IMPACT Project Protocol: Enhanced Population-based Core Surveillance of Meningococcal Invasive Infections at Participating Centers Across Canada

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[1] to Jan. 2013, [2]to June 2007, [3]to Dec. 2016, [4]to June 2005, [5]to June 2017, [6]to Dec 2017 [7]to July 2016, [8]to Dec 2019, [9]to Jan. 2012

IMPACT Project Protocol: Enhanced Population-based Core Surveillance of Meningococcal Invasive Infections at Participating Centers Across Canada

1. PROJECT SUMMARY

Active metropolitan area surveillance for hospital admissions related to invasive infection with *Neisseria meningitidis* will be conducted at the 13 centers in the IMPACT network in collaboration with Public Health officials, local infection specialists (many of whom are members of the Public Health Agency/Canadian Institutes of Health Research Canadian Immunization Research Network (CIRN)) and infection control practitioners during the interval from January 1, 2016 to December 31, 2022. Meningococcal surveillance expanded to a new center in Hamilton, Ontario (center 13) on January 1, 2019. The objectives are 3-fold, including:

- description of affected children and adults and the nature and outcome of the infection episodes
- incidence rate determination in defined populations, by age, serogroup and study year
- detailed study of the organisms recovered from cases

The nurse monitor at each center will seek to identify meningococcal cases admitted to the IMPACT hospital through regular contacts with the bacteriology laboratory, infection control practitioners and staff of the wards and intensive care unit. Both local and referred cases will be reported. In addition, in collaboration with CIRN monitors where they are present, IMPACT monitors will identify meningococcal infections affecting children and adults at other acute care hospitals within defined population areas surrounding the IMPACT center, using expedient case-finding strategies. Completeness of case-finding will be audited bi-annually by contacting local Public Health Units, liaising with microbiologists and/or infection control practitioners at all hospitals in the

specific catchment areas and searching health records at local hospitals for relevant discharge codes. The case definition will be based on identification of *N. meningitidis* in a normally sterile body fluid or site such as blood or cerebrospinal fluid (CSF) by culture or PCR test. Case information will be entered electronically on the standardized case report form. No personal identifiers will be included in these reports, which will be assigned an individual code number upon data entry.

2. BACKGROUND

2A. 2002-2016 Summary

Since 2002, 12 IMPACT centers have been searching their defined catchment populations for cases in order to calculate the annual incidence rate for invasive meningococcal infection among children and adults. The defined population areas encompassed over 17 million adults and children, just over 50% of the Canadian population. With 12 IMPACT centers, the network encountered approximately 100 cases per year, although local outbreak activity and previous and new immunization programs influenced this. The case totals amounted to half of the national total. The population data was census-based. Analyses addressed the effects of age, meningococcal serogroup and impact of new immunization programs on incidence rates.

Hospital microbiology labs forwarded all invasive meningococcal isolates to the provincial laboratories as per local arrangements. The isolates were then shipped to the National Microbiology Laboratory where they were typed in detail. Isolates were matched with the case and identified with an IMPACT code number. Test results were collated at the IMPACT data center.

This study has assembled the largest and most complete picture of meningococcal disease to date in Canada, just in time to measure the effects of group C conjugate vaccine programs, assess the burden of disease associated with other serogroups, for which multi-valent conjugate vaccines are now available and predict and monitor the effects of new serogroup B vaccines as they become available.

2B. Meningococcal Invasive Infections

Meningococci rank second in Canada among bacteria causing life-threatening infection in children, adolescents and adults. With the initiation of group C immunization programs overall incidence has declined from 0.6 per 100,000 to <0.05[1]. Peak incidence occurs in children under 1 year of age (at 6.0 per 100,000 per year) but a smaller secondary peak is also apparent in the adolescent age group. Bloodstream invasive infections can progress very rapidly, causing shock and microvascular damage, with high mortality [2, 3]. Bacteremia can also result in purulent meningitis, septic arthritis, serosal space infections etc. Pneumonia features in some cases, either as the portal of entry or a complication of bacteremia. In previous IMPACT reports of meningococcal cases [2, 4, 5], 68% of cases required initial intensive care. Median length of stay in hospital was 8 days (range 1-107 days). Overall mortality averaged 9.3% [4]. Sequelae at discharge including deafness, amputations and neurological deficits occurred in about 18% of cases, with highest rates following group C disease [2, 5].

