COMMON INFECTIOUS DISEASES CAUSED BY BACTERIA

ADVICE
Invasive meningococcal disease (IMD) 358

EPIDEMIOLOGIC STUDY
Haemophilus influenzae bacteriemia in children 368

COMMENTARY
Public health risks of raw milk consumption 375
The Canada Communicable Disease Report (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice. The CCDR Editorial Board is composed of members based in Canada, United States of America, European Union and Australia. Board members are internationally renowned and active experts in the fields of infectious disease, public health and clinical research. They meet four times a year, and provide advice and guidance to the Editor-in-Chief.

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TABLE OF CONTENTS

ADVISORY COMMITTEE STATEMENT
A National Advisory Committee on Immunization (NACI) update on invasive meningococcal disease (IMD) epidemiology and program-relevant considerations for preventing IMD in individuals at high risk of exposure
A Pham-Huy, J Zafack, C Primeau, O Baclic, M Salvadori, S Deeks
on behalf of the National Advisory Committee on Immunization

C Frankel, J Robinson, S Khan, M Alghounaim, J McDonald, A Lopez, S Fanella, J Gunawan, J Wong, J Comeau, J Bowes, R Slinger, A Kalia, A Roberts, K Leifso, M Ulanova, M Barton

COMMENTARY
Public health risks of raw milk consumption: Lessons from a case of paediatric hemolytic uremic syndrome
A Silveira, J Pinheiro Carvalho, L Loh, M Benusic

OUTBREAK REPORT
Community Legionella outbreak linked to a cooling tower, 2022
S Rebellato, C Lee, C Gardner, K Kivilahti, J Wallace, D Hachborn, J Fenik, A Majury, J Kim, A Murphy, J Mnenery

INFOGRAPHIC
Screening recommendations for chlamydia and gonorrhea during pregnancy in Canada, 2023

SURVEILLANCE
Antimicrobial susceptibilities of Neisseria gonorrhoeae in Canada, 2021
P Sawatzky, B Lefebvre, M Diggle, L Hoang, J Wong, S Patel, P Van Caeseele, J Minion, R Garceau, S Jeffrey, D Haldane, L Lourenco, G Gravel, M Mulvey, I Martin
Surveillance of laboratory exposures to human pathogens and toxins, Canada, 2022
C Abalos, A Gauthier, A Davis, C Ellis, N Balbontin, A Kapur, S Bonti-Ankomah
A National Advisory Committee on Immunization (NACI) update on invasive meningococcal disease (IMD) epidemiology and program-relevant considerations for preventing IMD in individuals at high risk of exposure

Anne Pham-Huy¹, Joseline Zafack², Courtney Primeau³, Oliver Baclic², Marina Salvadori³,4, Shelley Deeks⁵ on behalf of the National Advisory Committee on Immunization*

Abstract

Following recent outbreaks of invasive meningococcal disease (IMD) in Canada and updates to provincial vaccination guidelines, the National Advisory Committee on Immunization (NACI) conducted a targeted review of evidence with a focus on immunization of adolescents and young adults. NACI reviewed national and international immunization recommendations for populations at high-risk of IMD, national IMD epidemiology and program-relevant considerations. Given the varied IMD epidemiology, NACI determined that recommending a pan-Canadian targeted program is currently challenging and that regional programs may be better suited to prevent IMD in population groups considered to be at high-risk of exposure. Further data is needed to ascertain contemporary risk factors for IMD (including activities and settings associated with bacterial acquisition, carriage and transmission) and estimate the true cost of meningococcal vaccine-preventable infections in Canada. To support provinces and territories in their decision-making, an outline of program-relevant elements for provincial and territorial consideration is provided.

Introduction

Invasive meningococcal disease (IMD) is a rare but serious bacterial disease with a relatively high case fatality rate and significant long-term sequelae, including limb amputations and permanent central nervous system injury (1). Following the recent cases of IMD on university campuses in the winter of 2022/2023 in Atlantic Canada (2) as well as the subsequent recommendations for the immunization of post-secondary students and other young adults living in congregate living settings by some provinces and territories (PTs) (3,4), the Public Health Agency of Canada and the National Advisory Committee on Immunization (NACI) were requested by the Council of Chief Medical Officers of Health to review the current national guidance on use of serogroup B meningococcal vaccines and quadrivalent conjugate meningococcal (Men-C-ACYW) vaccine boosters in post-secondary settings. Specifically, the policy question reviewed by NACI was, “Should additional high-risk populations be offered a serogroup B meningococcal vaccine and/or Men-C-ACYW booster vaccine in order to prevent IMD outbreaks in older adolescents and young adults, 15 to 24 years of age?”
Methods

To answer the policy question, NACI conducted a targeted review of evidence, with a focus on adolescents and young adults, that included national and international guidelines for the prevention of IMD in populations at high risk of IMD exposure, national and international definitions of high-risk populations, meningococcal vaccine characteristics, and EEFA (ethics, equity, feasibility, acceptability) programmatic considerations related to immunization of individuals at high risk of IMD exposure. The epidemiological data for IMD cases with disease onset between January 1, 2012 and December 31, 2019, in Canada was obtained from a previous analysis (5). The Public Health Agency of Canada compiled updated Canadian epidemiological data, including an outbreak analysis for IMD cases occurring between 2020 and 2022, through a data request to PTs participating in the National Enhanced Invasive Meningococcal Disease Surveillance System, through which PTs voluntarily report epidemiologic data on confirmed IMD cases on an annual basis. A request was made to PTs not currently participating in the National Enhanced Invasive Meningococcal Disease Surveillance System to also obtain these data for the same period. The data were validated for 12 of the 13 PTs, while the analyses for the remaining PTs was based on the isolate submissions provided to the National Microbiology Laboratory for confirmation of serogroup and further strain characterization. All age-standardized analyses were done with the direct method using the 2011 Canadian census data. The NACI IMD Working Group met on May 10 and 24, 2023, and the full committee reviewed the evidence presented to the NACI IMD Working Group on June 5, 2023. NACI approved the conclusions on July 14, 2023.

National and international immunization recommendations

Currently, NACI recommends that adolescents and young adults, depending on local epidemiology and programmatic considerations, receive a dose of monovalent conjugate meningococcal C (Men-C-C) or quadrivalent Men-C-ACYW vaccine routinely at the age of 12 (grade six or seven), even if previously vaccinated as infants or toddlers (6). NACI also recommends the use of protein-based meningococcal vaccines that primarily target serogroup B (serogroup B meningococcal vaccines: Bexsero™, 4CMenB; or Trumenba™, MenB-fHBP) on an individual basis, taking into consideration the individual preferences, regional serogroup B epidemiology and strain susceptibility. For individuals at high risk of IMD due to exposure or underlying medical conditions, NACI recommends immunization with a serogroup B meningococcal vaccine and Men-C-ACYW vaccine, as well as Men-C-ACYW booster immunization for those at ongoing risk (7).

In Canada, the adolescent dose of Men-C-ACYW is primarily provided through school-based immunization programs in grades four through 12 (children 9–17 years of age) (8,9). Eight PTs (Prince Edward Island [PE], British Columbia [BC], Alberta [AB], Nunavut [NU], New Brunswick [NB], Yukon [YT], Northwest Territories [NT], Québec [QC]) currently provide vaccination in grade nine or later, typically less than five years prior to the initiation of post-secondary studies. Based on a generally accepted assumption that protection from vaccination lasts at least five years, immunization offered through late adolescent school-based programs is likely to see protection last into the first years of post-secondary settings. Recently, PE and Nova Scotia [NS] also expanded their IMD programs to include serogroup B meningococcal immunization of adolescents and young adults who are living in group settings while attending post-secondary education (e.g. living in dormitory or other residence) and living for the first time in a youth-based congregate living setting, respectively (3,4).

In 2021, 89% of 17-year-old adolescents in Canada had received at least one dose of meningococcal vaccine, which is consistent with the national goal of 90% vaccine coverage at this age (10,11). In addition, through its current immunization programs, Canada has also been able to achieve its disease reduction goal of fewer than five cases per year of IMD caused by serogroup C in children younger than 18 years of age (10). Most cases of serogroup C IMD currently occur in unvaccinated adults over 40 years of age (5).

While the majority of IMD cases in Canada are sporadic, outbreaks have occurred across the country with variable magnitudes. As part of a comprehensive public health responses to these outbreaks, Canadian PTs have previously implemented targeted immunization programs (12). Most recently, meningococcal vaccines have been used to control hypervirulent serogroup B (ST-269) and W (ST-11) clones at the provincial or regional level in QC, BC and AB (12,13).

Internationally, several jurisdictions recommend catch-up or an additional dose of meningococcal vaccine to adolescents and young adults who are attending post-secondary studies or living in close quarters, including university students living in residential colleges and residential accommodation. The United States, United Kingdom, Australia and New Zealand identify post-secondary students, particularly those during the first year of attendance and those residing in close-living situations, as being at increased risk of IMD and have recommended vaccination (14–17). Increased relative risk for serogroup B IMD in these jurisdictions has previously been estimated to be approximately three times higher for students compared to non-students in the same age group (18,19).
Epidemiology of invasive meningococcal disease in Canada, 2012–2022

NACI reviewed the epidemiological risks associated with different serogroups of IMD in Canada by age group and geography. Since the introduction of meningococcal immunization programs in the early 2000s, the epidemiology of IMD in Canada has changed significantly. The incidence of IMD due to serogroup C declined by 93% and the overall IMD incidence declined by 55% from the pre-vaccine era to 2015 (20).

Between 2012 and 2022, there were a total of 1,196 cases of IMD reported in Canada. Overall, the mean incidence of IMD during this period was 0.31 cases per 100,000 population per year (Table 1); however, the distribution according to the number of cases, incidence rates and serogroups varied substantially across age groups and PTs (Figure 1).

When considering age, the highest annual incidence rates between 2012 and 2022 were observed for infants younger than one year of age (mean incidence: 3.11 cases per 100,000 population), followed by children 1–4 years of age (0.82 cases per 100,000 population). Adolescents 15–19 years of age and young adults 20–24 years of age had slightly lower mean incidence compared to children 1–4 years of age at 0.58 cases per 100,000 population and 0.37 cases per 100,000 population, respectively. From 2012 to 2022, children younger than five years of age accounted for the largest number of cases (N=265, or 23% of total IMD cases) followed by adolescents 15–19 years of age (N=138, or 12% of total IMD cases) and adults 20–24 years of age (N=98, or 8% of total IMD cases).

Between 2012 and 2022, the highest incidence of IMD was serogroup B (0.14 cases per 100,000 population), followed by serogroup W and serogroup Y (both 0.06 cases per 100,000 population, respectively). Serogroup B incidence was highest in children younger than one year of age and children in the 1–4 years age group (2.03 and 1.73 cases per 100,000 population, respectively). Serogroup W and serogroup Y incidence was highest in children younger than five years of age and young adults 20–24 years of age (1.02 and 0.65 cases per 100,000 population, respectively).

Table 1: Incidence rates, per 100,000 population, of invasive meningococcal disease in Canada by age group and year, 2012–2022 (N=1,178 cases)

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<td>1–4</td>
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<td>1.17</td>
<td>0.97</td>
<td>0.91</td>
<td>0.84</td>
<td>0.51</td>
<td>0.83</td>
<td>1.02</td>
<td>0.65</td>
<td>0.39</td>
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<td>5–9</td>
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<td>0.20</td>
<td>0.20</td>
<td>0.05</td>
<td>0.15</td>
<td>0.20</td>
<td>0.10</td>
<td>0.15</td>
<td>0.17</td>
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<tr>
<td>10–14</td>
<td>0.68</td>
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<td>0.21</td>
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<td>0.16</td>
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<tr>
<td>15–19</td>
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<td>0.73</td>
<td>0.84</td>
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<td>0.71</td>
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<td>0.14</td>
<td>0.19</td>
<td>0.47</td>
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<td>20–24</td>
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<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.17</td>
<td>0.12</td>
<td>0.39</td>
<td>0.36</td>
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<td>25–29</td>
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<td>0.25</td>
<td>0.12</td>
<td>0.12</td>
<td>0.16</td>
<td>0.08</td>
<td>0.12</td>
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<td>30–39</td>
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<td>0.06</td>
<td>0.15</td>
<td>0.10</td>
<td>0.10</td>
<td>0.16</td>
<td>0.20</td>
<td>0.19</td>
<td>0.07</td>
<td>0.09</td>
<td>0.13</td>
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<td>40–59</td>
<td>0.31</td>
<td>0.16</td>
<td>0.18</td>
<td>0.20</td>
<td>0.13</td>
<td>0.15</td>
<td>0.31</td>
<td>0.20</td>
<td>0.19</td>
<td>0.15</td>
<td>0.19</td>
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<tr>
<td>60 and older</td>
<td>0.28</td>
<td>0.42</td>
<td>0.22</td>
<td>0.33</td>
<td>0.41</td>
<td>0.42</td>
<td>0.52</td>
<td>0.42</td>
<td>0.20</td>
<td>0.06</td>
<td>0.14</td>
<td>0.31</td>
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<td>Overall (crude rate)</td>
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<td>0.35</td>
<td>0.29</td>
<td>0.30</td>
<td>0.27</td>
<td>0.33</td>
<td>0.37</td>
<td>0.37</td>
<td>0.23</td>
<td>0.13</td>
<td>0.21</td>
<td>0.30</td>
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</tbody>
</table>

Table 1 notes:
- Cases of total sample were missing age
- Coronavirus disease 2019 (COVID-19) pandemic, public health measures (e.g. lockdown, physical distancing) were implemented
- Data sources: National Enhanced Invasive Meningococcal Disease Surveillance System (eIMDSS), data request to provinces and territories not participating in eIMDSS, and National Microbiology Laboratory

Figure 1: Serogroup distribution of invasive meningococcal disease case isolates by province/regions, 2015–2020

Abbreviations: AB, Alberta; BC, British Columbia; MB, Manitoba; MenB, Neisseria meningitidis serogroup B; MenC, Neisseria meningitidis serogroup C; MenW, Neisseria meningitidis serogroup W; MenY, Neisseria meningitidis serogroup Y; ON, Ontario; QC, Quebec; SK, Saskatchewan

Data source: National Microbiology Laboratory
0.59 cases per 100,000 population, respectively), followed by serogroup W in children younger than one year of age (0.48 cases per 100,000 population) and serogroup B in the 15–19 and 20–24 years age groups (0.34 and 0.17 cases per 100,000 population, Table 2). During this period, the highest number of cases were reported for serogroup B in the younger than five (N=189), 15–19 (N=79) and 20–24 (N=46) years age groups. This was followed by cases caused by serogroups W and Y in children younger than five years of age (N=39 serogroup W cases), adolescents 15–19 years of age (N=15 and N=30 serogroup W and Y cases, respectively) and young adults 20–24 years of age (N=18 and N=23 serogroup W and Y cases, respectively).

Most PTs had an annual mean IMD incidence rate of less than 0.50 cases per 100,000 population (Table 3). However, the age-standardized incidence rates were highest in NU (1.15 cases per 100,000 population per year, 95% CI: 0.28–2.00), followed by NT (0.49 cases per 100,000 population per year, 95% CI: 0.07–1.10), NS (0.47 cases per 100,000 population per year, 95% CI: 0.27–0.66) and QC (0.44 cases per 100,000 population, 95% CI: 0.29–0.59).

Table 2: Incidence rates, per 100,000 population, of invasive meningococcal disease in Canada by age group and serogroup, 2012–2022 (N=1,178 cases)

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Younger than 1</th>
<th>1–4</th>
<th>5–9</th>
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<th>15–19</th>
<th>20–24</th>
<th>25–29</th>
<th>30–39</th>
<th>40–59</th>
<th>60 and older</th>
<th>Overall</th>
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<tr>
<td>B</td>
<td>2.03</td>
<td>0.59</td>
<td>0.12</td>
<td>0.10</td>
<td>0.34</td>
<td>0.17</td>
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<td>0.05</td>
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<td>0.14</td>
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<td>C</td>
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<tr>
<td>W</td>
<td>0.48</td>
<td>0.09</td>
<td>0.01</td>
<td>0.01</td>
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<td>0.06</td>
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<td>0.01</td>
<td>0.02</td>
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a N=18 cases of total sample missing age
b Other are those cases with the serogroup noted as: A, E, Z, 29E and non-encapsulated
c Unknown are those cases missing serogroup information

Table 3: Age-standardized incidence rates, per 100,000 population, of invasive meningococcal disease by province/territory and year

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<tr>
<td>British Columbia</td>
<td>0.36</td>
<td>0.24</td>
<td>0.29</td>
<td>0.22</td>
<td>0.18</td>
<td>0.54</td>
<td>0.52</td>
<td>0.25</td>
<td>0.13</td>
<td>0.08</td>
<td>0.30 (0.19–0.41)</td>
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<td>Alberta</td>
<td>0.41</td>
<td>0.35</td>
<td>0.22</td>
<td>0.28</td>
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<td>0.20</td>
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<td>0.32</td>
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<td>0.28 (0.20–0.37)</td>
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<td>0.20 (0.15–0.25)</td>
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<td>0.40 (0.30–0.51)</td>
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<td>0.22</td>
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<td>0.25</td>
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<td>0.07</td>
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<td>0.74</td>
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<td>0.44</td>
<td>0.30</td>
<td>0.14</td>
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<td>0.95</td>
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<td>0.31</td>
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<td>0.21</td>
<td>0.03–0.67</td>
<td>0.21 (0.03–0.67)</td>
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<td>1.15 (0.28–2.00)</td>
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</table>

Direct method age standardization using the 2011 Canadian census data

Data sources: National Enhanced Invasive Meningococcal Disease Surveillance System (eIMDSS), data request to provinces and territories not participating in eIMDSS, National Microbiology Laboratory


Recently, trends in geographical differences across Canadian jurisdictions have been observed for prevalent serogroups. Between 2015–2020, culture-confirmed IMD due to serogroup W was common in Western Canada, accounting for more cases (60.2% and 55.6% of IMD cases in BC and AB, respectively) than all other serogroups combined. In contrast, IMD due to serogroup B was more common in Eastern Canada in QC and Atlantic Canada, accounting for 55.3% and 73.3% of IMD cases, respectively (Figure 1).

