Outcomes of Invasive Meningococcal Disease in Adults and Children in Canada Between 2002 and 2011: A Prospective Cohort Study

Manish Sadarangani,1,2 David W. Scheifele,1 Scott A. Halperin,3 Wendy Vaudry,4 Nicole Le Saux,5 Raymond Tsang,6 and Julie A. Bettinger1; for the investigators of the Canadian Immunization Monitoring Program, ACTive (IMPACT)*

1Vaccine Evaluation Center, Division of Infectious and Immunological Diseases, Department of Pediatrics, BC Children’s Hospital and the University of British Columbia, Vancouver, Canada; 2Department of Paediatrics, University of Oxford, United Kingdom; 3Canadian Center for Vaccinology, IWK Health Centre and Dalhousie University, Halifax, Nova Scotia; 4Division of Infectious Diseases, Department of Pediatrics, Stollery Children’s Hospital and University of Alberta, Edmonton; 5Division of Infectious Disease, Children’s Hospital of Eastern Ontario, Ottawa, and 6Vaccine Preventable Bacterial Diseases, National Microbiology Laboratory, Winnipeg, Manitoba, Canada

Background. Neisseria meningitidis causes 500 000 cases of septicemia and meningitis worldwide annually, with approximately 200 cases in Canada each year. Previous studies describe a case-fatality rate of 5%–15% and up to 20% of survivors suffering from long-term disability.

Methods. This study was performed in Canada between 2002 and 2011; the study area included >50% of the country’s population. We identified risk factors associated with death and the development of complications in children and adults admitted to hospital with confirmed invasive meningococcal disease (IMD). Clinical information was obtained from hospital records. Risk factors for death and complications were analyzed by univariate and multivariable analyses.

Results. Of 868 individuals hospitalized with IMD, there were 73 deaths (8.4%) and 157 (18%) developed complications. The most common complications were hearing loss (5.4%), skin scarring (5.4%), amputation (3.4%), renal dysfunction (2.6%), and seizures (2.5%). Mortality was independently associated with shock (adjusted odds ratio [aOR], 23.30; P < .0001), age (aOR, 1.02 per 1-year increased age; P < .0001), symptom onset within 24 hours of admission (aOR, 1.80; P = .0471), and admission to the intensive care unit (aOR, 0.41; P = .0196). Development of complications was independently associated with seizures (aOR, 4.55; P < .0001), shock (aOR, 3.10; P < .0001), abnormal platelet count (aOR, 2.14; P = .0002), bruising (aOR, 3.17; P = .0059), abnormal white blood cell count (aOR, 0.52; P = .0100), and prior antibiotic exposure (aOR, 0.27; P = .0273).

Conclusions. Outcomes following IMD remain poor in this resource-rich setting in the 21st century. These data identify priorities for clinical management of adults and children with IMD, and provide prognostic information for affected patients and their families and cost-effectiveness analyses for meningococcal vaccine programs.

Keywords. death; morbidity; meningitis; Neisseria meningitidis; septicemia.

Neisseria meningitidis causes approximately 500 000 cases of meningitis and septicemia globally every year, although incidence rates vary from <1 per 100 000 per year in North America and Europe to 10–1000 per 100 000 per year in the meningitis belt of sub-Saharan Africa [1]. The peak incidence of invasive meningococcal disease (IMD) occurs in children between 6 months and 2 years of age, with a second smaller peak in adolescents and young adults; approximately 50% of cases occur in adults.

In resource-rich settings, the case-fatality rate (CFR) following IMD has generally been reported at around 10%, with little change since the 1950s [2]. Survivors have very high rates of significant sequelae leading to...
long-term disability, including neurological sequelae attributed to meningitis (most notably sensorineural hearing loss) and consequences of severe tissue ischemia, leading to amputation of partial or entire limbs. Other common complications include epilepsy, learning difficulties, and motor/cognitive impairment [3].

Over the last 15 years, different meningococcal conjugate vaccines have been successfully introduced globally, resulting in a reduction in the overall burden of disease. These include monovalent capsular group A and C vaccines and a quadrivalent vaccine against capsular groups A, C, W, and Y [1]. Capsular group B is therefore the major disease-causing group against which a vaccine is not in routine use in most countries, and causes the highest rates of disease in North America, Europe, and Australasia, including recent outbreaks in the United States and Canada (www.cdc.gov/meningococcal/outbreaks and www.mss.gov.qc.ca/sujets/santepub/vaccination). In the last 12 months, a new group B vaccine (4CMenB) has been approved for use in Europe, Australia, and Canada [4], and has been recommended in the United Kingdom for introduction into the routine infant schedule [5].