Prevention of meningococcal infections using vaccines is complicated by the existence of multiple serogroups, which are immunologically unrelated. Serogrouping is based on the polysaccharide capsular material that coats the bacteria and impedes uptake by phagocytic cells. Antibodies directed against the capsular polysaccharide afford protection against the particular serogroup but do not cross-react with other serogroups. Purified polysaccharides are the basis of first generation vaccines, which typically contain antigens of serogroups A, C, Y and W. The polysaccharide-based meningococcal vaccines are poorly immunogenic in young children [6] (the age group at highest risk of infection) and protect for only a few years, for lack of immunologic memory [7]. Thus their use has been limited to special circumstances, such as control of outbreaks and protection of individuals at increased risk [8].

Since 2001 a second generation of meningococcal vaccines was introduced in which capsular polysaccharide is chemically linked to a carrier protein such as tetanus

toxoid. These conjugate vaccines are able to elicit protective responses from 2 months of age and establish immunologic memory, which lasts longer than that provided by the polysaccharide-based vaccines. Their safety and effectiveness were demonstrated in a nationwide program in the United Kingdom. Serogroup C conjugate vaccines are recommended for routine administration to infants and children and have been supplied as part of the public program in all provinces since 2005.

Conjugate vaccines targeting all four of the preventable meningococcal serogroups have been developed and licensed in Canada. They include serogroups A, C, Y and W and since 2011, have been supplied as part of the public program for adolescents in 6 provinces [9]. Group Y meningococci increased in importance during the 1990s in Canada and the USA to account for one-third of cases in the USA [10] and about 12%-18% in Canada [4, 11, 12]. Highest rates occur in adolescents and young adults [13]; however one third of serogroups Y cases are in adults $\geq$ 60 years of age [5]. Meningococci belonging to serogroup W typically cause sporadic cases but have the potential to cause outbreaks [14]. Serogroup A strains have not been endemic in Canada for several decades but cause epidemic disease in other parts of the world (e.g. sub-Saharan Africa). Protection is desirable for travelers to endemic areas [15] and residents therein. Population immunity may help to prevent re-introduction of group A strains to Canada. Finally, potential shifts in serogroup predominance due to programs aimed at preventing group C disease should be considered.

The capsule of group B strains is not immunogenic and until recently no licensed vaccine was available. This was an unfortunate gap because group B strains cause a substantial portion of infections in young children [10]. A newly developed third generation of vaccines containing surface-exposed proteins to protect against multiple strains of serogroup B was recently approved in Canada. One of the vaccines has been used epidemic/outbreak control in mass immunization programs in regions of Quebec and at one university campus in Nova Scotia. Much like the conjugate pneumococcal vaccines [16, 17], these serogroup B vaccines will not provide protection against all serogroup B strains that cause invasive disease. Thus continued surveillance will be

particularly important to monitor epidemiologic shifts in invasive meningococcal disease as these vaccines are used in the population.

Most cases of meningococcal infection occur in previously healthy individuals. The rate or severity of infection is increased among persons with complement disorders [18], other immunodeficiencies and asplenia [8]. Among healthy individuals, the risk of infection is increased among those exposed to a recent case, those newly housed in crowded groupings (military recruits, university dormitories, homeless shelters) [19], smokers (especially in crowded social settings) and possibly in those with recent influenza or other viral respiratory infection [10].