Overall, the majority of IMD cases in Canada occurred in the fall and winter months with the peak onset observed in the month of January (N=116, 11.8%), March (N=111, 11.3%) and December (N=97, 9.9%) (Figure 2).

Based on the genetic testing of IMD strains from Canadian provinces that was conducted by the National Microbiology Laboratory for the period from 2010 to 2020, over 90% of serogroup B strains have been predicted to have a sufficient antigen expression that would elicit an immune response in individuals vaccinated with either of the two currently authorised serogroup B vaccines (21–23). Similarly, based on the level of bacterial antigen surface expression determined by the meningococcal antigen typing system, 4CMenB vaccine was previously predicted to confer protection against a high proportion of serogroup B IMD isolates collected between 2010 and 2014 from all parts of Canada (21).

**Vaccine protection against invasive meningococcal disease**

High levels of antibody are important for protection against IMD due to the rapid disease progression and because bactericidal activity (the presumed primary immunologic mechanism of protection) is predominantly achieved through antibody-mediated complement activation (24,25). Available data suggest that protection against IMD decreases in many adolescents and young adults within five years following immunization with conjugate meningococcal vaccines (14,17,26–28). While vaccine effectiveness data are limited for serogroup B vaccines, it is likely that over 50% of vaccine recipients maintain protection up to four years post immunization (13,29–34). Serogroup B vaccines are also likely to broaden the protection against non-B serogroups expressing the vaccine-contained antigens. While not authorized for this indication, 4CMenB may also provide some cross-protection against Neisseria gonorrhoeae (29,35–37). However, neither of the serogroup B vaccines appear to have an effect on carriage and, consequently, herd immunity (38–40).

**Invasive meningococcal disease risk assessment and program-relevant considerations**

In addition to the assessment of the national disease burden, vaccine characteristics and existing PT immunization programs, NACI also considered EEFA program-relevant elements in the context of the Canadian Immunization Guide definitions and NACI recommendations for high-risk groups due to increased risk of exposure.

Based on the principle of equity and ethics, it was acknowledged that all population groups identified as being at high risk of exposure should be equally considered for, and have access to, vaccination against IMD. However, it was also recognized that, given the very small number of cases, as well as due to high cost of meningococcal vaccines, immunization of all individuals who may be at increased risk of exposure may not be equally feasible across PTs.

In general, NACI concluded that, given the diversity of the Canadian health care system and differences in the individual PT disease burden, it was important to allow flexibility for PTs to make individual decisions about which populations they wish to prioritize for immunization. However, while the level of risk is influenced by local epidemiology and the timing and type of adolescent PT programs, it was recognised that any permissive recommendations should not lead to increased inequity relative to vaccine access (e.g. depending on the place of residence or ability of high-risk individuals to purchase the recommended vaccines).

To support PTs in their decision making, NACI provided an outline of program-relevant elements to be considered when assessing the population-group risk and deciding on whether an IMD program for that population is warranted (Table 4).
<table>
<thead>
<tr>
<th>Program-relevant factors</th>
<th>Elements for consideration</th>
</tr>
</thead>
</table>
| **Epidemiology and risk factors** | - IMD is a rare (approximately 100 cases per year over the last decade) but serious disease with high case fatality and life-long sequelae.  
- IMD epidemiology varies between Canadian PTs, with IMD incidence being highest in individuals younger than five years of age and followed by those in the 15–24-year-old age group.  
- While there were regional differences in serogroups causing IMD in 2012–2022, serogroup B disease represents the largest proportion of IMD cases, including in individuals 15–24 years of age.  
- Population activities and settings that have previously been associated with increased risk of IMD may have changed over the last several decades, and no activities or settings were identified through the available Canadian epidemiological data as leading to increased risk of IMD in Canada. Age remains a highly reliable predictor of risk. |
| **Vaccine characteristics** | - High levels of antibody are important for protection against IMD due to the rapid disease progression and because bacterial killing is primarily achieved through antibody-mediated complement activation (24,25).  
- Available data suggests that protection against IMD decreases in many adolescents and young adults within five years following immunization with conjugate meningococcal vaccines (14,17,26–28) or serogroup B vaccines.  
- Based on the genetic testing, over 90% of recent serogroup B isolates in Canada have been reported to express antigens at levels that are predicted to be susceptible to the bactericidal immune response elicited following the vaccination with serogroup B vaccines (21–23).  
- Although it is currently not authorized for protection against N. gonorrhoeae, outer membrane vesicles-based vaccines, such as the 4CMenB vaccine, have been reported in small studies to potentially offer some level of cross-protection against gonococcal infection (29,35–37). Clinical trials evaluating vaccine effectiveness are ongoing (NCT04350138).  
- Both serogroup B and serogroup C-containing vaccines authorized for use in Canada have an acceptable safety profile (30,41).  
- Booster vaccination with Men-C-ACYW vaccine five years following the primary schedule is safe and recommended by NACI for preventing IMD in high-risk individuals. |
| **Ethics and equity** | - Equity deliberations should take into consideration the variation in IMD burden in different population groups with the goal of reducing inequity in disease outcomes.  
- When considering age, the highest annual incidence rates between 2012 and 2022 were generally observed for infants less than one year of age, followed by children 1–4 years of age. Adolescents 15–19 years of age and young adults 20–24 years of age had slightly lower mean incidence compared to children 1–4 years of age.  
- Previously conducted studies have shown high rates of N. meningitidis acquisition and carriage in late adolescence and young adulthood (18,42–45).  
- When considering the immunization of older adolescents and young adults planning to or currently attending post-secondary education, it is important to consider PT variations in epidemiology and the timing of routine adolescent Men-C-C or Men-C-ACWY vaccination programs. IMD risk in individuals 15–24 years of age may not be limited to their educational status or living situation.  
- Some Canadian jurisdictions have introduced serogroup B vaccination programs for population groups that are believed to be at higher risk of disease due to increased exposure. However, while inequity may result from PT differences in vaccine access, the ultimate goal of IMD programs should be the reduction of differences in disease outcomes between populations, which is likely to be impacted significantly by regional epidemiology as well as the timing and composition of PT adolescent immunization programs.  
- Permissive recommendations may lead to potential inequities relative to access and the ability of high-risk individuals to purchase the recommended vaccine(s). |
| **Feasibility** | - There are currently six meningococcal vaccines that are purchased by PTs through the national vaccine bulk procurement program and to date there have been no reported shortages.  
- Given its broader age group indication (2 months–25 years), 4CMenB has been to date the serogroup B vaccine product of choice compared to MenB-FHbp (10–25 years).  
- University/college aged students may move to attend post-secondary education in a PT with different IMD epidemiology than where they are from.  
- Program cost and complexities associated with new program implementation should be weighed against the challenges, costs, and limitations of outbreak mitigation and contact tracing in the absence of programs. |
| **Acceptability** | - The level of individual and population group risk is influenced by local epidemiology and the timing and type of adolescent PT programs.  
- Acceptability is likely to be increased as a result of higher awareness of risk among populations that are considered to be at higher risk of IMD.  
- Vaccine uptake among adolescents and young adults living in shared accommodation settings is likely to be high given the media attention that was focused on previous outbreaks in post-secondary educational settings. |
| **Others** | - Canada has aligned with the World Health Organization Global call to action to defeat meningitis by 2030 and provides continued immunization against vaccine preventable serogroups (46,47). |

Abbreviations: IMD, invasive meningococcal disease; MenB-FHbp, bivalent factor H binding protein meningococcal serogroup B; Men-C-ACWY, meningococcal quadrivalent ACYW conjugate vaccine; Men-C-C, monovalent conjugate meningococcal C vaccine; NACI, National Advisory Committee on Immunization; Neisseria gonorrhoeae, N. gonorrhoeae; Neisseria meningitidis, N. meningitidis; PT, provinces and territories; 4CMenB, serogroup B meningococcal vaccines
Conclusion

In Canada, the age groups with the highest incidence of IMD include children younger than five years of age, followed by people 15–24 years of age. Determining particular risk factors (e.g., those associated with a particular activity or setting) beyond age and underlying medical conditions is challenging due to the limitations of currently collected data. Given that IMD epidemiology varies across the country, jurisdictions with higher incidence in specific population groups may therefore consider introducing targeted programs (e.g., offering a serogroup-appropriate meningococcal vaccine to an age group with a higher incidence of IMD), which may also include populations that are believed to be at higher risk of exposure (e.g., students residing in congregate settings or children and adolescents living in regions with circulating hypervirulent clones). When planning targeted programs, consideration should be given to the specific regional circulating strains and epidemiology.

Due to the PT differences in circulating strains and epidemiology, NACI concluded that recommending a single pan-Canadian program targeting additional population groups at high risk of exposure would be challenging and that regional programs may be better suited to address the currently circulating serogroups and prevent IMD in population groups considered to be at high risk of exposure.

While much is known about IMD, further studies are needed to better understand the contemporary risk factors of IMD in high-incidence population groups (including adolescents and young adults) in Canada, including activities and settings associated with bacterial acquisition, carriage and transmission. In addition, further research is needed with regards to estimating the true cost of IMD and meningococcal infections in Canada, including those associated with the absence of immunization programs (e.g., costs associated with contact tracing, school disruptions, outbreak management, etc.). Robust surveillance systems with enhanced data collection are required for the continuous monitoring of vaccine-preventable diseases, program evaluation and timely adjustment of recommendations that are focused on equity.

Authors’ statement

APH — Review, editing
JZ — Writing, original draft, review, editing
CP — Writing, review, editing
OB — Writing, review, editing
MS — Review, editing
SD — Review, editing

The update was prepared by J Zafack, C Primeau, A Pham-Huy and S Deeks, on behalf of the National Advisory Committee on Immunization (NACI) Invasive Meningococcal Disease Working Group and was approved by NACI.

Competing interests

None.

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References


A Pediatric Investigators Collaborative Network on Infections in Children (PICNIC) multi-centre Canadian descriptive analysis of *Haemophilus influenzae* bacteremia in children: Emerging serotypes

Craig Frankel¹, Joan Robinson², Sarah Khan³, Mohammad Alghounaim⁴, Jane McDonald⁴, Alison Lopez⁵, Sergio Fanella⁵, John Gunawan², Jacqueline Wong³, Jeannette Comeau⁶, Jennifer Bowes⁷, Robert Slinger⁷, Angela Kalia⁸, Ashley Roberts⁸, Kirk Leifso⁹, Marina Ulanova¹⁰, Michelle Barton¹

**Abstract**

**Background:** There has been dramatic reduction in *Haemophilus influenzae* serotype b (Hib) since introduction of Hib vaccines, but children still experience serious invasive *Haemophilus influenzae* (Hi) disease caused by various serotype and non-typeable bacteria. The object of this study was to describe the serotype distribution and clinical spectrum of Hi bacteremia in children admitted to Canadian hospitals.

**Methods:** All children with Hi bacteremia admitted 2013 through 2017 to 10 centres across Canada were included. Demographic, clinical, treatment and outcome data were collected.

**Results:** *Haemophilus influenzae* bacteremia occurred in 118 children of median age 12 months (inter-quartile range: 7–48 months). Forty-three (36%) isolates were non-typeable (NTHi) and 8 were not typed. Of the 67 typeable (THi), Hia (*H. influenzae* serotype a) (n=36, 54%), Hif (serotype f) (n=19, 26%) and Hib (serotype b) (n=9, 13%) dominated. The THi was more likely than NTHi bacteremia to present as meningitis (p<0.001), particularly serotype a (p=0.04) and less likely to present as pneumonia (p<0.001). Complicated disease (defined as intensive care unit admission, need for surgery, long-term sequelae or death) occurred in 31 (26%) cases and were more likely to have meningitis (p<0.001) than were those with uncomplicated disease.

**Conclusion:** In the era of efficacious conjugate Hib vaccines, NTHi, Hia and Hif have emerged as the leading causes of invasive Hi in Canadian children, with Hia being most likely to result in meningitis and complicated disease. A vaccine for all NTHi and THi would be ideal, but knowledge of the current disease burden from circulating strains will inform prioritization of vaccine targets.


**Keywords:** *Haemophilus influenzae*, invasive disease, bacteremia, meningitis, serotype a, serotype b, serotype f, non-typeable, children

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**Introduction**

*Haemophilus influenzae* serotype b (Hib) was overwhelmingly the leading cause of invasive Hi disease until the introduction of the Hib vaccines into the routine childhood immunization schedule in the United States (US) and Canada in the late 1980s (1). This was followed by the emergence of Hi serotype a, particularly in Indigenous children in Canada and in Alaska (2–4). Recent publications from the US reported an increase in the incidence of invasive Hi disease in children, possibly due to an increase in the incidence of cases due to non-typeable Hi (NTHi) (5,6). We sought to describe the serotype distribution and clinical spectrum of Hi bacteremia in Canadian children across several provinces and to determine factors associated with complicated disease.

**Methods**

**Study population and design**

Ten centres within the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) retrospectively enrolled all hospitalized children younger than 18 years of age with blood culture isolates of Hi from January 1, 2013, through December 31, 2017. For nine centres (London, Ontario; Hamilton, Ontario; Ottawa, Ontario; Kingston, Ontario; Winnipeg, Manitoba; Edmonton, Alberta; Vancouver, British Columbia; Halifax, Nova Scotia and Montréal, Québec), this was a sub-study arising from a retrospective cohort of Gram-negative bacteremia, while the tenth centre (Sioux Lookout, Ontario) was added for this sub-study due to their known high incidence of Hi infections. Ethics approval was obtained at each participating centre and the need for parental consent was waived.

**Study definitions**

The focus of infection was classified as meningitis, pneumonia, epiglottitis, skin and soft tissue infection, osteoarticular infection, other or none (isolated bacteremia with no focus). Multifocal disease was defined as bacteremia with two or more foci.

Disease was defined as complicated if any of the following occurred related to Hi disease: intensive care unit (ICU) admission; organ failure; surgical interventions including amputations for purpura fulminans or drainage of purulent collections (arthrocentesis did not qualify unless performed more than once); complications relating to disease focus including motor deficits, seizures, hydrocephalus, visual or hearing deficits, or necrotizing skin or lung infections; and death.

**Serotyping**

Serotyping of isolates was completed using monovalent antisera at reference laboratories. Strains were classified by capsular type (a to f) or as non-typeable. When serotyping was not available, the isolates were recorded as not typed.

**Data collection**

Demographic, clinical, microbiological, treatment, outcome and follow-up data were extracted from medical records and entered into REDCap (Research Electronic Data Capture) tools hosted at the University of Alberta by each participating centre (7).

**Statistical analysis**

Descriptive analysis was conducted. Chi-square or Fisher's exact test was used to compare categorical variables and nonparametric tests were used to compare continuous variables. Univariate analysis was used to explore potential factors associated with Hia disease and complicated disease course. Variables with a univariate p value of ≤0.2 and potential confounding factors (e.g. age and sex) were considered for inclusion in multivariable logistic regression model aimed at determining independent risk factors for complicated disease. The IBM SPSS version 28 was used for statistical analysis.

**Results**

There were 118 cases of Hi bacteremia of which 74 (63%) were male (Table 1). The median age was 12 months (interquartile range [IQR]: 7–48 months) with 7 cases (6%) being neonates and 25 (21%) being 5 years or older.