These vaccines will result in further reductions in disease, although this will be dependent upon achieving high population coverage and, in the case of group B vaccines, broad protection against different strains. At present, there are no efficacy or effectiveness data regarding group B vaccines, so the true impact remains unknown. It is, therefore, important to have high-quality contemporary data on the outcomes following IMD, to enable appropriate allocation of healthcare resources and counseling of patients and their families. Furthermore, recent debates surrounding the potential cost-effectiveness of capsular group B vaccines [5] have highlighted the importance of outcome data to enable policy makers to reach evidence-based conclusions when making decisions regarding the introduction of new vaccine programs.

The objectives of this study were to describe the outcomes following IMD in a prospective cohort of children and adults, and to identify specific risk factors for death and development of neurological and nonneurological complications.

**PATIENTS AND METHODS**

**Study Locations**
Active, prospective, population-based surveillance of IMD in children and adults across Canada has been conducted by the Canadian Immunization Monitoring Program ACTive (IM-PACT) since 2002. Surveillance was coordinated by 12 urban centers, collecting data from >150 hospitals in 8 provinces. The combined catchment areas included >16 million individuals, around 50% of the Canadian population, and approximately 90% of the pediatric tertiary care beds in Canada. This study included patients admitted to hospital with IMD between 1 January 2002 and 31 December 2011. Introduction of meningococcal vaccines in this population has been previously described [6].

**Study Subjects**
Patients with *N. meningitidis* identified by culture and/or polymerase chain reaction (PCR) from a normally sterile body fluid or tissue, most commonly blood and/or cerebrospinal fluid (CSF), were included. Cases were actively identified via microbiology laboratories, infection control practitioners, ward and intensive care unit (ICU) staff, and local public health units, and by interrogation of hospital databases for relevant discharge codes based on the *International Classification of Diseases, Ninth Revision and Tenth Revision*, which included terms for meningococcal disease. Individuals <18 years of age were classified as children and those aged ≥18 years were considered to be adults. Bacteremia was defined as positive culture and/or PCR from blood. Meningitis was defined as positive culture and/or PCR from CSF, and/or CSF pleocytosis (CSF white blood cell [WBC] count ≥5 cells/µL).

**Data Collection**
Clinical data were collected from hospital records, including demographics, clinical features, comorbidities, laboratory results, treatment administered, and outcome at hospital discharge. Complications were defined as significant abnormalities present at hospital discharge. Seizures occurring as part of the clinical presentation were considered a risk factor in analyses, whereas those present at hospital discharge were considered complications. Prior antibiotic exposure was considered to be any antibiotic immediately before the diagnosis of meningococcal infection was first considered and/or before the person was admitted to the hospital. All information was collected from the hospital records as documented by the medical teams and recorded into a standard form, which was reviewed at the IM-PACT data center before being entered into an electronic database. A dual data entry process was used with separate operators and preprogrammed consistency checks.

**Characterization of Bacterial Isolates**
All isolates were characterized initially in the local and provincial laboratories according to standard procedures and then sent to the National Microbiology Laboratory where the capsular group was confirmed, additional identification of serotypes and serosubtypes was performed, and isolates were stored.

**Statistical Analysis**
Data were analyzed with SAS software version 9.3 (SAS Institute, Cary, North Carolina). Categorical variables were compared using Pearson $\chi^2$ test (2-tailed). Fisher exact test was used if the expected value of any variable in the $\chi^2$ test was <5. Odds ratios (ORs) for mortality and complications were obtained using binomial regression with a log link. Exploratory investigation of
confounding and interaction were assessed using Mantel-Haenszel methods. Risk factors were entered into a multivariable (MV) model using a forward stepwise approach based on the strength of the univariate (UV) associations. Models were compared using a likelihood ratio test. All variables with a P value <.25 in an unadjusted UV analysis, and no interaction terms, were included in the MV model; only those with a P value <.05 were retained in the model. Factors where >20% of the population had missing data were excluded from the MV model. Unadjusted effects were estimated using all available data, and MV analyses were carried out in subjects with complete data for the factors included. Individuals who did not survive were excluded from the analyses of complications.