It is particularly timely to continue enhanced surveillance of meningococcal infections in children and adults. Robust surveillance systems are necessary in order to determine the impact of new vaccination strategies for targeted or universal prevention programs. Just as the use of conjugated pneumococcal vaccine in infants has caused a decrease in the incidence of invasive disease in adults [20], the implications of such programs for meningococcal disease in the entire population are critical. Data from 2002-2013 will provide baseline information for most provinces, against which the benefits of new immunization programs using group B vaccines and expansion of quadrivalent vaccine programs can be measured. The relative importance of serogroup B strains not included in the vaccine will be of interest, particularly any shifts upward in specific strains or changes in the clinical presentation as serogroup B disease is curbed. Additionally, the effects of group C and quadrivalent conjugate vaccines can continue to be measured and monitored. Decisions to routinely use multivalent vaccines will require detailed information about group-specific risk of disease, complications and deaths. This study will continue to be a principal source of such information and will form a foundation upon which additional research (such as health economic research, health policy research, etc.) can be undertaken.

3. STUDY PLAN

The study plan has 3 related elements:

- case surveillance
- incidence rate determination
- isolate studies

3A. **Case surveillance**

Active surveillance for invasive meningococcal disease (IMD) will continue at 13 participating IMPACT centers [21, 22], which admit over 75,000 children annually, in the age group 0-16 years. Centers account for over 90% of Canada's tertiary care pediatric beds. Each IMPACT center employs a nurse monitor to seek out and report specified target conditions. The current targets include a range of post-immunization adverse events, acute flaccid paralysis, invasive pneumococcal, meningococcal and *H. influenzae* infections and admissions with pertussis, varicella, zoster or rotavirus infection. Monitors work part or full time depending on the size of the center, under the supervision of a volunteer investigator. The latter are pediatric infectious disease specialists.

Case-finding at IMPACT centers is based on frequent contacts with the hospital microbiology laboratory, infection control practitioners, staff of the wards and intensive care unit and local public health. Both local and referred cases are reported.

Case finding in surrounding areas includes all pediatric and adult cases arising from defined populations. Surveillance will encompass all acute care hospitals within the specific area generally corresponding with Statistics Canada Metropolitan census areas. Situationally appropriate strategies will be used to facilitate surveillance. Collaboration with the CIRN Severe Outcome Surveillance Network (CIRN-SOS) will enhance involvement of adult infectious disease specialists located at the adult care facilities in the IMPACT cities. Where microbiology services are regionally centralized, close liaison with the laboratory will suffice to detect cases. Where a close working relationship is possible between regional public health officials and the IMPACT team, monitors will arrange to be advised of new cases as public health officials receive the required case notifications from regional hospitals and physicians. Where few other hospitals exist

within a specific area, monitors will liaise with laboratory and/or infection control staff at those hospitals to identify new cases. Various combinations of such methods may be used to best suit local circumstances. The objective for each locale is to ascertain as many cases in real time as possible with the remainder being identified by periodic record reviews.

At all healthcare sites, approval for enhanced surveillance of invasive meningococcal disease will be obtained and renewed as required. With approval, the nurse monitor will review the patient chart to complete the case report form. Data will be collected in a confidential fashion without case identification.

Completeness of case finding will be audited every 6 months by searching microbiology records and health records (using relevant discharge codes) at each area institution and by cross-checking cases with local Public Health officials. The complete list of ICD10 codes is appended.

The **surveillance case definition** will include each of the following elements:

- *Neisseria meningitidis* isolated or detected by PCR from a normally sterile body site or fluid, such as blood, CSF, joint fluid, pleural, peritoneal, pericardial fluid or tissue biopsy.
- persons of all ages
- with onset between January 1, 2002 and December 31, 2022
- For Hamilton between January 1, 2019 and December 31, 2022

Patients who are **not eligible for inclusion** in the surveillance of cases:

- diagnosis based only on clinical signs, gram stain, or antigen test
- meningococci isolated only from respiratory tract, including conjunctiva, sinuses, middle ear/mastoid, throat, peritonsillar abscess, cervical lymph node, tracheal aspirate, bronchial lavage etc. (While such isolates could be linked with invasive infection they do not define it adequately.)