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**Table 1: Demographic, clinical, microbiological and outcome-related patterns across serotypes in paediatric population, Canada**

<table>
<thead>
<tr>
<th>Features*</th>
<th>Total N=118</th>
<th>THi (a–f) n=67</th>
<th>Hia n=36</th>
<th>Hib n=9</th>
<th>Hic n=1</th>
<th>Hie n=3</th>
<th>Hif n=18</th>
<th>NTHi n=43</th>
<th>Untyped n=8</th>
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</thead>
<tbody>
<tr>
<td>Age 1 month or younger</td>
<td>7 (6%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>4 (9%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Age younger than 12 months</td>
<td>43 (36%)</td>
<td>24 (36%)</td>
<td>14 (39%)</td>
<td>5 (56%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>4 (22%)</td>
<td>17 (40%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Age younger than 24 months</td>
<td>69 (58%)</td>
<td>45 (67%)</td>
<td>26 (72%)</td>
<td>8 (89%)</td>
<td>1 (100%)</td>
<td>1 (33%)</td>
<td>9 (50%)</td>
<td>20 (47%)</td>
<td>4 (50%)</td>
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</table>
Table 1: Demographic, clinical, microbiological and outcome-related patterns across serotypes in paediatric population, Canada (continued)

<table>
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<tr>
<th>Features*</th>
<th>Total N=118</th>
<th>THi (a–f) n=67</th>
<th>Hia n=36</th>
<th>Hib n=9</th>
<th>Hic n=1</th>
<th>Hie n=3</th>
<th>Hif n=18</th>
<th>NTHi n=43</th>
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<tr>
<td>Age younger than 60 months</td>
<td>93 (79%)</td>
<td>59 (88%)</td>
<td>32 (89%)</td>
<td>9 (100%)</td>
<td>1 (100%)</td>
<td>2 (67%)</td>
<td>13 (72%)</td>
<td>31 (72%)</td>
<td>5 (63%)</td>
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<tr>
<td>Male sex</td>
<td>74 (63%)</td>
<td>38 (57%)</td>
<td>16 (44%)</td>
<td>9 (100%)</td>
<td>1 (100%)</td>
<td>1 (33%)</td>
<td>11 (61%)</td>
<td>30 (70%)</td>
<td>6 (75%)</td>
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<tr>
<td>Meningitis</td>
<td>25 (21%)</td>
<td>21 (31%)</td>
<td>14 (39%)</td>
<td>3 (33%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>3 (17%)</td>
<td>3 (7%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>SSTI</td>
<td>8 (7%)</td>
<td>8 (12%)</td>
<td>4 (11%)</td>
<td>4 (44%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Osteoarticular infection</td>
<td>6 (5%)</td>
<td>6 (9%)</td>
<td>4 (11%)</td>
<td>2 (22%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Pneumonia</td>
<td>41 (35%)</td>
<td>13 (19%)</td>
<td>5 (14%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>7 (39%)</td>
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<td>5 (63%)</td>
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<tr>
<td>Epiglottitis</td>
<td>1 (1%)</td>
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<tr>
<td>Infective endocarditis</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Multifocal disease</td>
<td>7 (6%)</td>
<td>7 (10%)</td>
<td>5 (14%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Isolated bacteremia</td>
<td>29 (25%)</td>
<td>11 (16%)</td>
<td>4 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (67%)</td>
<td>5 (28%)</td>
<td>16 (37%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number of isolates with laboratory confirmed viral co-infection</td>
<td>32 (27%)</td>
<td>14 (21%)</td>
<td>10 (28%)</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (17%)</td>
<td>15 (35%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Number of isolates with ampicillin resistance</td>
<td>25/106 (24%)</td>
<td>6/63 (10%)</td>
<td>0/34 (0%)</td>
<td>2/8 (25%)</td>
<td>0/1 (0%)</td>
<td>0/3 (0%)</td>
<td>4/17 (24%)</td>
<td>18/35 (51%)</td>
<td>1/8 (13%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>39 (33%)</td>
<td>21 (31%)</td>
<td>13 (36%)</td>
<td>1 (13%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>6 (33%)</td>
<td>14 (33%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Complicated course (% with CNS complication)</td>
<td>31 (26%)</td>
<td>24 (36%)</td>
<td>14 (39%)</td>
<td>2 (22%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>7 (39%)</td>
<td>6 (14%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2%)</td>
<td>2 (3%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Death/sequelae</td>
<td>17 (14%)</td>
<td>14 (21%)</td>
<td>9 (25%)</td>
<td>2 (22%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>2 (5%)</td>
<td>1 (13%)</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; Hia, Haemophilus influenzae serotype a; Hib, Haemophilus influenzae serotype b; Hic, Haemophilus influenzae serotype c; Hie, Haemophilus influenzae serotype e; Hif, Haemophilus influenzae serotype f; ICU, intensive care unit; IE, infective endocarditis; IQR, interquartile range; NTHi, non-typeable Haemophilus influenzae; SSTI, skin and soft tissue infection; THi, typeable Haemophilus influenzae
* Values shown as totals (%) for categorical variables and medians with IQRs for continuous variables
+ Pairwise comparison of medians across serotype distribution was not significantly different after adjusting by Bonferroni correction for multiple tests
1 Unless listed as multifocal disease (more than two systems) or same system disease in distant sites, the focus listed was the sole focus identified during the admission. A sinusitis case was classified as pneumonia given that both are respiratory foci. Skin and soft tissue infections included unspecified cellulitis, facial cellulitis (n=3) and cellulitis with fasciitis (n=1); caused by Hia. The latter case with associated supplicative myositis.
2 Infective endocarditis refers to endovascular infection (n=1) or endocarditis (n=2); the latter occurred in absence of preceding cardiac disease. Two cases caused by Hia and Hib respectively were multifocal with CNS involvement. The endovascular infection occurred in an adolescent (without immunodeficiency) who presented with Lemierre syndrome with thrombosis of both internal jugular veins with associated Hif meningitis (patient also grew Streptococcus anginosus in blood)
3 Thirty-nine (33%) of patients had preceding viral symptoms. Thirty-two had viral polymerase chain reaction (PCR) test confirmation as enterovirus/rhinovirus (n=12), influenza (n=8), respiratory virus (n=5), parainfluenza (n=3), human coronavirus (n=1) and human metapneumovirus (n=1). Two children had multiple viral infections including 1) enterovirus/rhinovirus and adenovirus and 2) enterovirus/rhinovirus and bocavirus
4 Courses were considered complicated if there was ICU requirement or if disease-specific complications (e.g. ventiliculitis, necrotizing pneumonia, need for infectious foci-related surgery, longer than usual course of antimicrobial therapy for a given focus). Complications in THi were mainly related to CNS infections. For NTHi, two of six children with complicated courses had CNS complications (ventriculitis and seizures). Other complications in NTHi were due to pneumonia (three needing chest tube, one of whom was ventilated) and another developing shock requiring ICU admission. Complications arising from treatment not included in disease complications included Clostridium difficile colitis in an oncology patient and a central line infection. Among THi, there was one treatment-related complication (cholelithiasis from ceftriaxone that was not included in complicated disease criteria)
5 Mean length of stay for ICU admissions was three days [IQR: 2–10]
Typing was available for 110 Hi isolates, of which 67 (61%) were typeable *Haemophilus influenzae* (THi) and 43 (39%) were NTHi. Serotypes a, f and b were the leading serotypes accounting for 36 (54%), 18 (27%) and 9 (13%) of THi respectively (Table 1).

Age distribution across serotypes was not significantly different (Table 1). Case numbers were similar across the years of the study (mean: 23.6±7.33), with a peak in 2016 (Figure 1).

Centre-specific contributions are shown in Figure 2. Centres in Winnipeg, Montréal and London contributed most Hi cases, with disease predominantly caused by THi.

**Figure 1: *Haemophilus influenzae* serotype distribution by year in paediatric population, Canada**

[Graph showing serotype distribution by year for *Haemophilus influenzae*]

Thirty-one (27%) of 116 children with available clinical details (data missing for two cases) had at least one underlying medical condition which included prematurity (n=11; 9%), malignancy (n=11; 9%), immunodeficiency (n=9; 8%) and genetic or metabolic syndrome (n=8; 7%). Of the 108 children with serotyping who had available data, 13/67 (19%) of THi versus 15/41 (35%) with NTHi had an underlying condition (*p*=0.048).

Among six Hib cases with available information on vaccine history, five (83%) had not received any Hib vaccine (n=3) or had inadequate number of doses for age (n=2).

Twenty-five (24%) of 106 isolates with susceptibility reporting available were resistant to ampicillin while none were resistant to ceftriaxone (Table 1). The NTHi isolates were more likely to demonstrate resistance to ampicillin than were THi (n=18/35, 51% vs. n=6/63, 9%; *p*<0.001).

Among 67 children with THi, 11 (16%) had isolated bacteremia with no focus. Forty-nine had a single focus, including meningitis (n=21), pneumonia (n=13), skin and soft tissue infection (n=8), osteoarticular infection (n=6) and epiglottitis (n=1) (Table 1). Multifocal disease occurred in seven other children (five due to Hia and two due to Hif), with five cases having meningitis as one of the foci.

**Figure 2: Serotype-specific distribution of *Haemophilus influenzae* invasive disease in ten centres across Canada**

[Graph showing serotype-specific distribution across ten centres]

Among 67 children with THi, 11 (16%) had isolated bacteremia with no focus. Forty-nine had a single focus, including meningitis (n=21), pneumonia (n=13), skin and soft tissue infection (n=8), osteoarticular infection (n=6) and epiglottitis (n=1) (Table 1). Multifocal disease occurred in seven other children (five due to Hia and two due to Hif), with five cases having meningitis as one of the foci.

Among the 43 children with NTHi, 16 (37%) had isolated bacteremia with no focus when compared with 11/67 (16%) of THi (*p*=0.013). The remaining 27 children had a single focus including pneumonia (n=23), meningitis (n=3) and infective endocarditis (n=1) (Table 1).

Meningitis was more common with THi than NTHi (n=26/67, 39% vs. n=3/43, 7%; *p*<0.001) and was equally common with Hia and Hib (47% vs. 33%; *p*<0.05). Pneumonia (as a single focus) was more common with NTHi than THi (n=23/43, 53% vs. n=13/67, 19%; *p*<0.001).

The median duration of antibiotic therapy in the entire cohort was 13 days [IQR: 10–23] with prolonged duration for osteoarticular infection and meningitis with median duration of 30 days [IQR: 26–41] and 24.5 days [IQR: 12–43], respectively.
(Table 1). Thirty (26%) of 113 cases with available information who received a median of 14 days (IQR: 11–28) in total were transitioned from parenteral after a median of 7 days (IQR: 4–13) to oral antibiotics to complete remainder as oral therapy.

Complicated disease was more common with THi than with NTHi (n=24/67, 36% vs. n=6/43, 14%; p=0.015). The fatal cases were both caused by Hia and occurred in an infant with meningitis and endocarditis despite no congenital heart disease and in a four-year-old with meningitis complicated by subdural empyema. One infant with Hib meningitis required bilateral limb amputations due to purpura fulminans but survived. The composite outcome of mortality or sequelae at discharge was significantly associated with Hia as compared to non-Hia disease (n=9/36, 25% vs. n=7/74, 9%; p<0.001) (see Appendix).

In the univariate analysis (after adjusting for multiple comparisons), Hi cases with meningitis (p<0.001) were more likely to have a complicated clinical course whereas those with isolated bacteremia were less likely (p<0.001) (Table 2). In the multivariate analysis, meningitis (p<0.001) predicted a complicated disease course after controlling for age (p>0.05) and Hia serotype (p>0.05) (Table 2).

### Discussion

This multicentre study from 10 sites across Canada provides insight into the current serotype distribution of Hi bacteremia in Canadian children. Prior to the era of Hib vaccine, invasive Hi disease was very rare in children over four years of age, while approximately one quarter of our cases were older. Invasive and non-invasive Hi disease from 2013 to 2019 has been reviewed from epidemiological data from a single Canadian site with a predominant Indigenous population (Sioux Lookout) (8). At this centre, invasive Hi disease was identified in 10 children under 4 years, in two aged 5–15 years and in eight aged 16 years and older (8), suggesting a bimodal distribution which differs from the pre-Hib vaccine era where younger children were primarily affected. Our data highlight the pediatric centres in Winnipeg, Montréal, London and Edmonton as the highest contributors to THi, and may reflect that these centres are referral centres for large communities of Indigenous children as well as communities with reduced Hib vaccine uptake. The Hib cases still accounted for almost 10% of cases in the current study. As expected, Hib occurred predominantly in unimmunized or under-immunized children.

### Table 2: Univariate and multivariate analysis of factors associated with complicated Haemophilus influenzae disease

<table>
<thead>
<tr>
<th>Features*</th>
<th>All N=118</th>
<th>Complicated disease n=31</th>
<th>Uncomplicated disease n=87</th>
<th>Significance p&lt;0.006*</th>
<th>Multivariate analysis&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Odds ratio, [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Males</td>
<td>74 (63%)</td>
<td>21 (68%)</td>
<td>55 (63%)</td>
<td>0.800</td>
<td>1.27, [0.445–3.62]</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Median age (months), [IQR]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12, [7–48]</td>
<td>12, [6–36]</td>
<td>12, [9–60]</td>
<td>0.021</td>
<td>1.02, [1.00–1.03]</td>
<td>0.12</td>
<td></td>
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<tr>
<td>Patients younger than 1 year</td>
<td>43 (36%)</td>
<td>15 (48%)</td>
<td>28 (32%)</td>
<td>0.107</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical spectrum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated bacteremia</td>
<td>29 (25%)</td>
<td>1 (3%)</td>
<td>30 (34%)</td>
<td>&lt;0.001</td>
<td>14.77, [5.22–41.76]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>29 (25%)</td>
<td>20 (65%)</td>
<td>9 (10%)</td>
<td>&lt;0.001</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>43 (36%)</td>
<td>11 (35%)</td>
<td>33 (38%)</td>
<td>0.809</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTHi</td>
<td>43 (36%)</td>
<td>6 (19%)</td>
<td>25 (29%)</td>
<td>0.029</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Hia</td>
<td>36 (31%)</td>
<td>14 (45%)</td>
<td>21 (24%)</td>
<td>0.028</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory markers</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median C-reactive protein (mg/L), [IQR]</td>
<td>155, [72–223]</td>
<td>194, [134–301]</td>
<td>114, [65–194]</td>
<td>0.03</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of antibiotic therapy (days), [IQR]</td>
<td>14, [10–23]</td>
<td>26, [11–44]</td>
<td>13, [10–20]</td>
<td>0.039</td>
<td>N/A</td>
<td>N/A</td>
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</tr>
<tr>
<td>Median length of stay (days), [IQR]</td>
<td>10, [5–21]</td>
<td>18.5, [9–43.5]</td>
<td>9, [4–16]</td>
<td>0.043</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Hia, Haemophilus influenzae serotype a; IQR, interquartile range; N/A, not applicable; NTHi, non-typeable Haemophilus influenzae
* Values shown as totals (%) for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Chi-square or Fisher exact test for categorical variables; Kruskal-Wallis test for continuous variables
+ Significance level was adjusted for multiple comparisons using Bonferroni correction
+ In the multivariate analysis, after controlling for age and Hia status, meningitis remained an independent predictor of a complicated course (p<0.001)
Serotypes a and f were the most common, accounting for 55% and 25% of THi, respectively, consistent with recent literature (4,6). While Hia meningitis was significantly associated with a complicated course, it otherwise mirrored the Hib experience in terms of age and clinical syndromes. Children with Hif were often older with pneumonia as the focus of infection.

The less virulent NTHi accounted for just over one third of all Hi bacteremic events, where fortunately the incidence of complicated disease was only 4%. The NTHi cases presented as isolated bacteremia or pneumonia and rarely as central nervous system disease, in keeping with recent US data (5,6). Comorbid medical conditions were a risk factor for developing NTHi disease. In a retrospective surveillance study of NTHi invasive disease in children and adults in the Netherlands, comorbid conditions in children, including immunocompromise, malignancy, neurological disease and other conditions, were identified in a large proportion of NTHi cases (n=327/396, 83%) over a seven-year span (9).

It is exciting that Phase I trials of a Hia vaccine will begin in Canada in 2023 (10) (personal communication, M. Ulanova, Canadian Immunization Research Network, 2022). A vaccine has been shown to be cost-effective in the Canadian territory of Nunavut, given the high incidence of Hia among Indigenous children and their high risk of disease (11). Post-marketing studies of the multivalent pneumococcal vaccines that employ protein D from NTHi as the carrier protein suggest that they prevent some otitis media due to NHTi diseases, so it is plausible that these vaccines may also prevent Hi bacteremia (12).

Limitations
A significant limitation of our study is that it did not capture ethnicity/race data as this variable is not reliably recorded in health records in Canada. This is especially important given the established high rates of Hia in Indigenous populations (4). Our study may underestimate the burden and spectrum of Hi disease given that it was limited to bacteremic cases; blood cultures are not always drawn prior to administration of antibiotics and can be falsely negative if an inadequate volume is obtained. As neurodevelopmental and long-term follow-up data were not uniformly available, we reported sequelae documented at or before discharge.

Conclusion
Our study provides detailed clinical comparisons of THi and NTHi, highlighting serotype-specific clinical patterns and outcomes. Although there has been dramatic reduction in Hib since introduction of Hib vaccines, children still experience serious invasive Hi disease caused by both NHTi and by non-b serotypes, especially Hia. Preventive strategies are needed to reduce the morbidity associated with this disease.

Authors’ statement
CF — Collected data, interpreted data, writing–original draft, writing–revision and editing, final approval
JR, SK — Data acquisition, writing–original draft, writing–revision and editing, final approval
MA, JM, AL, SF, JG, JW, JC, JB, RS, AK, AR, KL and MU — Data acquisition, revised manuscript
MB — Conceptualized, data acquisition, data analysis, data interpretation, writing–revision and editing, final approval

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests
None.

Acknowledgements
None.

Funding
None.

References


Appendix

Table A1: Univariate analysis of factors associated with Haemophilus influenzae serotype a invasive disease

<table>
<thead>
<tr>
<th>Features</th>
<th>All N=110 (excluding untyped)</th>
<th>Hia n=36</th>
<th>Non-Hia n=74</th>
<th>Univariate analysis significance</th>
<th>p value&lt;0.006b</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Females</td>
<td>42 (38%)</td>
<td>20 (56%)</td>
<td>22 (30%)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Median age (months), [IQR]</td>
<td>12, [7–48]</td>
<td>12, [7–24]</td>
<td>12, [7–60]</td>
<td>0.155</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical spectrum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>29 (26%)</td>
<td>17 (47%)</td>
<td>12 (16%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>38 (35%)</td>
<td>7 (19%)</td>
<td>31 (42%)</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>27 (25%)</td>
<td>4 (11%)</td>
<td>23 (31%)</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Complicated disease</td>
<td>30 (27%)</td>
<td>14 (39%)</td>
<td>16 (22%)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment/outcome</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/sequelaec</td>
<td>16 (15%)</td>
<td>9 (25%)</td>
<td>7 (9%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Hia, Haemophilus influenzae serotype a; IQR, interquartile range
* Values shown as totals (%) for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Chi-square or Fisher exact test for categorical variables; Kruskal-Wallis test for continuous variables
* Significance level was adjusted for multiple comparisons using Bonferroni correction
* Sequelae includes all neurological complications arising from Haemophilus influenzae disease persisting at discharge or end of antibiotic therapy (including those who received outpatient parenteral antibiotics). Central nervous system complications (i.e. ventriculitis, empyema, cerebritis) that resolved prior to the end of therapy were not included as sequelae
Public health risks of raw milk consumption: Lessons from a case of paediatric hemolytic uremic syndrome

Angela Silveira¹,²*, Julia Pinheiro Carvalho³, Lawrence Loh⁴,⁵, Michael Benusic⁶

Abstract

Pasteurization of raw milk is mandatory before sale in Canada and has been demonstrated to reduce the risk of food-borne illness associated with milk consumption. Consumption of raw milk sparks urgent concern from a public health perspective since it has been linked to numerous outbreaks by enteric organisms, particularly Escherichia coli-related illnesses and complications in pediatric populations. The sale and distribution of raw milk is illegal in Canada, based on these significant health risks, but growing popular interest and trends in consuming raw dairy products reflect changes in consumer preferences. Although the consumption of raw milk has been an ongoing issue, this new trend is alarming and action is needed to prevent serious consequences as seen in children and other populations with reduced immunity such as the elderly and pregnant people. This commentary explores key issues identified by a local public health unit during the investigation of a recent paediatric case of hemolytic uremic syndrome related to an E. coli O157:H7 infection that occurred within the context of consumption of raw milk. The main objective of this article is to highlight that the health risks and sequelae associated with consumption of raw milk far outweigh any potential benefits, with severe consequences particularly among children. Data and health impacts, distribution, regulation, pasteurization and proposed practice recommendations are also identified and discussed.


