Two instances believed secondary to acute otitis.

<sup>f</sup> Two cases secondary to diabetes and herniated disc.

**Table 6. Follow-up Study of Survivors Results of Mental Health Questionnaires Scores**

Scale	Serogroup		F value	Reference mean	T value	
	B (n = 56) mean (SD)	C (n = 43) mean (SD)			B	C
DASS-D	3.2 (6.1)	4.1 (7.1)	0.43	4.58	-1.68	-0.45
DASS-A	2.5 (4.4)	3.0 (3.7)	0.60	4.26	-2.93 <sup>a</sup>	-2.24 <sup>a</sup>
DASS-S	6.5 (6.4)	6.4 (7.8)	0.90	7.57	-1.24	-0.99
BDI-II	7.6 (8.1)	6.6 (8.6)	0.37	8.80	-1.05	-1.72

DASS-D, DASS-A, DASS-S, and BDI-II are presented according to the serogroups of the invasive meningococcal isolates. No difference appeared between MenB and MenC patients with respect to any of the scores. Scores for a reference group of students are also shown, showing a significantly lower anxiety scores for the patients.

Abbreviations: BDI-II, Beck's depression inventory II, DASS-A, Depression Anxiety Stress Scale for anxiety; DASS-D, Depression Anxiety Stress Scale for depressive symptoms; DASS-S, Depression Anxiety Stress Scale for stress; SD, standard deviation.

<sup>a</sup>  $P < .05$ .

## DISCUSSION

This study addresses the prevalence of both acute complications and long-term health among patients with IMD. Retrospective analysis was performed of all cases diagnosed in the country during a 30-year period, and a cohort of survivors with a history of MenB or MenC disease was recruited to study the long-term health of the patients. The sample was population-based, participation was high, and the cohort included representative survivors of IMD. The severity of invasive disease was greater in patients with MenC, and arthritis was more commonly identified in patients with MenC than in patients with MenB. Disease severity, case fatality rate, and the rate of sequelae have been shown to be significantly higher in children with MenC than in children with MenB diseases [25–27]. In the retrospective part of this study, skin scarring was reported in 2.4%, which is substantially lower than figures from a large study in Quebec, Canada (7.7%) [27]. In the Canadian study, the risk of skin scarring and amputations was associated with serogroup C, which was associated with two-thirds of the cases [27]. In contrast, serogroup C caused 37% of all IMD cases with a known serogroup in our study. On the other hand, we identified a higher prevalence of hearing loss and renal failure (2.6% and 2.8%, respectively, compared with 1.9% and 0.7% in Quebec). Although it is conceivable that complications of IMD may be dependent on specific interactions between the host and the pathogen, including the serogroup of the isolate, they could also be explained by differences in documentation in the 2 studies.

Meningococcal arthritis can result from direct infection of the joint space, which is relatively rare, or from type III immune complex-mediated inflammation, which is believed to be more common [28]. These complications are noted in 5% of children and 11%–12% of adults with IMD [29, 30]. Based on our data, patients with MenC were significantly more likely than were MenB patients to develop arthritis. It has been postulated that pericarditis, which may have a similar pathogenesis, may be more prevalent in MenC infections [31]. In our follow-up study,

no difference in antibody titers was noted between patients who reported arthritis and those who did not.

Interestingly, patients with MenC were more likely than patients with MenB to report migraine headaches during follow-up. This has not been previously reported and warrants further study. Similar to the results of Howitz et al [13], we detected no increase in autoimmune disorders in the MenB cohort, compared with that of the MenC cohort, but the number of cases was low.

Antibodies of patients with a history of MenB meningitis have been reported to react in vitro against the embryonic form, but not the adult form, of NCAM in cell cultures from mice [11]. In addition, patients as young as 3 years of age recovering from MenB disease demonstrate both serum IgM and IgG antibody response against the capsular polysaccharide of MenB [32]. NCAM may be important for regeneration of neural tissue, including promotion of Schwann cell migration [33]. Therefore, it was of interest to compare patients with MenB and patients with MenC with respect to neurological symptoms and symptoms of depression, anxiety, and stress. Borg et al [26] recently demonstrated that children who survived IMD had greater depressive symptoms and greater fatigue at 18–36 months after the infection, compared with matched control subjects, but no difference was noted between patients infected with MenB and those infected with MenC. Our study addresses a similar issue, with 2 important exceptions: the timing of follow-up was, on average, more than a decade later, and participants were not exclusively children at the time of the infection. Nevertheless, the prevalence of mental health complaints was similar overall in the 2 groups. Therefore, although poorer mental functioning has been demonstrated in children at 18–36 months after IMD [26], our results do not suggest that psychiatric morbidity is permanently increased in the survivors at long-term follow-up. The results therefore provide support for the notion that psychological functioning continues to improve slowly during the first decade after the infection [34]. At the time of follow-up, the IgG titers against MenB were not significantly different between the groups, whereas prior MenC infection was associated with higher MenC

titers. Almost all adults have “natural” MenB (and C) antibodies that are most likely induced by cross-reactive organisms such as *Escherichia coli* K1 [12]. Disease-induced antibody levels have likely waned with time, leaving similar levels in both groups.

In Iceland, the incidence of MenB disease has historically been higher than the incidence of MenC disease [3]. Therefore, in this study, the number of patients with MenB was greater, and their follow-up was longer, which increases the chances of finding an association of this serogroup with long-term sequelae. It should be cautioned that the incidence of most autoimmune diseases is low, and the study may lack statistical power to detect a small increase in risk (type II error). Nevertheless, the results are consistent with those of 2 previous studies from Denmark that showed no evidence of increased autoimmunity or adverse birth outcome after MenB disease [13, 14]. Another potential weakness of the study is the use of patients with MenC, rather than age-matched healthy controls, as a control group. We believe, however, given the relatively high risk of sequelae following IMD [4], that patients with MenC were a more relevant comparison group for invasive MenB infection than was the general population. Another potential weakness is the assumption that natural infection with MenB produces serum antibody responses that are identical to vaccination with a PSA-based vaccine. Experiences with vaccines, however, including polysaccharide conjugates with other capsulated pathogens, have not shown qualitative differences in the serum antibody levels induced by infection or by vaccination.

In summary, results from this long-term nationwide study do not support a link between MenB infections and autoimmunity, neurological or mental symptoms. MenC infections were more severe than were MenB infections, especially in children. During long-term follow-up, antibody levels are generally low in patients with a history of IMD, and no association was noted between IgG titers to MenB or MenC and patient complaints. In our opinion, additional studies of PSA as a potential vaccine candidate against MenB should not be ruled out on the basis of theoretical concerns alone.

## Notes

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