Monitors will complete a **standardized case report** electronically. Information to be gathered will include the following subject to availability in the health record:

- demographic data: birthdate, sex, ethnic origin, partial postal code (first 3 digits) of community of residence
- health history: general state of health, any chronic condition (including smoking, alcoholism, IV non-prescription drug use), any immune disorder
  previous meningococcal or other invasive infection
  previous meningococcal vaccination (product, date)
- current illness: dates of onset, admission to hospital
  extent, severity and complications of infection, level of care required; duration of stay; outcome
- isolate data: source, susceptibility to antibiotics, serogroup (or PCR-based data where available, if culture negative)
- risk factors identified: complement disorder, other immunocompromise(including HIV/AIDS), recent contact with a meningococcal case, demographic factors, recent foreign travel (e.g. to Africa, Saudi Arabia), or group living arrangement (college dormitory or residence, barracks or homeless shelter), teaching profession

No personal identifiers will be collected, such as name, initials or address. Community of residence will be identified from the first 3 digits of the postal code. For linkage purposes, a local inventory number will be assigned to each case. This number can be used by the monitor to link the case report form with the person's hospital registration number. A separate record with the local inventory number and the hospital registration number is kept at each IMPACT center in a locked, secure file. This information does not leave the IMPACT center. **Subjects will not be contacted to supply missing information.** The family physician or health department may be contacted to obtain pertinent immunization information, per IMPACT routine.

Patient data will be entered electronically on the case report form. Completed electronic case reports will be accessed by the IMPACT data center in Vancouver where they will be scrutinized for completeness. Any queries will be resolved with the monitor. Data security measures include code-limited access to the main database, with frequent tape backups of the main and working databases. A tally of reports received will be issued at the end of each month, indicating by center the number of cases reported that month and during the year to date.

Data submitted to the data center is encrypted and stored on a physically secure, non-public SQL Server database located at the Child and Family Research Institute in Vancouver. The data is entered through the web-based Daciforms application software based on user account role verification. All user accounts have specific rights/restrictions clearly stated within the system, including read/write ability, scope accessibility (by centre and individual data forms), data querying, and data extraction rights. All users' passwords are encrypted within the database and all data traffic between the users and the database is encrypted (SSL protocol).

The database will be reviewed in depth at least annually, usually prior to the annual meeting of Investigators.

3B. **Incidence Rate Determinations**

Age-group specific, serogroup-specific and regional incidence rate determinations will be made. Completeness of the case totals (numerators) will be verified by audit of laboratory and health records data, as above. Duplicate cases will be removed. Audits will extend to any other acute care hospitals in the defined areas, to identify eligible cases. Monitors will complete standard case reports for such cases, to provide a complete picture of the disease burden locally. Where appropriate, audits will extend to selected hospitals just outside the defined areas, to ascertain whether any individuals from the defined areas are admitted there for illness care.

The defined areas will correspond with established census tracts, permitting use of population census data. Defined catchments have been determined for 13 IMPACT centers. Current population data will be used, using best estimates for inter-census years, to be obtained from Statistics Canada or local health authorities.

3C. **Studies of Case Isolates**

Every reasonable effort will be made to ensure that an isolate is saved from each eligible case, including those diagnosed at a referring hospital or other local hospital, for special studies.

If the isolate has been identified at an IMPACT hospital, their microbiology laboratory will forward the isolate to the provincial laboratory as per the established protocols. If the isolate has been identified at a non-IMPACT hospital or laboratory, the isolate will be sent to the provincial laboratory as per the expected protocol for notifiable infections. Monitors will encourage or confirm compliance on a case by case basis.