**Ethical Considerations**
Appropriate approvals for the study were obtained in all hospitals.

**RESULTS**

**Study Population**
There were 868 individuals hospitalized with IMD during the study period—419 (48%) children and 449 (52%) adults. There were 73 deaths (8.4%), and the CFR was lower in children (17/419 [4.1%]) than in adults (56/449 [12%]). In contrast, 88 of 419 (21%) children had at least 1 complication compared with only 69 of 449 (15%) adults (Figure 1). The highest CFR occurred in adults aged ≥60 years (17.1%), whereas the highest rate of complications was in children aged <5 years (23.9%) (Figure 1). The majority of deaths occurred early during hospitalization—death had occurred by 3 days in 16 of 17 (94%) children and 40 of 56 (71%) adults. The median length of hospital stay in survivors was 8 days (range, 1 day to 9 months). The majority of cases were due to capsular group B (478/868 [55%]), and worst outcomes of the most common groups were associated with group C (Table 1), although the group was not significant in any of the MV analyses. Bacteremia alone was the most common syndrome (352/868 [41%]), due to its predominance in adults. An additional 220 (25%) had meningitis alone, with 284 (33%) being admitted with both (Supplementary Table 1).

The highest CFR occurred in adults with septic shock without meningitis (30/90 [33%]), whereas the lowest occurred in adults with meningitis alone (2/89 [2.2%]) (Supplementary Table 1). Highest rates of complications occurred in children with septic shock without meningitis (23/60 [38%]). Neurological complications (n = 54) were slightly more common than nonneurological complications (n = 45) in children, whereas the numbers were similar in adults (41 neurological, 42 nonneurological)

![Figure 1](https://academic.oup.com/cid/article-abstract/60/8/e27/2462960/11-August-2018)

**Figure 1.** Age-specific outcomes of hospitalized children (<18 years) and adults (≥18 years) with invasive meningococcal disease. "+" indicates reference group for comparisons; *P* < .05 compared to reference group. Abbreviations: CI, confidence interval; n/a, not applicable; OR, odds ratio.
In children, deafness, seizures, amputation, and skin scarring were the most common complications. In adults, deafness and skin scarring were common in addition to motor neurological deficits and renal dysfunction (Figure 2). Multiple complications affected 58 of 157 (37%) of those with morbidity.

### Risk Factors for Death

In the entire study population, shock was the most significant risk factor for death in the MV analysis (OR, 23.30; \(P < .0001\); Supplementary Table 2). Age (OR, 1.02 per 1-year increased age; \(P < .0001\)) and rapid onset of symptoms (within 24 hours of admission) (OR, 1.80; \(P = .0471\)) were additional independent factors associated with increased mortality. Admission to ICU was associated with higher mortality in the UV analysis, but after adjusting for these other factors, ICU admission was protective (OR, 0.41; \(P = .0196\); Figure 3A and Supplementary Table 2). In children, shock was the only independent predictor of death (OR, 8.31; \(P < .0001\); Figure 3A and Supplementary Table 3). In adults, shock (OR, 20.66; \(P < .0001\)), onset of symptoms within 24 hours of admission (OR, 2.31; \(P = .0212\)), and an abnormal platelet count (OR, 3.45; \(P = .0275\)) were independently associated with increased mortality, whereas admission...
to ICU resulted in decreased mortality (OR, 0.34; \( P = .0403 \); Figure 3A and Supplementary Table 4).

### Risk Factors for Complications

Overall, seizures (OR, 4.55; \( P < .0001 \)), presence of bruising (OR, 3.17; \( P = .0059 \)), shock (OR, 3.10; \( P < .0001 \)), and an abnormal platelet count (OR, 2.14; \( P = .0002 \)) were independent predictors of complications (Supplementary Table 2). There were 2 independent factors associated with a lower risk of complications—an abnormal peripheral WBC count (OR, 0.52; \( P = .0100 \)) and exposure to antibiotics immediately prior to hospital admission (OR, 0.27; \( P = .0273 \); Figure 2B). In children, seizures, shock, bruising, and abnormal platelet count were independent risk factors for development of complications (Supplementary Table 3). In adults, the only significant predictors in the MV analysis were shock, an abnormal platelet count, and smoking (Figure 3B and Supplementary Table 4).