Keywords: raw milk, raw dairy, unpasteurized, hemolytic uremic syndrome, EHEC, illegal milk consumption

Clinical case

An eight-year-old male child presented to a hospital emergency department in southern Ontario with low-grade fever, abdominal pain and bloody diarrhea over four days. He reported no other sick contacts and immunization status was up to date. A detailed food history done in the emergency department identified recent consumption of raw, unpasteurized milk. Baseline testing revealed thrombocytopenia, hemolytic anemia and elevated leukocytes, and subsequent stool cultures were positive for Escherichia coli O157:H7.

The patient was admitted and started with intravenous cefuroxime and metronidazole. Despite antibiotic therapy, bloody stools and abdominal pain persisted following admission. On day 6, the patient started to deteriorate rapidly, exhibiting neurological symptoms and renal failure, which prompted intensive care unit admission and a colonoscopy, which identified pseudomembranous exudate.

Hemolytic uremic syndrome (HUS) was subsequently diagnosed given the clinical picture and findings highly suggestive of enterohaemorrhagic E. coli (EHEC) (1). Enterohaemorrhagic E. coli is a subtype of Shiga toxin-releasing E. coli. Shiga toxin-releasing E. coli strains are a prime concern to food establishments because the disease can progress to HUS, a potentially fatal illness (1). The discontinuation of antibiotics allowed the patient to gradually improve with supportive treatment and fluid resuscitation.

A concurrent public health investigation in the same health unit also identified three other cases of Shiga toxin-releasing E. coli infections from individuals between five and 25 years of age also associated with the consumption of raw milk. Confirmation arose through molecular testing of stool samples from all four cases and a sample of raw milk kept by one of the cases’ parents. The raw milk in question had been obtained from an illicit network...
that distributed three-litre glass jars from a delivery vehicle at various points within the local community. Further investigation failed to identify the distributor or the production facility that provided the product.

**Background**

*Escherichia coli* is a diverse group of bacteria categorized into six pathotypes referred to as diarrheagenic *E. coli*. Infection with a particular *E. coli* strain is attributed to developing HUS, which presents with anemia, severe renal failure, seizures and risk of death, as was seen in the presented case.

Typically occurring in childhood, HUS is commonly caused by *E. coli* O157:H7 Shiga toxin-producing bacteria (1). In cases of *E. coli* O157:H7 gastroenteritis, bloody diarrhea occurs 3–4 days after ingestion of contaminated food, such as raw milk. Patients may also report severe abdominal pain and painful defecation, which can help to distinguish *E. coli* O157:H7 from other causes of bacterial gastroenteritis (1). Treatment is typically supportive. Antibiotic therapy is contraindicated since it increases the risk of HUS.

The case presented here is a prime example of how infection with *E. coli* can be traced to the consumption of raw dairy products (2). In a recent systematic review, the majority of HUS cases (83%) in North America from 2007 to 2020 can be attributed to 20 outbreaks due to raw dairy consumption, with 14 of these outbreaks involving raw milk consumption. From these 20 outbreaks, 530 illnesses were reported, with 98 paediatric cases (confirmed and suspected) (2). As in this case, the risk of acute and chronic renal failure with HUS is high. Rare and serious complications were included in six cases of HUS (2), similar to the case presented in this article. To reduce the risk of infection, it is important to improve the measures of control by enhancing the management and preventing the transmission of *E. coli* strains among animals, environment and humans (3). Despite widespread public health messaging around the dangers of consuming raw milk, a Canadian Community Health Survey (in-person and telephone interviews) revealed that 3.6% of participants had consumed raw milk in the seven days prior to the interview (2). Parents providing their children with raw milk should be educated about the risk of HUS.

**Data and health impact of raw milk consumption**

Between 2005 and 2013, 263 confirmed cases of enteric and zoonotic illnesses in Canada were attributed to the consumption of raw milk products (3). This number is likely an underestimate, as the vast majority of enteric illnesses often do not present to health care or are tested to a confirmatory extent; literature has identified that there may be nearly 25 times the number of unreported cases of illness as compared to confirmed cases in at least one jurisdiction in the United States (4). According to a 2017 study, unpasteurized dairy products cause 840 times more illnesses and 45 times more hospitalizations than pasteurized products, making raw milk a dangerous food (4).

Consumption of raw milk is often driven by the perception that consumption can “boost the immune system” and “tastes better than pasteurized milk” and some links that raw milk products can prevent atopy in children and adults (5). These perceptions are not evidence-based and a review of the literature, including reports of outbreaks, suggests that the overall risk of consuming these products outweigh the health claims, particularly among those with decreased immunity (children and the elderly) and pregnant people. In North America, from 2000 to 2009, there were a total of 26 outbreaks related to raw milk resulting in an estimated 545 illnesses, more than 23 hospitalizations and 7 infant deaths (6). In Ontario alone, from 2005 to 2007, there were 92 cases of illness associated with the consumption of raw milk and raw milk cheese (3). These numbers likely represent an underestimate of the true extent of the problem as many of these illnesses are underreported and do not present to the hospital unless symptoms are severe.

While consumption of raw milk is not prohibited, it is illegal to sell, deliver or distribute raw milk in Ontario under the Milk Act, a regulatory context mirrored in other Canadian provinces through similar acts (Table 1). This means that interested consumers continue to access raw milk products through illegal distribution networks (6). The obscure nature of such networks naturally limits the amount of data on the extent and magnitude of distribution (6).

<table>
<thead>
<tr>
<th>Province</th>
<th>Provincial regulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>Milk Industry Act</td>
</tr>
<tr>
<td>Alberta</td>
<td>Dairy Industry Act 2000</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>The Milk Compositional Standards Regulation</td>
</tr>
<tr>
<td>Manitoba</td>
<td>The Dairy Act</td>
</tr>
<tr>
<td>Ontario</td>
<td>Milk Act</td>
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<tr>
<td>Québec</td>
<td>Food Products Act</td>
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<tr>
<td>New Brunswick</td>
<td>Dairy Products Regulation</td>
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<tr>
<td>Nova Scotia</td>
<td>Dairy Industry Act</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>Dairy Producers Act</td>
</tr>
<tr>
<td>Newfoundland and Labrador</td>
<td>Milk Regulations</td>
</tr>
</tbody>
</table>

*Reference 7*

**Distribution, regulation and pasteurization**

A 2018 study found raw milk to be responsible for almost three times more hospitalizations than any other food-borne illness (8). With health implications in mind, it is essential for consumers and policy-makers alike to understand the need for
Pasteurization. Laws requiring pasteurization can be traced back to a 1927 typhoid epidemic in Montréal caused by contaminated milk (9). In 1938, Ontario became the first Canadian province to ban all sales of raw milk (9). In 1991, Canada’s Food and Drug Regulations officially banned the sale of raw milk due to concerns over food-borne illnesses like E. coli and severe sequelae from HUS following raw milk consumption (9). Health Canada data shows that mandatory pasteurization has been linked with a decrease in the number of food-borne illness outbreaks from milk, with 45 linked outbreaks between 1975 and 1982 compared against 7 linked outbreaks between 1998 and 2021 (10).

Health Canada establishes regulations and standards through the Canadian Food Inspection Agency relating to the safety and nutritional quality of milk sold in Canada (10). The Canadian Food Inspection Agency verifies that milk sold in Canada meets Health Canada’s requirements. Sampling of dairy products is performed by an Agency inspector as part of the Agency’s monitoring and compliance activities to verify any suspected problems of potential health risk to the public at a federal level. Provincially, the Ontario Ministry of Agriculture, Food and Rural Affairs licenses all dairy plants under the Milk Act (11). Ontario Ministry of Agriculture, Food and Rural Affairs requires all raw milk to be graded before being transported from the farm and prior to being received at a processing plant as part of a thorough quality-control process. To maintain Canadian standards, dairy farmers must be licensed and their farms inspected before receiving authorization to ship milk. They must also follow provincial regulations on food safety, animal care and the environment. In Canada, the federal government regulates pasteurization of milk used in the production of cheese, butter, yogurt and other products (11). Health officials state that pasteurization of milk retains all the nutrients and health benefits of raw milk, significantly reduces potential human pathogens and increases milk’s shelf life (6).

Proposed recommendations for practice

In the case presented here, raw milk consumption led to a severe paediatric presentation of HUS. Here are proposed solutions that need to be assessed for efficacy.

Hygiene and rehydration
Practising good hygiene, such as washing hands before handling food and using clean utensils, is crucial to prevent the spread of contaminants. In cases of suspected raw milk consumption-related illnesses, maintaining adequate rehydration is key for better treatment outcomes.

Physician awareness
Physicians play a vital role in identifying patients at risk of raw milk consumption. By asking directed questions, particularly about raw milk purchases from farm gate sales or “herd shares,” they can counsel patients about the risks associated with the consumption of raw milk (and milk products) and the symptoms of related illnesses. Further recommendations should highlight the importance of consuming only pasteurized milk products, especially for the immunocompromised, pregnant people and those at extremes of age. Physicians should also recommend the purchase of milk products from grocery stores and checking labels on milk products to ensure it has been pasteurized at a licensed dairy plant.

Public education initiatives
Targeted messaging: Tailor public education campaigns to address specific demographics and communities where raw milk consumption is more prevalent. Develop culturally sensitive and linguistically appropriate content to effectively reach diverse populations.

Health risks awareness: Clearly communicate the potential dangers of consuming raw milk, such as bacterial infections and food-borne illnesses, especially among vulnerable groups like pregnant people, children and individuals with compromised immune systems.

Benefits of pasteurization: Highlight the numerous benefits of pasteurization in preventing food-borne illnesses and protecting public health. Emphasize that opting for pasteurized milk is a responsible choice for personal and community well-being.

Promote safe handling: Educate consumers on safe milk handling practices, including proper storage, refrigeration and expiration date checks. Encourage adherence to guidelines to minimize risks associated with milk consumption.

Collaboration with health professionals: Engage health care providers in disseminating information about raw milk safety to patients, reinforcing key messages during routine medical appointments.

On-farm food safety training
Introducing on-farm food safety training programs for raw milk producers can be an effective risk management option. Evaluating the efficacy of these programs can contribute to reducing outbreak rates and enhancing public health. Similar programs have been adopted in the United States and may be a factor in the recent decline in outbreak rates (5).

Research and standards development
Conduct comprehensive research: Undertake in-depth research to understand the prevalence of raw milk consumption, associated health risks, and factors influencing consumer decisions in Canada. These data will serve as the foundation for informed policy-making and public awareness campaigns.

Standards development: Collaborate with regulatory bodies, dairy industry stakeholders and health experts to establish and update stringent standards for milk safety. Regularly review the literature and update recommendations based on new findings.
and improve safety guidelines to align with the latest scientific findings and ensure consumer protection.

**Improved surveillance**
Current surveillance of raw milk consumption is limited by the clandestine nature of raw milk distribution and the limited reporting of enteric illness associated with consumption. Continued surveillance efforts and outbreak management is critical to identifying specific raw milk and milk product vehicles that can cause enteric outbreaks of *E. coli* and other organisms. For example, larger-scale future food consumption and behavioural risk factor surveys could include questions on raw milk product consumption (3).

**Public awareness**
Public education campaigns should highlight the health risks of raw milk consumption and promote safe milk handling practices. Raising awareness about the benefits of pasteurization and the importance of purchasing from licensed dairy plants can lead to informed consumer choices.

**Collaborative efforts**
Addressing raw milk-related risks requires collaboration among health care professionals, regulatory bodies, dairy industry stakeholders, and the public. By working together, we can protect our communities from the dangers associated with raw milk consumption and promote safer milk consumption practices.

**Conclusion**
The popular movement towards raw milk consumption is an ongoing trend that carries preventable risks. Consumption of pasteurized milk and milk products has long been the mainstay in preventing unnecessary food-borne illness and lethal sequelae (12). For both physicians and public health agencies, greater surveillance, stricter regulation and enforcement and intensive public education and counselling will create the broad context required to limit raw milk consumption and prevent illnesses in Canada.

**Authors’ statement**

AS — Investigation, writing–review and editing  
JPC — Writing original draft, investigation, writing–review and editing  
MB — Writing–review and editing  
LCL — Investigation, writing–review, and editing

**Competing interests**
None.

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**References**


Community *Legionella* outbreak linked to a cooling tower, 2022

Steven Rebellato¹*, Colin Lee¹, Charles Gardner¹, Karen Kivilahti¹, Jenee Wallace¹, Danielle Hachborn¹, Jillian Fenik¹, Anna Majury², JinHee Kim², Allana Murphy², John Minnery²

Abstract

**Background:** Thirty-five laboratory-confirmed legionellosis cases were reported to the Simcoe Muskoka District Health Unit (Ontario, Canada) between September 27, 2022, and October 15, 2022, resulting in one death and 29 hospitalizations. This article describes the *Legionella* outbreak and highlights activities for managing the outbreak, including various environmental and infrastructural controls associated with the public health response and some of the unique challenges and potential solutions to mitigate future outbreaks.

**Methods:** All cases of legionellosis were reported to and investigated by the local provincial health unit. Within a 6 km radius around the community, 27 cooling towers (CTs) were identified as potential sources of *Legionella*. Environmental samples were collected from 19 CTs and a long-term care home.

**Outcome:** Of the 35 cases, 29 (83%) were hospitalized (including three long-term care residents) with two requiring intubation/ventilation. Of the five sputa (clinical isolates) collected from confirmed cases, four tested positive for *Legionella pneumophila* (one was positive for *L. pneumophila* serogroup 1—with the same sequence type as one of the CT isolates). Education and recommendations were provided by the local provincial health unit to operators to improve CT operation.

**Conclusion:** Detection and management of community legionellosis outbreaks associated with CTs involve resources and time to properly identify and control risks. Measures for community risk mitigation included coordinating with provincial and community partners, developing methods to rapidly identify CTs as a likely source of infection and applying operational/maintenance/testing standards for CTs to control bacterial growth and minimize the dispersion of contaminated aerosols.


Keywords: *Legionella*, outbreak, cooling tower, Ontario, Canada

Introduction

Legionellosis is caused by the *Legionella* bacteria; most commonly *Legionella pneumophila* (1). While the bacteria are commonly found in natural, freshwater environments, it can become a health concern in human-made water systems (e.g. plumbing systems of large buildings, cooling towers [CT], certain medical devices, decorative fountains) where conditions allow it to multiply. People contract *Legionella* by inhaling aerosolized water droplets containing the bacteria or, less commonly, by aspiration of contaminated drinking water. Legionellosis may present as Legionnaires’ Disease or Pontiac Fever with symptoms including anorexia, malaise, myalgia, headache, productive cough, fever, pneumonia, confusion, chills, nausea and diarrhea (1). Ontario provincial data (2) reported a rise in legionellosis incidence from 2012 (rate=1.4/100,000; 191 cases) through 2021 (rate=2.6/100,000; 385 cases) with individuals 50 years of age or older representing most reported cases. Legionellosis is a disease of public health significance under the Government of Ontario’s *Health Protection and*
Thirty-five laboratory-confirmed cases of legionellosis were reported to the Simcoe-Muskoka District Health Unit (Ontario, Canada) between September 27, 2022, and October 15, 2022. An outbreak of legionellosis in the same community in 2019 resulted in 10 cases (all admitted to hospital) and one death. A CT was linked by laboratory testing with one of the cases. Given the 2019 outbreak, and recognizing that CTs are the most frequent source of large community outbreaks (8–12), CTs were investigated in 2022 as a source.

This report describes a community outbreak of legionellosis in the fall of 2022 in Ontario. The article focuses on the epidemiology and investigative processes leading to the outbreak’s conclusion. The article highlights the continued challenges that public health practitioners experience in the identification and control of Legionella in relation to CT units and how a registry could facilitate rapid identification of CTs in a region of interest, as well as how guidance and/or regulations could support ongoing maintenance and monitoring as preventive public health measures.

Methods

Case investigation

The first confirmed case of legionellosis was reported to the health unit on September 27, 2022. On October 4, 2022, four cases of legionellosis were admitted to the local hospital, presenting with pneumonia. Analysis of case movement and exposures revealed that all four cases resided or worked in the same community based on postal code. Given the monthly expected case counts, based on the five-year mean for the public health region is between one and three cases in September and October, the observed case count (n=4) in a single community was aberrant. Accordingly, an outbreak was declared by the health unit on October 4, 2022. An outbreak case was defined as any individual who lived, worked or visited the identified community in Simcoe County, with compatible signs and symptoms of legionellosis, on or after September 5, 2022, and who had laboratory confirmation of legionellosis. The outbreak investigation was initiated on October 4, 2022.