The IMPACT data centre communicates with the National Microbiology Laboratory in Winnipeg on reported cases, at intervals throughout the year, once the data has been entered electronically by the centers. In order to maintain confidentiality, information will include only date of birth, date of culture, province, (and hospital where the isolate was recovered), source of the specimen, and the assigned IMPACT number. Dr. Tsang at the National Laboratory will match the isolates received with our case list and label the isolates with the IMPACT numbers.

At the National Laboratory isolates will be subjected to serotyping and serosubtyping on the basis of their major outer membrane proteins, multilocus sequence typing (MLST), the Meningococcal Antigen Typing System (MATS), and nucleotide sequencing of antigen genes. PCR-based serogrouping will be attempted for isolates that are non-groupable by standard serologic means [23]. As test results are completed they will be reported electronically to the IMPACT data center and collated with case reports.

Isolates will be identified only by their IMPACT code number. Isolates will be kept in storage as the IMPACT collection, for future studies. Isolates may be used to facilitate detailed studies of meningococcal B in anticipation of new vaccines to prevent serogroup B infections. Isolates or details about the isolates subtypes may be shared upon appropriate request to the IMPACT executive.

4. LOGISTICS

With the current roster of 13 centers and defined population areas exceeding 17 million persons, the projected case total in 2016 is 80 to 100 cases per year. This projection is based on the incidence rate of 0.45 per 100,000 observed in recent years across Canada [4, 24]. Case totals will be influenced by variability in sporadic disease activity, and outbreaks. New immunization programs using group C conjugate have reduced serogroup C case totals [4, 25].

Monitors will be provided with a time allocation budget based on the expected number of cases in adults and children encountered annually at each center with an increase provided to those centers where the majority of cases occur outside of the IMPACT hospital. Allocations will encompass all activities related to the study.

The expected distribution of cases per year in children and adults in 2016 is summarized as follows:

Halifax	2-5	Vancouver	14-17	Ottawa	5-7
Quebec	14-17	St. John's	2 – 4	Calgary	4-5
Toronto	15-20	Montreal	15-20	Edmonton	6-8
Winnipeg	3-5	Saskatoon	2 – 4	Hamilton	4-6

Budget allocations recognize that some of the work involved in this project is independent of caseload, including annual REB renewals and periodic amendments, monitor orientation, ascertainment audits etc. Centers are given equal time allowances

for such activities. Caseload dependent activities are based on the higher figures in the above ranges.

The project will assemble 20 years of case information (2002-2022). An annual report for the preceding year on surveillance activities will be written at the end of the second quarter that will include surveillance through December 31, of each year. Surveillance will conclude on December 31, 2022 but wrap-up and analysis activities will continue to June 30, 2023.

5. ANALYSIS PLAN

All of the eligible cases seen at the 13 centers will be combined for a **case series analysis**, reflecting the total experience of centers with local and referred cases. This analysis will consider the age distribution of infections (overall and by serogroup); presenting syndromes; length of hospital stay and utilization of intensive care facilities; case fatality rate and risk factors for fatal outcome; and major sequelae of infection.

Annual **population-based analyses** will be made based on populations at the 13 centers. Analyses will include: age-specific attack rates; serogroup-specific attack rates; regional incidence rates; estimated cumulative risk of meningococcal infection by serogroup; case-fatality rates by age, syndrome and serogroup; decline in rates of group B disease in provinces with new immunization programs; and difference in rates of group B and other groups in provinces with and without immunization programs or with differently structured programs. Disease burden will be described in detail, similar to the case series. Comparison with national notifiable diseases data will be made when notifiable disease data are available.

Of interest regarding the **infecting organisms** will be an analysis of diversity within the major serogroups, looking particularly for evidence of dominance of particular strain characteristics. MATS results will be summarized, if available. Population-based

data will lend itself to an analysis of the severity of disease associated with each serogroup.