Further analysis was undertaken to confirm if there were differences between risk factors for neurological and nonneurological complications. In the overall cohort, independent risk factors for development of neurological complications were seizures, meningitis, shock, and abnormal platelet count (Figure 3C). An abnormal peripheral WBC count was an independent predictor for decreased risk of neurological complications. In children, seizures, meningitis, and an abnormal WBC count were significant independent risk factors for neurological complications, with similar ORs to the overall study population. In contrast, an abnormal platelet count was the only factor associated with neurological complications in the MV analysis of adults (Figure 3C).

Analysis of all subjects revealed that similar factors were associated with increased odds of nonneurological complications, specifically, shock and an abnormal platelet count (Figure 3D). However, meningitis was a protective factor for development of...
nonneurological complications. The same factors remained significant in the MV analysis for children, whereas shock was the only independent risk factor for development of nonneurological complications in adults (Figure 3D).

An abnormal platelet count was an independent risk factor in many of the models, so further analysis was performed to investigate the relationship between the degree of abnormality and outcome. The risks of both death and development of complications were specifically associated with thrombocytopenia (platelet count of <100 x 10^9 platelets/L), and the risk was greatest with a platelet count <50 x 10^9 platelets/L (OR, 15.40; P < .0001 for death and OR, 12.14; P < .0001 for complications; Figure 4).

**DISCUSSION**

This is the largest prospective study exploring risk factors in all adults and children with IMD, without restriction to a specific subgroup, such as those with meningococcal septic shock. Overall, 27% of individuals had a bad outcome (death or significant complication at hospital discharge) with higher CFRs and lower complication rates in adults compared with children. Shock was the most significant factor determining mortality in adults and children and the only protective factor in the overall adjusted analysis was admission to ICU. Shock and thrombocytopenia, in particular having platelets <50 x 10^9/L, were the best predictors of nonneurological complications. Although these were
also significant predictors of neurological complications, seizures and presence of meningitis were more important. These findings have important implications with regard to identifying priorities for management of patients with IMD and providing adequate prognostic information, and can also be used to inform cost-effectiveness calculations for meningococcal vaccine programs.

The CFR of 4% in children and 12% in adults and the rates of complications (18% overall) are similar to published data from many previous studies [3, 7–10], although some have reported lower rates of complications [11–14]. Studies with follow-up of 15 years posthospitalization have found rates of sequelae as high as 50%–60%, including physical and neuropsychiatric problems [15–21]. Age was a major independent factor in predicting death; adults aged ≥60 years were 5-fold more likely to die than children aged 1–4 years. A similar relationship has also been found in other studies from Europe and the United States [7, 11, 14, 22–24]. Although the CFR was lower in children, complications in children aged <5 years was particularly high (24%). Hearing loss and seizures were most common in those aged <1 year and skin scarring and amputation was most common in 1- to 4-year-olds. These are all likely to have long-term impact on health and healthcare costs and are therefore of considerable importance when evaluating the value of infant meningococcal vaccines. Of note, capsular group B disease was much more common in children than adults (70% vs 41%), highlighting the importance of an effective capsular group B vaccine in childhood.

We have identified a number of factors that highlight the priority for management of IMD. One of the most important findings was that admission to ICU was a protective factor in the adjusted analysis, with a >2-fold reduction in death compared to those not admitted to ICU, despite being associated with higher mortality in the UV analysis. Requirement for ICU should be considered early in all cases of suspected IMD, especially if there may be significant delay before transfer to ICU can be achieved. This is supported by previous smaller studies, which have reported a reduction in CFR with intensive care management [25, 26]. Our study provides further compelling evidence for the need of careful monitoring of circulatory status and early and aggressive management of shock, as this was the most significant predictor of death in adults and children and also an important predictor for development of complications. The finding that prior antibiotic exposure was associated with a lower risk of developing complications was interesting, and, although it was statistically significant, it was based on a small number of individuals who had received a variety of different antibiotics.