Using the seven-day median reporting time from symptom onset plus the maximum incubation period of 15 days, in addition to allowing for two additional days of coordinating communications, the outbreak was declared over on November 8, 2022, which represented 24 days from the last reported case (October 15, 2022). The outbreak lasted 35 days.

Urine specimens were submitted to the Public Health Ontario Laboratory. Urinary antigen tests were performed by the laboratory for all suspect cases. Upon report of a new case, the health unit conducted a case interview and exposure history that included the 14 days prior to symptom onset, identifying home location, work location and any other locations visited during this period. An exposure associated with this outbreak was defined as any location within the area of investigation, where the case spent any amount of time during their period of acquisition (e.g. workplace, home, shopping, day excursion).

Interventions and environmental investigation

Given the hospitalization and laboratory confirmation of five cases of legionellosis with pneumonia at the local hospital from September 27 to October 4, 2022, the health unit initiated an investigation into potential environmental sources. Community and healthcare providers were informed of the outbreak to assist in facilitating case finding, prompt diagnosis and management of persons with potential legionellosis. The public was notified of the outbreak via local media to 1) inform those who may be at risk, 2) describe clinical signs and symptoms, and 3) recommend that those who are symptomatic seek medical attention if their symptoms are severe or do not resolve.

A review of case investigation data revealed that no single exposure site or activity was common among the five cases, other than travelling to, living or working in the community. A line list of cases with exposures was developed and, on review, no common exposures for the cases were identified other than geography suggesting an environmental exposure covering an area defined by a 6 km radius. Through elimination of other potential sources, including municipal drinking water, CTs were identified as the probable source. On October 5, 2022, 15 CTs were identified within the 6 km radius using location data collected during the 2019 outbreak. A 6 km radius was established based on previous literature (13) that described this radius as a reasonable distance for aerosol dispersion. The health unit requested operators of these known CTs to immediately cease operation unless deemed by the operator as essential to the facility’s operation. The CTs that remained operational were required to provide maintenance and testing records from July to October 2022 and directed to arrange for immediate cleaning and disinfection.

The owners/operators for 11 of 15 CTs provided monitoring data collected through routine Legionella maintenance programs. All quantitative Legionella culture results were reported as fewer than 10 colony forming units (CFU)/mL for Legionella species.
According to the Canadian guidelines for federal buildings (14), a value of fewer than 10 *Legionella* spp. CFU/mL is considered within the acceptable limit. Laboratory data for the remaining four CTs were not available from the CT owner/operator as no sampling program was in place. From October 8 to November 1, 2022, public health inspectors identified additional CTs (total n=27) and collected water and biofilm samples from 19 CTs for submission to the Public Health Ontario Laboratory. Eight other CTs could not be sampled due to seasonal shut down. During the investigation, one operator/owner was ordered to shut down their CT due to unsanitary conditions, lack of routine maintenance and lack of testing. The CT previously identified as the source of the 2019 outbreak could not be immediately sampled by public health officials due to a mechanical failure that rendered it devoid of water.

On October 17, 2022, the health unit received culture results from a CT showing *L. pneumophila* serogroup 1 levels of 2,575 CFU/mL. The sample was collected on September 27 and tested as part of routine monthly testing. The health unit arranged to have the September 27 isolate transported to the Public Health Ontario Laboratory for sequence-based typing (SBT). Sequence-based typing was performed to determine the relatedness of the clinical and environmental isolates. The SBT method at Public Health Ontario Laboratory is based on the epidemiological typing scheme for clinical and environmental isolates of *L. pneumophila*, which was developed by members of the European Legionnaires’ Disease Surveillance Network and evaluated for implementation in the investigation of outbreaks of legionellosis caused by *L. pneumophila*. Culture results can take up to 14 days to be received, which can delay interventions. In this case, no other immediate action was required given the CT had already been shut down on October 7 due to mechanical failures. Between October 17 and November 10, the health unit also conducted quantitative polymerase chain reaction (qPCR) testing using field equipment to quantify results for further decision-making. The Federal Standard guided the corrective actions taken and the interpretation of results. The CTs selected for qPCR testing were prioritized based on 1) lack of maintenance and testing, 2) missing test results or 3) requirement to further evaluate samples from those CTs where qPCR and culture showed the presence of *Legionella* spp.

Epidemiologic and statistical analyses

Descriptive epidemiology was used to enumerate total cases, the severity of cases and their outcomes. An epidemic curve was created in Microsoft Excel (Figure 1). It displays cases over time, with differentiation between community cases, cases residing in a LTCH, and cases from out of jurisdiction of the local health unit. The environmental investigation results of CTs are displayed above the cases over the same time scale.

To explore sources of disease, ESRI ArcGIS Desktop® 10.6.1 was used to map cases by home location and assess clustering in investigation, followed by mapping of cases’ exposure locations and 27 known CTs identified during the outbreak period (and the testing results, as available). A hotspot analysis was undertaken using the Optimized Hot Spot Analysis Spatial Statistic Tool using a 6 km radius buffer around the area of investigation and a cell size of 200 m.

Hotspot analysis and exposure history analysis were rerun as new confirmed cases were identified and the outbreak progressed. Upon identification of a sequence type (ST) match between the isolate cultured from a case’s sputum and an isolate cultured from the implicated CT, assessment of each case’s nearest exposure to the CT was conducted.

Results

Thirty-five laboratory-confirmed cases were identified in this outbreak and were associated with having a residence and/or having visited locations within a 6 km radius of a community within the jurisdictional area of the local health unit. Of the 35 laboratory confirmed cases, 29 were hospitalized. One case died, resulting in a case-fatality rate of 2.9%. Twenty-six cases resided in the community, seven cases were LTCH residents, and two cases were residents of other communities who visited the area during their acquisition period. Table 1 shows a breakdown of cases by demographics (age, sex, location), health conditions and severity. Twenty-nine of the 35 cases (83%) were hospitalized, including three of the LTCH residents, with two hospitalized cases admitted to the intensive care unit requiring intubation/ventilation.

A separate environmental investigation took place for a sub-cluster of cases identified at a long-term care home (LTCH) within the 6 km radius. Three residents of the LTCH were hospitalized and determined to be *L. pneumophila* serogroup 1-positive based on urinary antigen tests. Due to the case investigation, two shower rooms were identified as potential sources and sampled on October 8, 2022. All samples yielded negative results by culture.
Table 1: Characteristics of confirmed Legionellosis cases included in the outbreak investigation

<table>
<thead>
<tr>
<th>Characteristics of cases</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>35</td>
<td>100%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>17</td>
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</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>51.4%</td>
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<td>Age group (years)</td>
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<tr>
<td>50–59</td>
<td>7</td>
<td>20.0%</td>
</tr>
<tr>
<td>60–69</td>
<td>12</td>
<td>34.3%</td>
</tr>
<tr>
<td>70–79</td>
<td>5</td>
<td>14.3%</td>
</tr>
<tr>
<td>80 and older</td>
<td>11</td>
<td>31.4%</td>
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<tr>
<td>Residential location</td>
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<tr>
<td>Local community</td>
<td>26</td>
<td>74.3%</td>
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<tr>
<td>Long-term care home</td>
<td>7</td>
<td>20.0%</td>
</tr>
<tr>
<td>Out of jurisdiction</td>
<td>2</td>
<td>5.7%</td>
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</table>

Table 1: Characteristics of confirmed Legionellosis cases included in the outbreak investigation (continued)

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<thead>
<tr>
<th>Characteristics of cases</th>
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<td>Chronic conditions</td>
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<tr>
<td>Any</td>
<td>27</td>
<td>77.1%</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>5.7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>17.1%</td>
</tr>
<tr>
<td>Hospitalization status</td>
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<td></td>
</tr>
<tr>
<td>Not hospitalized</td>
<td>6</td>
<td>17.1%</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>27</td>
<td>77.1%</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>2</td>
<td>5.7%</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered</td>
<td>34</td>
<td>97.1%</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

Abbreviations: LTCH, long-term care home; OOJ, out of jurisdiction; PHU, public health unit; qPCR, quantitative polymerase chain reaction; Sg, serogroup; +ve, positive; -ve, negative
Data sources: Investigation Line List and Environmental Health Sample Collection spreadsheet
Of the five sputa collected from laboratory-confirmed cases, four specimens were found to be positive for L. pneumophila via polymerase chain reaction (PCR), with one of the five also having a positive culture for L. pneumophila serogroup 1. Given that culture isolates were available for both a clinical and an environmental source, SBT followed.

Of the 27 CTs identified in the 6 km radius zone, environmental samples were collected from 19 CTs and 2 samples from plumbing within the involved LTCH. Legionella spp. was not detected in any of the samples collected from the LTCH. Of the 19 CTs, eight had Legionella spp. detected by PCR (which detects DNA from both viable and non-viable Legionella), three of which were identified as L. pneumophila serogroup 1. Legionella pneumophila serogroup 1 was isolated by culture from only one of the CTs. Subsequent SBT of the L. pneumophila serogroup 1 isolate was genetically similar to the isolate from the case’s sputum, as both were identified as ST 272.

### Mapping and hotspot analysis

The hotspot analysis of case exposure locations identified two clusters: a large (approximately 2 km²) cluster in the north-west of the investigation area and a smaller 600 m² cluster in the centre of the area (Figure 2). Samples from the CT from which Legionella was isolated had the same ST as the Legionella isolated from the case and was located at the southern end of the large cluster. All cases had at least one exposure within a 6 km buffer from the subject CT:

- 2 cases were onsite
- 2 cases within 500 m
- 7 cases between 500 m and 1 km
- 21 cases between 1 km and 3 km
- 3 cases between 3 km and 6 km

**Figure 2: Closest case exposure locations in relation to suspected source with hotspot analysis**

Abbreviations: m, metres; qPCR, quantitative polymerase chain reaction

Source: Legionellosis Cluster 2022 Investigation Case Data and Environmental Health Data

### Discussion

Thirty-five laboratory-confirmed cases of legionellosis were investigated between September 27, 2022, and October 15, 2022. Through epidemiological and geospatial/hotspot analysis of case exposure locations, it was hypothesized that a community source(s) was responsible for the outbreak since no common single location/facility was identified amongst case histories for the majority of cases. Furthermore, the approximately 2 km² cluster in the north-west area and smaller 600 m² cluster in the centre of the area of the community (Figure 2) contain several large retail stores that were common destinations amongst the cases.

In addition to urine specimens being submitted for testing, sputum specimens were submitted for five cases, one of which was positive for L. pneumophila serogroup 1 by culture. Of the 19 CTs investigated and tested for Legionella, L. pneumophila serogroup 1 was cultured from one CT. Using SBT, it was determined that the isolate from the CT and the clinical isolate were the same ST. Despite remediation of the CT being identified as the outbreak source, subsequent testing for Legionella continued to yield positive results of L. pneumophila via qPCR, PCR and culture. Thus, the CT was shut down indefinitely on November 6, 2022. Following two incubation periods with no reported cases in the defined geographical area, the investigation was concluded and the public was notified that the outbreak was declared over.

This outbreak highlights the need to rapidly identify CTs during public health investigations to assess their design, maintenance and operation from the Legionella risk mitigation perspective. Seventeen days had elapsed by the time all CTs within the 6 km radius were identified and confirmed following the declaration of the outbreak on October 4, 2022. Should a registration system been in place, it is likely that CTs would have been accessed and investigated in an accelerated manner. Further, multiple outbreaks within the same community within a three-year period reinforce the need for CT monitoring, maintenance, risk assessment and risk management—which did not occur in a number of systems that were previously investigated. The outbreak also highlights the value of coordinated environmental and clinical sampling to assist in source identification using molecular typing strategies and to support effective public health action. Frequent and timely availability of quantitative Legionella monitoring may serve as an important adjunct to routine maintenance, particularly if adverse findings are reportable as an indicator of the effectiveness of maintenance and remediation practises. Moreover, even in the absence of Legionella cases being identified in the community, routine Legionella monitoring would result in increased awareness by owners and operators of the risks and expectations and should help mitigate future outbreaks given adverse results would prompt immediate remediation practises, acting as an early warning system.
The outbreak epidemiology and investigation results were similar in scope to a community outbreak reported in Montréal, Québec in 2019 (1). Both investigations involved intensive public health investigation resources (extensive environmental sampling, coordination, communication) along with the challenges of seeking a clinical-environmental link, including the need for additional clinical isolates for typing to assist in the investigation process. With several similarities between outbreaks, there were some notable differences. In particular, the province of Québec already requires CTs to be registered and have maintenance programs in place (8). While it could be argued that the Québec outbreak puts into question those jurisdictions with existing registries for CTs, the study concluded that the province of Québec would benefit from further development of provincial registries for other water aerosolization sources given the potential of CTs for transmission of Legionella and the inability of the outbreak investigation to identify a source.

Challenges
Several challenges were identified throughout this outbreak investigation. Of the 35 cases, only one of the five clinical sputum specimens submitted yielded a culture isolate, which is required to perform SBT. Providers had started appropriate antibiotic treatment for hospitalized patients with pneumonia before receiving a positive urinary antigen test. Respiratory specimens for culture were not usually taken after those urinary antigen test results, as clinicians do not require test results from sputum specimens for further antimicrobial management of those patients. Moreover, those patients may have already been discharged. In this outbreak, SBT of a clinical isolate was genetically similar to an isolate cultured from a single CT sample. In addition to a lack of clinical specimens, not all CTs in the identified 6 km radius could be sampled and tested given some were not operational at the time sampling was being undertaken, despite being in operation during the incubation period. Furthermore, many facilities do not participate in a routine Legionella monitoring program; thus, historical data were not available for retrospective review to assess which CTs may have been highest risk. An ongoing challenge for public health in lieu of an accessible community or provincial CT registry is the identification of CTs during an outbreak situation and the requirement for CTs to be maintained and sampled on a routine basis. If a registry and requirement for sampling and maintenance existed, it would allow for accelerated communication and appropriate analysis of sampling records to take place to focus on higher-risk systems. Particularly for systems within an identified geographical area of interest based on case analysis for suspect community Legionella outbreaks, historical sampling data for suspected systems would assist in determining trends in seasonality, operational periods, and in turn, provide the opportunity for education and intervention in seeking optimal system operation. Finally, hotspot analysis was simplified and did not account for some cases having multiple exposures in a small geographical area.

Conclusion
This community outbreak resulted in 35 laboratory-confirmed cases of legionellosis. Using sequence-based typing, it was determined that one environmental isolate from a CT and one clinical isolate were the same (relatively uncommon) ST.

This report describes the challenges of managing a coordinated clinical and environmental investigation of a community Legionella outbreak in Ontario and reiterates the broader public health risks posed by the organism in CTs. The detection and management of community Legionella outbreaks associated with CTs is complex. Coordination with provincial and community partners is critical to the investigation process. Challenges in other jurisdictions similar to the one described here have resulted in the introduction of universal CT registries, which have facilitated the identification of community CTs during a rapid public health response. Moreover, some responses have included the implementation of CT monitoring programs that include Legionella testing at regular intervals, with prompt and mandatory reporting requirements to public health authorities, to proactively identify potential Legionella sources. Ultimately, what is essential is appropriate management and maintenance programs, with oversight from qualified water quality personnel for optimal operation of CTs, reduced bacterial growth and the associated public health risks.

Authors’ statement
SR — Lead author
CL — Author, analysis and interpretation of data, writing—original draft, writing—revision and editing
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The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

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References


Screening recommendations for chlamydia and gonorrhea during pregnancy in Canada, 2023

An update from the National Advisory Committee on Sexually Transmitted and Blood-Borne Infections (NAC-STBBI)

Screen all asymptomatic pregnant women/pregnant individuals (PWPI) for Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG)

SCREEN DURING PREGNANCY

During the first trimester or at the first antenatal visit AND again in the third trimester*

* Conditional recommendation; low certainty evidence

SCREEN AT THE TIME OF LABOUR

In any of the following situations*:

- No prenatal screening has occurred (no valid results available at the time of labour)
- Third trimester screening has not occurred
- A positive test result was obtained for CT or NG during pregnancy without appropriate follow-up, including treatment and a test-of-cure

* Conditional recommendation; low certainty evidence

CT and NG cases are increasing

33% increase in overall chlamydia rates from 2010 to 2019

182% increase in overall gonorrhea rates from 2010 to 2019

Untreated CT and NG in pregnancy can cause adverse pregnancy outcomes (e.g., pre-term birth) and serious illness in neonates (e.g., ophthalmia neonatorum, neonatal pneumonia)

Routine screening can help identify CT and NG to protect the health of PWPI and their neonates

For more information, visit PHAC’s STBBI Guides for Health Professionals


SOURCE

National Advisory Committee on Sexually Transmitted and Blood-Borne Infections (NAC-STBBI). Recommendations on Screening for Chlamydia trachomatis and Neisseria gonorrhoeae in Pregnancy. 2023 [cited 2023 Aug 30]. Available at:
Antimicrobial susceptibilities of Neisseria gonorrhoeae in Canada, 2021

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Abstract

Background: In Canada, gonorrhea is the second most prevalent bacterial sexually transmitted infection. The Gonococcal Antimicrobial Surveillance Programme (GASP - Canada), a passive surveillance system monitoring antimicrobial resistance in Neisseria gonorrhoeae in Canada since 1985, is the source for this summary of demographics, antimicrobial resistance and N. gonorrhoeae multi-antigen sequence typing (NG-MAST) of gonococcal isolates collected in Canada in 2021.

Methods: Provincial and territorial public health laboratories submitted N. gonorrhoeae cultures and data to the National Microbiology Laboratory in Winnipeg as part of the surveillance system. The antimicrobial resistance and molecular type of each isolate received were determined.