6. ETHICAL CONSIDERATIONS

This project is being done in collaboration with Medical Officers of Health in all jurisdictions. Meningococcal infections are reportable communicable diseases in Canada. This obligation is met by the infection control practitioner or laboratory staff of the participating hospitals reporting to Public Health authorities in all jurisdictions and will not be duplicated by IMPACT monitors. Similarly, the forwarding of meningococcal isolates to the provincial and national laboratories is standard public health practice, to which hospitals are expected to comply.

The IMPACT project will collect more detailed information about cases than accompanies communicable disease reports (enhanced surveillance). IMPACT staff and procedures will protect the confidentiality of personal information. Case report forms will not contain personal data, apart from birthdate (necessary for calculation of age incidence, vaccine failures and linkage of isolate information) and partial postal code (necessary for distinguishing cases from defined census areas). The latter will be limited to the first 3 digits, to preserve anonymity.

Case audits at all hospitals will observe the same principles of ethics and safeguards. With approval of local ethics boards, contact will be made with the health records supervisor, requesting a search for eligible cases (specified discharge codes, time period, area of residence). If additional cases are identified, the monitor will seek permission to review the medical record and complete a case report, as above.

Isolates will be linked with IMPACT cases only after they have made their way through routine channels to the National Microbiology Laboratory in Winnipeg, where the assigned IMPACT code number will be added. The IMPACT project will fund more

detailed characterizations of isolates than is routinely performed. Results will be analyzed and reported in collaboration with the laboratory director, Dr. Raymond Tsang.

Additional funding for related projects may be provided by other industry partners or government agencies. All industry and government partners providing funding will be provided with summaries of interim data analyses, final reports and completed manuscripts from data generated by the project.

7. FUTURE PLANS

The surveillance network provides a platform for additional research studies, such as past collaborations to examine the long-term morbidity of subjects who survive invasive meningococcal disease or to further characterized the strains circulating in Canada. Other future collaborations with industry partners and/or public health are also envisioned.

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International Classification of Diseases: Meningococcal Infection

Syndrome	ICD10 Code
Meningococcal meningitis	A39.0
M. encephalitis	A39.8 (G05.0)
Meningococcemia/septicemia	A39.2
Chronic meningococcemia	A39.3
M. hemorrhagic adrenal syndrome (Meningococcal sepsis with disseminated intravascular coagulation, shock)	A39.1
M. carditis	A39.5
M. optic neuritis	A39.8 (H48.1)
Meningococcal infection NOS	A39.9
Other meningococcal infection	
Septic arthritis	A39.8 (M01.0)
Post-meningococcal reactive arthritis	A39.8 (M03.0)

IMPACT – Defined Population Areas and Case Projections, 2012

Center	Children (0-16 yr)	Adults	Total	Predicted Cases per year*
1. Halifax	90,900	323,100	414,000	2.8
2. Quebec City	128,300	525,400	653,700	12.4
3. Toronto (GTA)	1,607,800	5,025,600	6,633,400	17.2 **
4. Winnipeg	164,900	522,700	687,600	2.6
5. Vancouver	586,600	2,097,500	2,684,100	11.8 **
6. Ottawa	202,600	679,900	882,500	6.8
7. Calgary	330,400	1,042,400	1,372,800	3.0
8. Montreal CH	392,900	1,507,600	1,900,500	15.2 **
9. St. John's	63,600	237,300	300,900	2.8
10. Montreal SJH	(included above)	-	-	-
11. Edmonton	264,300	814,600	1,078,900	3.8 **
12. Saskatoon	169,600	447,900	617,500	1.8
13. Hamilton	142,900	550,000	692,900	2.9
TOTALS	4,215,300	14,055,900	18,271,200	84.6

* Based on average number of cases at each center from 2006-2010 for centers 1-12. For center 13 based on the 2009 incidence of 0.42 per 100,000. Includes referred pediatric cases and adult cases. Population figures from 2009.
** Centers where the majority of cases occur outside of the IMPACT center and require additional funding to capture all cases.