In addition to the factors described above, a number of other risk factors for death or development of complications were identified that are not easily amenable to modification through better management, but could still be used in advising patients and their families about likely outcome. Rapid onset of symptoms (within 24 hours of admission) was a predictor of death overall, and is likely to represent a more fulminant course of disease either due to host or bacterial factors. Development of petechiae within 12 hours of admission was a risk factor for mortality in a previous study that published the first prognostic score for IMD [24]. This suggests that patients whose symptoms require medical attention quickly after onset are at higher risk and should be monitored more closely. As in previous studies, meningitis was a risk factor for neurological complications, but protective against nonneurological complications. The latter case may be explained by a theory that the infection and host inflammatory response occurs predominantly in the central nervous system, with relative sparing of other tissues. Thrombocytopenia has been found to be a predictor of mortality in adults with meningococcal meningitis and children with meningococcal sepsis, and is included in the newly devised base excess and platelet prognostic score [8, 23, 27, 28]. This study demonstrates that when all individuals with IMD are considered, it is a significant predictor of death in adults and complications in adults and children. It would be expected that thrombocytopenia would lead to vascular-related complications. Perhaps surprisingly, it was a predictor only for neurological complications. Perhaps surprisingly, it was a predictor only for neurological complications in adults and nonneurological complications in children. This might reflect differences in susceptibility of different tissues to ischemic damage in these age groups, or may be due to confounding with shock and other factors in the MV analysis.

The major strengths of this study are that it was a prospective cohort based on active surveillance and included a wide range of clinical and basic laboratory information that would routinely
be collected for all patients admitted to hospital with suspected meningococcal disease. The results, therefore, can be easily applied to a range of other similar settings. Although previous studies have identified risk factors for poor outcomes following IMD, none have undertaken a MV analysis of prospectively collected data in adults and children. Previous studies have been based on retrospective data or restricted to specific populations, either based on age (usually studies of children), acuity of illness (such as those admitted to ICU), or syndrome (septicemia or meningitis).

The study also has some limitations. Some individuals with IMD residing within the defined study population area may have attended hospitals outside the IMPACT network, although it is unlikely that the characteristics of these patients would differ from those of the study cohort. If individuals were too sick to have appropriate samples taken early in their illness or if they died before samples could be obtained, the bacteria would not be isolated and such cases would be excluded; it is therefore possible that true outcomes are worse than found in this study. Some of the sickest patients would have died prior to possible ICU admission, which may underestimate the relative mortality of those admitted to ICU. The study areas are predominantly urban, so data from cases in rural areas were limited, and it is possible that features in this population may be different. Some specific variables included in previous meningococcal prognosis scoring systems were not collected in this study, so it was not possible to compare these data to previously published scoring systems. However, many of these scores include data that would only be routinely collected from ICU patients and which would have therefore excluded a significant proportion of our study population from the analysis. Only laboratory-confirmed cases of IMD were included in the study, to guarantee standardization across study sites. There may have been additional cases of IMD that were not laboratory confirmed, and which therefore would have been excluded from the analysis.

We have demonstrated that even with modern medical advances, outcome in adults and children following IMD are poor, with high morbidity and mortality in a resource-rich setting. Our large dataset has enabled specific analyses to identify risk factors for death and neurological and nonneurological complications in children and adults hospitalized with IMD, which will be of benefit in determining management priorities and providing prognostic information to patients and their families. This study also provides additional resources to aid cost-effectiveness analyses for new meningococcal vaccines. It is highly likely that the significant burden of this disease will only be reduced by use of effective meningococcal vaccines against all capsular groups.

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 copyrighted. 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

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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.

References


APPENDIX

IMPACT network investigators from 2002 included the following: N. Bridger and R. Morris, Janeway Children’s Health and Rehabilitation Centre, St John’s, Canada; S. Halperin and K. Top, IWK Health Center Halifax, Canada; P. Déry, Centre Mère-Enfant de Québec, Quebec City, Canada; D. Moore, Montreal Children’s Hospital, Montreal, Canada; M. Lebel, Hôpital Ste-Justine pour les enfants, Montreal, Canada; N. Le Saux, Children’s Hospital of Eastern Ontario, Ottawa, Canada; D. Tran and L. Ford-Jones, The Hospital for Sick Children, Toronto, Canada; J. Embree and B. Law, Winnipeg Children’s Hospital Winnipeg, Canada; R. Tsang, National Microbiology Laboratory, Winnipeg, Canada; B. Tan, Royal University Hospital, Saskatoon, Canada; W. Vaudry, Stollery Children’s Hospital, Edmonton, Canada; T. Jadavji and O. G. Vanderkooi, Alberta Children’s Hospital, Calgary, Canada; D. Scheifele, L. Sauvé, J. Bettinger, BC Children’s Hospital, Vancouver, Canada.