Results: In total, 3,439 N. gonorrhoeae cultures were received from laboratories across Canada in 2021, a 9.9% increase since 2020 (n=3,130). Decreased susceptibility to cefixime increased significantly (p<0.001) in 2021 (1.5%) compared to 2017 (0.6%). No significant change in decreased susceptibility to ceftriaxone was detected between 2017 and 2021 (0.6%) (p>0.001); however, one ceftriaxone-resistant isolate was identified. Azithromycin resistance decreased significantly (p<0.001) in 2021 (7.6%) compared to 2017 (11.7%); however, there was a significant increase (p<0.001) in the proportion of cultures with an azithromycin minimum inhibitory concentration of at least 1 mg/L (2017=22.2% to 2021=28.1%). In 2021, NG-MAST-19875 (15.3%) was the most prevalent sequence type in Canada; 20.3% of isolates with this sequence type were resistant to azithromycin.

Conclusion: The spread of antimicrobial-resistant gonorrhea is a significant public health concern. The continued regional and national surveillance of antimicrobial resistance in N. gonorrhoeae is essential in ensuring effective treatment therapies are recommended.

Introduction

Gonorrhea, caused by Neisseria gonorrhoeae, is the second most reported bacterial sexually transmitted infection (STI) in Canada. It causes urethritis in males and while in females it is often asymptomatic, it can present as cervicitis and lead to serious complications such as infertility and pelvic inflammatory disease (1). Left untreated, disseminated gonococcal infections (DGI) may occur if the bacterium enters the blood and other sterile sites. Disseminated gonococcal infections have not been considered common in Canada but have increased from 2017 to 2021 (2) and can cause arthritis, dermatitis, migratory polyarthritis, tenosynovitis and, in rare cases, endocarditis (3,4).
Canada reported 30,883 cases of gonorrhea in 2020 (2,5). This is slightly lower than the number reported in 2019 (n=35,443), likely due to the effects of coronavirus disease 2019 (COVID-19) on public health care (2,5,6). Even with the decrease in reported gonorrhea cases, the 2020 gonorrhea rate (80.1 per 100,000 population) is twice the rate reported in 2013 (40.56 per 100,000 population) (1).

*Neisseria* gonorrhoeae has constantly evolved to resist antimicrobials used for gonorrhea treatment. The World Health Organization’s (WHO) Global Action Plan was released with the objective to control the spread and minimize the impact of antimicrobial resistant *N. gonorrhoeae* (3,4). The Public Health Agency of Canada currently recommended treatment regimen of ceftriaxone 250 mg intramuscularly plus azithromycin 1 g orally (7) is at risk due to persistent azithromycin resistance (AzIR) and the decreased susceptibility (DS) to cephalosporins observed among Canadian *N. gonorrhoeae* isolates. Cases of cephalosporin-resistant *N. gonorrhoeae* were identified in Canada between 2017 and 2021 (2,8,9) and AzIR has increased beyond the 5% resistance cut-off recommended by the WHO to trigger a review of current recommended therapies (4).

The Gonococcal Antimicrobial Surveillance Program (GASP - Canada) is a passive national surveillance program that has been operating since 1985. Antimicrobial susceptibility testing (AST) and molecular characterization using *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST) are performed on isolates that are submitted to GASP - Canada. The NG-MAST is highly distinctive and can be used to investigate treatment failures and outbreaks and NG-MAST sequence types (ST) have also shown a close association with antimicrobial resistance (AMR) (10–12).

Gonorrhea is an important public health concern with its ability to cause infertility, pelvic inflammatory disease and DGI (13,14). The capacity for *N. gonorrhoeae* to constantly evolve to resist antimicrobials means that continued surveillance is necessary to ensure treatment therapies are effective against currently circulating strains and to slow the spread of AMR strains.

As in 2020, decreased testing capacity of laboratories across Canada for *N. gonorrhoeae* cultures due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic contributed towards a considerable decrease in the number of isolates received by GASP - Canada in 2021 and included in this report compared to previous years. This report summarizes the AMR trends and molecular types of *N. gonorrhoeae* cultures in Canada from 2017 to 2021.

**Methods**

**Surveillance**

As part of GASP - Canada, provincial and territorial partners voluntarily send *N. gonorrhoeae* cultures to the National Microbiology Laboratory (NML) predominately when the provincial laboratories detect resistance/decreased susceptibility to at least one antimicrobial or if the provincial laboratories do not perform AST. Commencing in 2019, certain provinces’ AST data (in the form of minimum inhibitory concentrations, MICs) of isolates not sent to NML for testing were used in our analysis in conjunction with MICs of isolates tested at NML. Alberta sends all their resistant gonorrhea cultures (n=652 in 2021) to NML for testing and submits their AST data for the remaining isolates (n=131 in 2021). Québec (n=985 in 2021) and British Columbia (n=119 in 2021) send isolates to NML that adhere to the following criteria: 1) resistant to azithromycin; 2) decreased susceptibility to cefixime and/or ceftriaxone; 3) approaching resistance/decreased susceptibility to these antimicrobials. These provinces submit AST and patient data for the remaining isolates tested: Québec (n=576) and British Columbia (n=210 in 2021). Ontario sends to NML all resistant isolates (n=250 in 2021) and informs NML of the total number tested in their province (n=636 in 2021). Manitoba (n=44 in 2021), New Brunswick (n=32 in 2021) and Saskatchewan (n=41 in 2021) send all isolates cultured if possible. Nova Scotia, Newfoundland and Labrador and the Northwest Territories also send all their gonorrhea cultures to NML (n=13 in 2021). A total of 3,439 *N. gonorrhoeae* isolates were cultured across Canada in 2021: 2,006 unique, viable cultures were submitted to NML for AST and molecular typing. The AST results as determined by provincial and territorial laboratories and patient demographics for another 903 cultures were submitted to NML. The remaining 530 cultures were tested by provincial and territorial laboratories and were recorded as susceptible by NML, as no AST or demographic data were submitted. **Table S1** includes the number of cultures submitted from each province or territory and the number of cultures with resistance to at least one antimicrobial. The total number of *N. gonorrhoeae* isolates tested across Canada was 3,439 and this was used as the denominator in resistance calculations, unless otherwise noted.

**Isolate testing**

Antimicrobial susceptibility testing using agar dilution (15) and/or whole genome sequencing (WGS) methods (11) was performed on all *N. gonorrhoeae* cultures received by NML (n=2,006). Minimum inhibitory concentrations for 10 antimicrobials were determined and interpretation of results were based on the Clinical and Laboratory Standards Institute for five of them (penicillin, tetracycline and azithromycin all resistant (R) when MIC is at least 2 mg/L; ciprofloxacin R when MIC is at least 1 mg/L; spectinomycin R when MIC is at least 128 mg/L) (14). The WHO guidelines were used for ceftriaxone (DS when MIC is at least 0.125 mg/L) and cefixime (DS when MIC is at least 0.25 mg/L) (4). Erythromycin (R when MIC is at least
least 2 mg/L, ertapenem (non-susceptible when MIC is at least 0.063 mg/L) and gentamicin (R when MIC is at least 32 mg/L) interpretations are based on publications (16–19) (Table S2). Testing of β-lactamase was performed on all cultures. Cultures with tetracycline MICs of at least 16 mg/L were tested for the tetM plasmid by polymerase chain reaction (20). Isolates were classified as susceptible, resistant, multi-drug resistant gonococci (MDR-GC, either DS or R to one recommended gonorrhea therapy at the time of the analysis, plus resistance to at least two other antimicrobials) or extensively drug-resistant gonococci (XDR-GC, either DS or R to two recommended gonorrhea therapies at the time of analysis, plus resistance to at least two other antimicrobials).

Genotyping of cultures was determined by NG-MAST using polymerase chain reaction (12) and/or WGS (11). SeqMan Pro 15 (DNASTar, Madison, Wisconsin) was used to assemble strands of Sanger-sequenced DNA and the ST was determined when sequences were submitted to the PubMLST Neisseria spp. database. The previous NG-MAST website (http://www.ng-mast.net) was decommissioned and several thousand previously identified STs were deleted. Therefore, some allelic profiles from previous years were updated with new STs in this report.

Whole genome sequencing
The DNA from isolates on which WGS was successfully performed (n=1,231) was prepared using the Epicentre Masterpure Complete DNA and RNA Extraction Kit (Mandel Scientific, Guelph, Ontario). Briefly, the sequencing method used involved creating libraries (using Nextera sample preparation kits [Illumina, San Diego, California]) with 300 bp paired-end index reads generated on the Illumina NextSeq platform (Illumina). Galaxy Version 1.0.4+galaxy was used to assess the quality of the reads, assemble them and analyze single nucleotide variants of Sanger-sequenced DNA and the ST was determined when sequences were submitted to the PubMLST Neisseria spp. database. Whole genome sequencing data was used to detect molecular AMR markers and to determine multi-locus sequence type (MLST), Neisseria gonorrhoeae sequence typing for antimicrobial resistance (NG-STAR) and NG-MAST STs (11).

Data analysis
Age, sex, isolation site, province and date of collection were provided with the N. gonorrhoeae isolates. Duplicate isolates were identified and removed from the denominator if multiple isolates from the same patient had the same ST and were collected within four weeks of each other. A hierarchy of isolation sites was used to determine which isolates were considered duplicates, the order of which was 1) sterile site (DGI), 2) throat, 3) rectal and 4) urogenital. Each figure includes the denominator used in its description. Trends of AMR and STs were determined nationally. Azithromycin resistance and cefixime and ceftriaxone DS (CeDS and CxDS, respectively) were also analyzed at the provincial or territorial level. Correlation of the most common STs with AMR was also indicated. Comparisons of AMR proportions were made using the Fisher’s exact test with a 99% confidence interval employing EpiCalc 2000 (version 1.02; Brixton Health).

Results
Isolates tested, demographics and isolation sites
In 2021, 3,439 N. gonorrhoeae isolates were tested across Canada. Over 70% (72.7%, n=2,501/3,349) were resistant to at least one antibiotic (Table S1). This proportion does not include the gonorrhoeae cases that were diagnosed using nucleic acid amplification tests (NAATs). Cases diagnosed by NAATs are not routinely tested for AMR and accounted for 90% of diagnosed and reported gonorrhea cases in Canada in 2020 (Figure 1).

Age, sex and isolation site information were submitted to NML for 2,909 cultures in 2021. Over 70% (71.2%, n=2,072/2,909) of N. gonorrhoeae cultures were from individuals between the ages of 21 and 40 years; 21.3% (n=620/2,909) from persons 41 years and older; 7.4% (n=214/2,909) from those younger than 21 years. Isolates were primarily from males 84.1% (n=2,446/2,909), with 15.0% (n=436/2,909) from females and 0.9% (n=27/2,909) from patients who are either gender-diverse or whose gender was not given. The prevalent isolation site in males was the penis/urethra (57.0%, n=1,395/2,446) and for females it was the throat (33.9%, n=148/436). See Table S3 for more details.

Cephalosporin antimicrobial trends in Canada, 2017–2021
There is a significant increase in CeDS (MIC of at least 0.25 mg/L), from 0.6% in 2017 to 1.5% in 2021 (p<0.001), and a significant decrease from the 2.8% reported in 2020 (p<0.001) (Figure 2).

Decreased susceptibility to ceftriaxone (CxDS, MIC of at least 0.125 mg/L) has not seen a significant change since 2017, ranging from 0.55% in 2017 and 2018 to 0.93% in 2020 and declining to 0.61% (n=21/3,349) in 2021 (Figure 3). Of note, one isolate was ceftriaxone-resistant (CxR) with an MIC of 1 mg/L, while the remaining 20 isolates classified as CxDS had MICs of 0.125 mg/L. The CxR isolate was isolated in British Columbia in October 2021 from a 25-year-old female. Original treatment with 800 mg cefixime orally failed; however, this was resolved with one intramuscular injection of 250 mg ceftriaxone. The isolate was identified as NG-MAST-19937, MLST-7365 and NG-STAR-3903 with the penA allele 60.001 (Table 1).
Figure 1: Reported *Neisseria gonorrhoeae* cases in Canada, 2011–2020\(^{a,b}\)

![Graph showing the number of gonorrhea cases reported in Canada from 2011 to 2020](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of gonorrhea cases reported (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>3,360</td>
</tr>
<tr>
<td>2012</td>
<td>3,036</td>
</tr>
<tr>
<td>2013</td>
<td>3,195</td>
</tr>
<tr>
<td>2014</td>
<td>3,809</td>
</tr>
<tr>
<td>2015</td>
<td>4,190</td>
</tr>
<tr>
<td>2016</td>
<td>4,538</td>
</tr>
<tr>
<td>2017</td>
<td>5,290</td>
</tr>
<tr>
<td>2018</td>
<td>5,607</td>
</tr>
<tr>
<td>2019</td>
<td>3,130</td>
</tr>
<tr>
<td>2020</td>
<td>3,370</td>
</tr>
</tbody>
</table>

Abbreviation: NAAT, nucleic acid amplification testing

* Approximately 10% of all gonorrhea cases were diagnosed by culture in Canada in 2020. The rest was detected using nucleic acid amplification test technology. The number of reported cases for 2021 had not yet been determined at the time of publication

* The number of gonorrhea cases diagnosed by nucleic acid amplification testing is determined by subtracting the number of cultures tested across Canada from the number of gonorrhea cases reported (1)

Figure 2: Percentage of *Neisseria gonorrhoeae* cultures with decreased susceptibility to cefixime by province, 2017–2021\(^{a,b}\)

![Graph showing the percentage of cefixime-resistant isolates by province from 2017 to 2021](image)

Provinces included in this figure are only those that submitted at least one culture to the National Microbiology Laboratory that had decreased susceptibility to cefixime

Denominators used for the calculations of the percentages are the number of cultures tested in each province (Table S4)

Table 1: Ceftriaxone-resistant *Neisseria gonorrhoeae* isolate, 2021

<table>
<thead>
<tr>
<th>NML #</th>
<th>Province</th>
<th>Collection date</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Isolation site</th>
<th>NG-MAST</th>
<th>Resistance profile</th>
<th>MIC (mg/L)</th>
<th>MLST</th>
<th>penA</th>
</tr>
</thead>
<tbody>
<tr>
<td>61829</td>
<td>British Columbia</td>
<td>2021-10-20</td>
<td>Female</td>
<td>25</td>
<td>Vagina</td>
<td>ST-19937</td>
<td>CeDS; CxDS; CipR; EryR; PenR; TetR</td>
<td>1</td>
<td>2</td>
<td>7365</td>
</tr>
</tbody>
</table>

Abbreviations: CE, cefixime; CeDS, cefixime decreased susceptibility; CipR, ciprofloxacin-resistant; CX, ceftriaxone; CxDS, ceftriaxone decreased susceptibility; EryR, erythromycin-resistant; MIC, minimum inhibitory concentration; MLST, multi-locus sequence type; NG-MAST, Neisseria gonorrhoeae multi-antigen sequence type; NML, National Microbiology Laboratory; PenR, penicillin-resistant; ST, sequence type; TetR, tetracycline-resistant
Azithromycin resistance in Canada, 2017–2021
Azithromycin resistance decreased significantly \( (p<0.001) \) from 11.7% in 2017 to 7.6% in 2021 (Figure 4); however, when a comparison of the proportion of isolates with a MIC of at least 1 mg/L is made between 2017 and 2021, there was a significant increase \( (p<0.001) \), from 22.2% \( (n=1,172/5,290) \) to 28.1% \( (n=968/3,439) \) (Figure 5).

Figure 4: Percentage of azithromycin-resistant \textit{Neisseria gonorrhoeae} cultures by province, 2017-2021\(^{a,b}\)

Resistance trends in other antimicrobials, 2017–2021
The proportion of \textit{N. gonorrhoeae} isolates resistant to ciprofloxacin has remained high but stable (between 49% and 57%) from 2017 to 2021. In 2021, tetracycline resistance was at an all-time high of 65.9%, erythromycin resistance was at 51.5% and penicillin resistance was below 7% (Figure 6). Non-susceptibility to ertapenem decreased significantly \( (p<0.001) \) but remained high from 87.2% in 2017 to 62.0% in 2021. Gentamicin resistance has remained at 0%.

Multi-drug resistant and extensively drug-resistant gonococci in Canada, 2017–2021
The number of MDR cultures decreased significantly \( (p<0.001) \) between 2017 (12.2%) and 2021 (7.8%) (Figure S1). No XDR cultures were identified in Canada in 2021; however, there were 29 XDR-GC isolates identified between 2012 and 2020 (Figure S2, Table S5).

Disseminated gonococcal infections cases in Canada, 2017–2021
Between 2016 and 2020, there was a significant increase \( (p<0.001) \) in both the number and proportion of DGI cases from 0.03% \( (n=6/23,708) \) to 0.20% \( (n=71/30,833) \) within Canada. In 2021, this proportion decreased slightly \( (p=0.001) \) compared to 2020, to 0.13% \( (n=40/30,833) \). The sources of the DGI in 2021 included synovial fluid (50.0%, \( n=20/40 \)), blood (45.0%, \( n=18/40 \)) and eyes, specifically designated as DGI (5.0%, \( n=2/40 \)). Nine of the DGI (22.5%) were susceptible to all tested antimicrobials,
two were resistant to azithromycin and the remaining 29 were resistant to other antimicrobials including erythromycin, tetracycline and ciprofloxacin. None had DS to cephalosporins. Note that the number of cases reported in Canada in 2020 was used as the denominator (n=30,833) to estimate the proportion of DGI amongst cases in 2021.

**Neisseria gonorrhoeae** multi-antigen sequence typing trends in Canada, 2017–2021

In 2021, 1,973 out of the 2,006 cultures submitted were successfully typed for NG-MAST. The most frequently detected NG-MAST sequence type in Canada was ST-19875 (n=306), followed by ST-11477 (n=137) and ST-17972 (n=127). Approximately 20% of ST-19875 isolates were identified with AzIR, while ST-11477 and ST-17972 isolates were primarily resistant to ciprofloxacin and tetracycline, or ciprofloxacin and erythromycin, respectively (Figure 7). Figure S3 displays the trend of prevalent STs over the last five years. From 2017 to 2020, ST-12302 and ST-14994 were the most prevalent, while in 2021, they were the eighth and ninth most prevalent STs, respectively. While the number of isolates with ST-12302 (n=47) has been decreasing, in 2021, 15 other STs (ST-8890, n=24; ST-19853, n=14; ST-19772, n=11; ST-17629, n=10; ST-19935, n=9; ST-19854, n=9; ST-19866, n=8; ST-20691, n=3; ST-19852, n=3; and ST-14076, ST-20388, ST-19924, ST-8241, ST-20379 all with n=1 each) were identified with two or fewer base pair differences compared to ST-12302. The number of isolates found in this cluster of STs, including ST-12302, was 144; 61.8% (n=89/144) were AzIR accounting for 34.1% (n=89/261) of isolates found in this cluster of STs, including ST-12302 and ST-14994 was the most prevalent, while in 2020, they were the eighth and ninth most prevalent STs, respectively. The proportion of isolates in 2021 demonstrating CeDS decreased compared to 2020, although it was higher than in 2017 and 2018. The 2020 higher proportion of isolates with CeDS was primarily caused by isolates identified as ST-16639 in Ontario and Québec. The proportion of this ST decreased from 3.3% (n=53/1,590) in 2020 to 1.3% (n=26/2,006) in 2021.

The increase in CeDS since 2018 could be a result of a potential increase in oral therapy using cefixime (combination therapy of 800 mg cefixime plus 1 g azithromycin) as opposed to the intramuscular injection of ceftriaxone (250 mg ceftriaxone intramuscularly plus 1 g azithromycin orally). Oral therapy does not require a visit to a doctor or clinic during times of limited health services and telehealth appointments. In 2021, fewer restrictions were in place in Canada, allowing in-office visits to resume which may have induced the decrease of CeDS in 2021.

The CxR isolate (isolate ID 61829) with the ceftriaxone MIC of 1 mg/L and the cefixime MIC of 2 mg/L is of concern. It was also resistant to penicillin, tetracycline, erythromycin and ciprofloxacin. Initial treatment of 800 mg orally failed and was followed up with one 250 mg ceftriaxone intramuscular injection. Test of cure confirmed treatment success.

**Discussion**

The SARS-CoV-2 global pandemic, declared in 2020 (6,21), was still affecting public health care in 2021 (22). Reported cases of gonorrhea for 2021 had not been released by the date of publication of this study, but this number dropped from 35,475 cases in 2019 to 30,833 cases in 2020. Reduced testing because of NAAT kit supply shortages (23), stay-at-home mandates by public health authorities and hesitancy of infected to seek care contributed to this decrease (24). While the number of gonorrhea cultured across Canada increased slightly between 2020 (n=3,130) and 2021 (n=3,439), it is still 30% less than what was seen in 2019 (n=4,859) (Table S1). It is unlikely that this is due to a decrease in infections and more probable that it is due to a decrease in testing (6,22). Continued interruptions in testing can cause major increases in the incidence of STIs, including *N. gonorrhoeae*, which may take years to return to levels seen before COVID-19 (25). In Canada, a report summarizing the impact of the pandemic on health care stated that since its beginning, people have been more hesitant to seek care (23). The negative impacts that the pandemic has had on the healthcare system will take years to correct (22). Long-term adverse consequences, such as an increase in pelvic inflammatory disease, DGI and infertility may be the result.

The proportion of isolates in 2021 demonstrating CeDS decreased compared to 2020, although it was higher than in 2017 and 2018. The 2020 higher proportion of isolates with CeDS was primarily caused by isolates identified as ST-16639 in Ontario and Québec. The proportion of this ST decreased from 3.3% (n=53/1,590) in 2020 to 1.3% (n=26/2,006) in 2021.

The CxR isolate (isolate ID 61829) with the ceftriaxone MIC of 1 mg/L and the cefixime MIC of 2 mg/L is of concern. It was also resistant to penicillin, tetracycline, erythromycin and ciprofloxacin. Initial treatment of 800 mg orally failed and was followed up with one 250 mg ceftriaxone intramuscular injection. Test of cure confirmed treatment success.

Ceftriaxone-resistant gonococcal isolates have been previously reported in Canada (8,9) and globally, including in Japan (26), Australia (27), China (28–31), Denmark (32) and Ireland (33). Three of the five Canadian CxR isolates reported since 2017, including 61829, have the penA allele 60.001 as well as the same
AMR-associated mutations (Table S6) seen in Japan and Australia (FC428 clone) (28). Isolate 61829 has an MLST (7365) that has been seen in a CxR/AziR isolate in China (31) but the NG-MAST and NG-STAR types are unique. The United Kingdom reported an isolate with both CxR and high-level AziR that failed treatment in 2018. This isolate had the same AMR-associated mutations as well, with an additional four copies of the A2059G mutation on the 23S rRNA (34).

The national levels of AziR in Canada have been inconsistent between 2017 and 2021, shifting between 12% and 6% in alternate years (Figure 4). In response to high levels of AziR, some regions/jurisdictions have updated their recommended treatment to either 250 mg or 500 mg of ceftriaxone intramuscular without azithromycin (35,36). Continued surveillance will determine the effects of the change in treatment recommendations to AziR rates in those regions. The high AziR levels seen between 2013 and 2018 were led by ST-12302. In 2021, while the number of isolates with ST-12302 has decreased, an ST cluster closely related to and including ST-12302 is responsible for 34.1% (n=89/261) of AziR isolates. ST-19875, the most prevalent ST in 2021, accounted for 23.8% (n=62/261) of AziR isolates, however, 75.8% (n=232/306) of isolates with this ST had azithromycin MICs of 1 mg/L, just one dilution beneath the resistance breakpoint MIC of 2 mg/L (15). The remaining AziR isolates are dispersed amongst various primarily unrelated STs with one to eight isolates in each.

As in 2020, the percentage of cultures with azithromycin MICs at or above the break point of 2 mg/L in 2021 was lower than in 2019. However, the proportion of N. gonorrhoeae cultures with a MIC of at least 1 mg/L increased significantly (p<0.001) in 2021 (Figure 5). Both ST-19875 and ST-17972, two of the most prevalent STs of 2021, have high proportions of isolates with an azithromycin MIC of 1 mg/L (75.8% and 58.3%, respectively). Although the Clinical and Laboratory Standards Institute’s recommended breakpoint for azithromycin is 2 mg/L (15), some countries including Australia have set their breakpoint at 1 mg/L, which is also the epidemiological cut-off value from the European Committee on Antimicrobial Susceptibility Testing (37,38). The shift to an azithromycin MIC of at least 1 mg/L in Canada should be monitored, as azithromycin is part of the dual therapy recommended for the treatment of gonorrhea.

While DGI cases in Canada decreased between 2020 and 2021, the decline was not significant, but is still an important concern. With the decrease in diagnosis of gonorrhea since the COVID-19 pandemic began, potentially from the impact that the pandemic measures had on STI testing, a further increase in DGI cases may be seen in the future and should be monitored.

Limitations
Isolates and associated data submitted to NML by the provinces and territories are done on a voluntary basis and therefore not consistent across the country. This limits the overall interpretation of results as only a subset of isolates may have been submitted for testing from a region. Also, as the majority of gonococcal cases are diagnosed by NAATs, AMR rates may not be reflected accurately in this report and resistance rates may be under-reported.

Since the SAR-CoV-2 pandemic began in 2020, significantly fewer (p<0.001) N. gonorrhoeae cultures have been collected in Canada and made available to NML. Trends in incidence, AMR and molecular types may have been affected, especially for smaller provinces and territories with limited resources and capabilities.

Conclusion
Gonorrhea remains an important public health concern due to its potential to cause infertility, pelvic inflammatory disease and DGI which can include dermatitis, arthritis, and in rare cases, endocarditis, meningitis or osteomyelitis (13,14). Neisseria gonorrhoeae has the ability to adapt to resist antimicrobials and this has been well documented (3).

Between 2017 and 2021, we have seen a number of trends in N. gonorrhoeae identified in Canada: 1) CxR isolates with a MIC equal to 1 mg/L; 2) a significant increase in the proportion of CeDS cultures; 3) AziR rates that exceed the WHO recommended levels required to change therapy and 4) a significant increase in the number of DGI cases across the country.

The continued surveillance of N. gonorrhoeae AMR trends is crucial to ensure national treatment guidelines are recommending the most effective therapies. Public health authorities can be informed of emerging AMR issues that could inform interventions when ongoing surveillance detects clonal outbreaks using molecular typing. The representativeness and interpretation of the current passive surveillance system data would be improved if epidemiological and laboratory data were linked. The Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea, initiated in 2014, was developed to address these gaps (39,40).
Authors’ statement
PS — Formal analysis, validation, investigation, data curation, visualization, writing–original draft, review and editing of final version
BL — Resources, methodology, writing–review and editing
MD — Resources, methodology, writing–review and editing
LH — Resources, methodology, writing–review and editing
SP — Resources, methodology, writing–review and editing
PVC — Resources, methodology, writing–review and editing
JM — Resources, methodology, writing–review and editing
RG — Resources, methodology, writing–review and editing
SJ — Resources, methodology, writing–review and editing
DH — Resources, methodology, writing–review and editing
LL — Writing–review and editing
GG — Writing–review and editing
MRM — Methodology, writing–review and editing
IM — Conceptualization, validation, methodology, supervision, project administration, writing–review and editing of final version

Competing interests
None.

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Supplemental material
These documents can be accessed on the Supplemental material file.

Table S1: Summary of the Neisseria gonorrhoeae culture and laboratory data received by the National Microbiology Laboratory, 2017–2021
Table S2: Neisseria gonorrhoeae antimicrobial resistance criteria
Table S3: Age of patient and isolation site of the Neisseria gonorrhoeae isolates tested at the National Microbiology Laboratory, 2021 (N=2,909)
Table S4: Neisseria gonorrhoeae cultures tested in each province, 2017–2021
Figure S1: Trends of multi-drug resistant Neisseria gonorrhoeae in Canada, 2017–2021

Figure S2: Trends of extensively drug-resistant Neisseria gonorrhoeae in Canada, 2017–2021
Table S5: All extensively resistant Neisseria gonorrhoeae isolated in Canada
Figure S3: Trends of prevalent Neisseria gonorrhoeae multi-antigen sequence types of isolates tested by the National Microbiology Laboratory, 2017–2021
Figure S4: Provincial distribution within Neisseria gonorrhoeae multi-antigen sequence types, 2021 (N=2,006)
Table S6: Ceftriaxone-resistant Neisseria gonorrhoeae identified in Canada, 2017–2021

References


Surveillance of laboratory exposures to human pathogens and toxins, Canada, 2022

Christine Abalos¹, Audrey Gauthier¹, Antoinette Davis¹*, Cailey Ellis¹, Nathalie Balbontin¹, Aryan Kapur¹, Samuel Bonti-Ankomah¹

Abstract

Background: The Laboratory Incident Notification Canada (LINC) surveillance system was launched in 2015 to monitor the mandated national reporting of laboratory incidents. This report describes the laboratory exposures reported in 2022.

Methods: Exposure incidents were analyzed by activity, occurrence, sector, root cause and pathogens/toxins implicated, while affected individuals were analyzed by education, exposure route, role and years of laboratory experience. An analysis of the median number of exposures per month was conducted, and time between the exposure incident date and the date the incident was reported to LINC was examined.

Results: Forty confirmed laboratory exposure incident reports were received, with two suspected laboratory-acquired infections. The exposure incident rate per 100 active licences was 3.8, and the number of exposure incidents was highest in September. The majority of exposure incidents involved risk group 2 pathogens (n=27; 63%) and non-security sensitive biological agents (n=36; 84%). Microbiology was the most cited activity occurring during the exposure event (n=20; 50%), and sharps and procedure-related issues were the most common occurrences (n=15; 24.2% each). Most incidents were reported by the academic sector (n=16; 40%). Human interaction was the most common root cause (n=20; 23.8%) and most affected individuals were technicians/technologists (n=68; 73.1%). The median time delay between the incident date and reporting date was 5.5 days.

Conclusion: The exposure incident rate was lower in 2022 than in 2021. Incidents related to sharps and standard operating procedures remained the most common occurrence types. The most cited root cause of exposure incidents involved human interaction.

Introduction

The accidental release or improper disposal of human pathogens and toxins (HPTs) can pose a biosafety or biosecurity threat to the laboratory personnel working with these agents, as well as the Canadian population in general. To improve the safety and security of laboratory personnel working with HPTs and protect the public from the risks posed by exposure to HPTs, the Human Pathogens and Toxins Act (HPTA) and the Human Pathogens and Toxins Regulations (HPTR) were enacted in Canada in 2015 (1). The HPTA classifies HPTs into four groups based on the level of risk they present to an individual and the community, with risk group 1 (RG1) pathogens being those pathogens that have little to no individual or community risk; risk group 2 (RG2) pathogens posing a moderate individual risk and low community risk; risk group 3 (RG3) pathogens posing a high individual risk and a low community risk; and risk group 4 (RG4) pathogens posing both a high individual and community risk (2). Under the HPTA, all laboratories conducting controlled activities with HPTs, such
as possessing, producing, storing, transferring or disposing of HPTs, must acquire a licence, unless an exclusion has been granted (3), and the reporting of incidents involving RG2, RG3 and RG4 pathogens is mandatory, unless the agent or incident falls outside the scope of the HPTA.

In 2015, the Public Health Agency of Canada (PHAC) established the Laboratory Incident Notification Canada (LINC) surveillance system to oversee the reporting of laboratory incidents involving RG2, RG3 and RG4 HPTs by regulated parties, in accordance with the HPTR. These incident reports not only allow for the identification, monitoring and analysis of trends related to exposures, but also ensure that an appropriate follow-up response and evidence-based recommendation can be provided to facilities by PHAC’s biocontainment inspectors to help minimize health risks and reduce the likelihood of similar incidents in the future. The data from these reports also inform the development of resources and tools by LINC to fill knowledge gaps and raise awareness of biosafety practises in laboratories.

Outside of Canada, there are surveillance systems that exclusively monitor agents that have the potential to pose a high biosecurity risk. In the United States, the Federal Select Agent Program, which was brought about as part of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (4), oversees the possession, usage and relocation of select agents and toxins that have the potential to pose a significant threat to the public (5). In Australia, the Security Sensitive Biological Agent Standards outline the requirements for the safe handling, storage, and removal of known or suspected security sensitive biological agents (SSBAs) within qualified facilities (6). Security sensitive biological agents are a subset of RG3 and RG4 human pathogens and prescribed toxins that have been determined to pose an increased biosecurity risk due to their potential for use as a biological weapon (2). Handling of SSBAs in Australia is managed by the Australian Department of Health and Aged Care, while other Australian agencies such as the Department of Agriculture, Fisheries and Forestry, the Department of Defence and the Department of Home Affairs monitor the importation and exportation of these agents (7). In contrast to these systems, LINC gathers and reviews data from exposure incidents that occurred in 2022 and informs laboratory safety. The aim of this report is to share data on laboratory exposure incidents that occurred in 2022 and inform laboratory safety measures by increasing awareness of the risks associated with working with HPTs and highlighting potential areas of concern. Exposure incidents are described by sector, HPT, occurrence type, main activity and root cause. The affected individuals will also be described by their role, level of education and years of experience.

### Methods

#### Data sources

The LINC surveillance system monitors exposure, non-exposure, and other incidents in laboratories in Canada regulated under the HPTA and HPTR. Under the HPTA and HPTR, an exposure incident is defined as a laboratory incident that could have resulted in intoxication/infection or did result in a suspected or confirmed laboratory-acquired infection (LAI) (9). A non-exposure incident refers to any of the following: 1) the inadvertent possession, production or release of a pathogen or toxin; 2) a missing, lost or stolen pathogen or toxin; or 3) an SSBA not being received within 24 hours of expected arrival.

After a laboratory incident has occurred, the laboratory must complete a standardized form through PHAC’s Biosecurity Portal and include specific information about the incident. Data are then captured using the Microsoft Customer Relationship Management system and reviewed for accuracy by a LINC team member. Data from exposure incidents that occurred between January 1, 2022, and December 31, 2022, as well as incidents with an unknown incident date that were submitted in the Biosecurity Portal in this timeframe, were retrieved and analyzed for this annual report. Data from the most recently submitted follow-up reports were used for analysis if multiple follow-up reports were submitted for a particular incident. In addition, if no follow-up report was submitted, data from the initial incident report were used. After extracting the data, outliers were investigated and duplicate entries were removed. The submission of an incident report involving agents classified as RG1 or in their natural environment are not required under the HPTA/HPTR and are considered as voluntary reports. Such incidents are often incomplete and were not included in the analysis for this report.

#### Analysis

Data from the LINC surveillance system were extracted on February 8, 2023, from PHAC’s Biosecurity Portal, validated using Microsoft Excel, and descriptive statistics were computed using R 4.1.1. Exposure incidents, including suspected and confirmed LAIs, were classified as confirmed or ruled out after investigation of the incident in the follow-up reports. If an exposure was ruled out, or if it was confirmed that the person was not exposed to the HPT, the affected persons in that report were also ruled out. Because regulated parties can update and provide details in their previously submitted reports at any time, data from reports received between 2016 and 2021 were reanalyzed. As a result, minor differences may exist between the values found in this year’s annual report and those from previous years.

This annual report is focused on confirmed exposure incidents. Of the confirmed exposure incidents, analysis was done at the level of the active licence holder and at the level of the affected person. The former included the distribution of incidents...
by sector, main activity, root cause(s), occurrence type and implicated pathogen/toxin. The latter examined distribution by highest level of education, years of experience, route of exposure, sector and main role.

The exposure incident rate per 100 active licences for 2016 to 2022 was also calculated and displayed, overlaying the trend of exposure incidents over time throughout these years. The exposure incident rate was calculated by dividing the number of exposure incidents reported during a one-year period by the total number of active licences in a one-year period and multiplying by 100 active licences (10). Finally, the median monthly number of exposure incidents of all previous years of the LINC program was compared to the number of monthly exposures in 2022. A median rather than a mean was calculated since this measure reduces noise from outlier data and offers a better measure of the central tendency of exposure incidents.

Results

There were 145 reports of laboratory incidents received between January 1 and December 31, 2022. Of these reports, 66 were exposure reports, 57 were non-exposure reports and 22 were other reports involving changes in biocontainment (Figure 1). Of the 66 reported exposure incidents, 40 were confirmed and 26 were ruled out. Two of the confirmed exposure incidents were suspected LAIs (Figure 1). Out of the 57 non-exposure incident reports received, 47 were confirmed and 10 were ruled out. While 94 people were initially reported as being exposed through these laboratory incidents, one person was later ruled out, bringing the total to 93 exposed people in 2022.

In 2022, there were 1,048 active licences held by laboratories working with HPTs in Canada, which means that for every 100 active licences, the exposure incident rate was 3.8 (Figure 2). This is the lowest rate observed since 2016.

Results

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In 2022, there were 1,048 active licences held by laboratories working with HPTs in Canada, which means that for every 100 active licences, the exposure incident rate was 3.8 (Figure 2). This is the lowest rate observed since 2016.

Figure 2: Confirmed exposure incidents, suspected and confirmed laboratory-acquired infections and exposure incident rate, Canada, 2016–2022

**Figure 2: Confirmed exposure incidents, suspected and confirmed laboratory-acquired infections and exposure incident rate, Canada, 2016–2022**

<table>
<thead>
<tr>
<th>Year</th>
<th>Exposure</th>
<th>LAI suspected</th>
<th>LAI confirmed</th>
<th>Exposure incident rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>20,000</td>
<td>1,000</td>
<td>500</td>
<td>3.0</td>
</tr>
<tr>
<td>2017</td>
<td>20,500</td>
<td>1,000</td>
<td>500</td>
<td>2.5</td>
</tr>
<tr>
<td>2018</td>
<td>21,000</td>
<td>1,000</td>
<td>500</td>
<td>2.5</td>
</tr>
<tr>
<td>2019</td>
<td>21,500</td>
<td>1,000</td>
<td>500</td>
<td>2.5</td>
</tr>
<tr>
<td>2020</td>
<td>22,000</td>
<td>1,000</td>
<td>500</td>
<td>2.5</td>
</tr>
<tr>
<td>2021</td>
<td>22,500</td>
<td>1,000</td>
<td>500</td>
<td>2.5</td>
</tr>
<tr>
<td>2022</td>
<td>23,000</td>
<td>1,000</td>
<td>500</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Abbreviation: LAI, laboratory-acquired infection

Figure 3 shows that in 2022, the number of confirmed exposure incidents was lowest in April, July, August and November (two incidents per month) and as was the case in previous years, the exposure incident rate was highest in September (six incidents per month).

**Figure 3: Seasonality analysis using median confirmed exposure incidents per month, Canada, 2016–2022**

<table>
<thead>
<tr>
<th>Month</th>
<th>Median confirmed exposure incidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>2</td>
</tr>
<tr>
<td>February</td>
<td>3</td>
</tr>
<tr>
<td>March</td>
<td>5</td>
</tr>
<tr>
<td>April</td>
<td>2</td>
</tr>
<tr>
<td>May</td>
<td>3</td>
</tr>
<tr>
<td>June</td>
<td>6</td>
</tr>
<tr>
<td>July</td>
<td>7</td>
</tr>
<tr>
<td>August</td>
<td>4</td>
</tr>
<tr>
<td>September</td>
<td>6</td>
</tr>
<tr>
<td>October</td>
<td>3</td>
</tr>
<tr>
<td>November</td>
<td>4</td>
</tr>
<tr>
<td>December</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: LAI, laboratory-acquired infection

Exposure incidents by main activity and sector

In 2022, the most common activity being performed at the time of a reported exposure incident was microbiology (n=20; 50.0%), followed by in vivo animal research (n=9; 22.5%). Other less cited activities include animal care (n=3; 7.5%), cell culture (n=2; 5%), autopsy/necropsy (n=1; 2.5%), microscopy (n=1; 2.5%), other (n=3; 7.5%) and unknown (n=1; 2.5%). Definitions of activities can be found in the Appendix, Table A1.
As shown in Figure 4, the majority of the reported confirmed exposure incidents in 2022 occurred in the academic sector (n=16; 40%), followed by the hospital sector (n=10; 25.0%). The sector with the highest number of exposure incidents per 100 active licences was the veterinary/animal health sector (25 exposure incidents per 100 active licences), followed by the public health sector (17 exposure incidents per 100 active licences).

Implicated human pathogens and toxins

Table 1 shows the distribution of biological agents (bacteria, fungus, parasite, prion, toxin, virus) involved in the exposure incidents reported in 2022 by risk group (RG2, RG3) and whether classified as SSBA. The majority of the 43 HPTs implicated in the 40 confirmed exposure reports were both non-SSBA (n=36; 83.7%) and human RG2 pathogens (n=27; 62.7%). Six SSBA agents were reported in 2022 (14.0%). Bacteria were the most reported agent type in 2022 (n=19; 44.2%), followed by fungus (n=10; 23.3%) and virus (n=7; 16.3%). One non-SSBA report involved parasites (2.3%). The most common RG2 agents involved in exposure incidents were Neisseria meningitidis (n=5; 11.6%) and Pertussis toxin (n=3; 7.0%). The most common RG3 agent involved was Brucella melitensis (n=3; 7.0%), followed by SARS-CoV-2 (n=2; 4.7%). Escherichia coli and Coxiella burnetii were the biological agents involved in the two suspected LAIs.

Occurrence types

As shown in Figure 5, 62 occurrence types were cited in the 40 confirmed exposure incidents reported in 2022. Sharps and procedure-related incidents (n=15; 24.2% each) were the most reported type of occurrences, followed by personal protective equipment (PPE)-related incidents (n=8; 12.9%) and animal-related incidents (n=6; 9.7%). Definitions of occurrence types are provided in Table A2.

Root causes

Through the investigation of follow-up reports, 84 root causes were identified (Table 2), resulting in an average of 2.1 root causes per confirmed exposure report. Human interaction was the most identified root cause (n=20; 23.8%), followed by issues with standard operating procedures (n=19; 22.6%). Training, communication and other root causes were the least common root causes reported (n=7; 8.3% each).

---

Table 1: Human pathogens or toxins involved in reported exposure incidents by risk group level and security sensitive status, Canada, 2022 (N=43)

<table>
<thead>
<tr>
<th>Biological agent type by risk group</th>
<th>Non-SSBA</th>
<th>SSBA</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG2 agents</td>
<td>27/63</td>
<td>0</td>
<td>0</td>
<td>27/63</td>
</tr>
<tr>
<td>Bacteria</td>
<td>15/35</td>
<td>0</td>
<td>0</td>
<td>15/35</td>
</tr>
<tr>
<td>Fungus</td>
<td>4/9</td>
<td>0</td>
<td>0</td>
<td>4/9</td>
</tr>
<tr>
<td>Parasite</td>
<td>1/2</td>
<td>0</td>
<td>0</td>
<td>1/2</td>
</tr>
<tr>
<td>Prion</td>
<td>1/2</td>
<td>0</td>
<td>0</td>
<td>1/2</td>
</tr>
<tr>
<td>Toxin</td>
<td>3/7</td>
<td>0</td>
<td>0</td>
<td>3/7</td>
</tr>
<tr>
<td>Virus</td>
<td>3/7</td>
<td>0</td>
<td>0</td>
<td>3/7</td>
</tr>
<tr>
<td>RG3 agents</td>
<td>9/21</td>
<td>6/14</td>
<td>0/0</td>
<td>15/35</td>
</tr>
<tr>
<td>Bacteria</td>
<td>0/0</td>
<td>4/9</td>
<td>0/0</td>
<td>4/9</td>
</tr>
<tr>
<td>Fungus</td>
<td>5/12</td>
<td>1/2</td>
<td>0/0</td>
<td>6/14</td>
</tr>
<tr>
<td>Parasite</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Prion</td>
<td>1/2</td>
<td>0</td>
<td>0</td>
<td>1/2</td>
</tr>
<tr>
<td>Toxin</td>
<td>0/0</td>
<td>0</td>
<td>0</td>
<td>0/0</td>
</tr>
<tr>
<td>Virus</td>
<td>3/7</td>
<td>1/2</td>
<td>0/0</td>
<td>4/9</td>
</tr>
<tr>
<td>Total</td>
<td>36/84</td>
<td>6/14</td>
<td>1/2</td>
<td>43/100</td>
</tr>
</tbody>
</table>

Abbreviations: RG, risk group; SSBA, security sensitive biological agent
* Percentages are rounded to the nearest whole number

Figure 4: Confirmed exposure incidents and active licences by sector reported to Laboratory Incident Notification Canada, Canada, 2022

Figure 5: Reported occurrence types in confirmed exposure incidents, Canada, 2022 (N=62)
Table 2: Root causes reported in follow-up reports of confirmed exposure incidents, Canada, 2022 (N=84)

<table>
<thead>
<tr>
<th>Root cause</th>
<th>Examples of areas of concern</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human interaction</td>
<td>A violation (cutting a corner, not following correct procedure, deviating from standard operating procedure)</td>
<td>20 23.8%</td>
</tr>
<tr>
<td></td>
<td>An error (a mistake, lapse of concentration or slip of any kind)</td>
<td></td>
</tr>
<tr>
<td>Standard operating procedure</td>
<td>Documents were followed as written but were not correct for activity/task</td>
<td>19 22.6%</td>
</tr>
<tr>
<td></td>
<td>Procedures that should have been in place were not in place</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Documents were not followed correctly</td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td>Equipment quality control needed improvement</td>
<td>14 16.7%</td>
</tr>
<tr>
<td></td>
<td>Equipment failed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Equipment was not appropriate for purpose</td>
<td></td>
</tr>
<tr>
<td>Training</td>
<td>Training not in place but should have been in place</td>
<td>7 8.3%</td>
</tr>
<tr>
<td></td>
<td>Training not appropriate for task/activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staff were not qualified or proficient in performing task</td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>Communication did not occur but should have</td>
<td>7 8.3%</td>
</tr>
<tr>
<td></td>
<td>Communication was unclear, ambiguous, etc.</td>
<td></td>
</tr>
<tr>
<td>Management and oversight</td>
<td>Supervision needed improvement</td>
<td>10 11.9%</td>
</tr>
<tr>
<td></td>
<td>Lack of auditing of standards, policies and procedures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk assessment needed improvement</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Not applicable</td>
<td>7 8.3%</td>
</tr>
</tbody>
</table>

Exposed individuals

A total of 93 individuals were exposed through the 40 exposure incidents reported and confirmed to LINC in 2022. Most exposed individuals held a bachelor’s degree (n=37; 39.8%), followed by a technical or a trade college diploma (n=27; 29.0%), a master’s degree (n=12; 12.9%) or were at high school level (n=7; 7.5%). Individuals with the highest education level, MD/PhD, were the least exposed to laboratory incidents (n=2; 2.2%).

As shown in Figure 6, most exposed individuals worked as a technician/technologist (n=68; 73.1%), a student (n=12; 12.9%), on another role (n=11; 11.8%) or as a researcher (n=2; 2.2%). The median number of years of experience for technicians/technologists was nine while the median number of years of experience for students was two.

Most of the 93 exposed individuals were exposed to HPTs through inhalation (n=73; 78.5%) or inoculation/injection through needle/sharps (n=11; 11.8%) (data not shown). Other routes of exposure for the rest of exposed individuals include absorption via contact with mucous membrane, absorption via contact with skin and inoculation/injection through bite/scratch.

Time between the incident and the reporting date

In 2022, 62.5% (n=25) of all confirmed exposure reports (n=40) were submitted to LINC within one week of the incident. The median number of days from incident occurrence to LINC reporting date was 5.5 days in 2022 (Figure 7), which is slightly shorter than the median delay of six days reported in 2020 and 2021.
Discussion

Forty confirmed laboratory exposure incidents were reported to LINC in 2022. This marks a slight decrease from the 44 confirmed exposure incidents reported in 2021. Two of the exposure incidents in 2022 led to suspect LAIs. Similar to 2021, most of the exposure incidents in 2022 occurred while performing microbiology activities and in academic and hospital sectors. The exposures were most commonly due to sharps and procedural breaches. Most biological agents involved were RG2 and non-SSBAs, while bacteria were the most reported agent type.

The exposure incident rate was lower in 2022 (3.8 incidents per 100 active licences) compared to the previous year (4.3 incidents per 100 active licences). This decrease in the rate could be due to heightened vigilance in laboratories related to coronavirus disease 2019 (COVID-19) biosafety measures and better knowledge of laboratory safety practices.

Increase in number of affected individuals

Ninety-three individuals were exposed to HPTs through 40 confirmed exposure incidents in 2022, which is an increase of 29% compared to 2021 (n=72). As in 2021, most of the affected individuals held the role of laboratory technicians/technologists. Technicians/technologists may also be the individuals who are most often in contact with HPTs in labs due to their qualifications or years of experience. While an exposure incident usually involves one to three individuals, further analysis of 2022 data showed that most of the individuals affected in 2022 were implicated through one specific laboratory incident, which affected 47 individuals by inhalation of B. melitensis, which is one of the most involved pathogens in laboratory-acquired infections (11,12).

Decline in SARS-CoV-2 exposures

Last year marked the second full year of the COVID-19 pandemic. In contrast to 2021, when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was the most implicated agent across all pathogen groups due in part to heightened laboratory activities focused on COVID-19, in 2022, SARS-CoV-2 was the fourth most implicated agent across all pathogen groups. The reduction in the proportion of reported exposures involving SARS-CoV-2 agents compared to the previous years of the pandemic might be due to a return to more normal operations in laboratories, which includes the manipulation of other pathogens besides SARS-CoV-2 towards the end of 2022. With the expectation of potential new variants in the future, it is reasonable for the virus to continue to feature among the commonly reported agents (13,14). It is important to note that as per the HPTA, reported exposure incidents involving SARS-CoV-2 did not include exposure incidents related to diagnostic activities.

Changes in seasonal exposure incidents trend

The median number of exposure incidents reported per month from 2016 to 2021 was lowest in June and August (2.5 incidents per month) and highest in September (6.5 incidents per month). The monthly occurrence of laboratory exposure incidents reported throughout 2022 followed a similar trend of the previous six years with a few exceptions. The number of exposure incidents reported remained highest in September 2022 (n=6); however, the number of exposure incidents was lowest in April, July, August and November (n=2 each). While the peak in September 2022 was expected and may be explained by the return of students and workers to laboratories after vacation in the summer months, the deviation from the normal trend observed for the low number of exposure incidents is notable. April and November 2022 had far fewer incidents reported than the median of the previous six years. The lower number of incidents in April 2022 may be explained by reduced laboratory staff due to sickness from the Omicron variant of the SARS-CoV-2 virus. It is possible that laboratory workers took more vacation in November following the easing of travel restrictions in October 2022.

Human interaction remains the leading root cause of incidents

Human interaction, which includes violations and errors, remained the dominant root cause cited in 2022 and made up nearly 23.8% of the total number of root causes cited. The stress and fatigue experienced by workers in the context of the COVID-19 pandemic could be a contributing factor to incidents attributed to human interaction in laboratories (15,16); however, the proportion of human interaction citations decreased by 4% compared to 2021. This decrease could be due to improvements in laboratory practises as a result of the adoption of new COVID-19 measures and increased biosafety vigilance in laboratories. Issues with standard operating procedures, equipment, management, and oversight were also frequently reported as root causes of laboratory incidents.

Strengths and limitations

The strength of the LINC program is that it allows for the collection of exposure incidents data from licensed laboratories across Canada through a standardized mandatory reporting system. The Public Health Agency of Canada’s Biosecurity Portal provides a user-friendly method to report laboratory exposure incidents and serves as a reliable source of data for analyzing exposure incident trends over time.

The possibility of under-reporting of laboratory exposure incidents remains a limitation that must be taken into consideration, as the rate of under-reporting is still unknown and can affect the results. To encourage the reporting of laboratory incidents, the Centre for Biosecurity offers an alternative method for incident reporting by email. Limited centralized information about laboratory incidents outside of Canada

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The possibility of under-reporting of laboratory exposure incidents remains a limitation that must be taken into consideration, as the rate of under-reporting is still unknown and can affect the results. To encourage the reporting of laboratory incidents, the Centre for Biosecurity offers an alternative method for incident reporting by email. Limited centralized information about laboratory incidents outside of Canada
makes it challenging to compare trends in Canada with those of other countries. Within Canada, the COVID-19 pandemic has impacted normal laboratory operations and potentially affected the overall trend of laboratory exposure incidents across Canada. Data collected in the upcoming years will allow for a better understanding of trends and will clarify COVID-19’s impact on laboratory incidents in Canada.

Neither information about the number of laboratory employees nor their respective roles were collected during the reporting process. As such, the number of active licences was used as a proxy for workforce size. However, this limited analysis of the data and understanding of exposure incident rates. The location of laboratories involved in exposure reports also was not collected. Therefore, the information provided in this report should be used only at a national level. Finally, it should be noted that slight decreases or increases in the number of exposure incidents may be due to natural variability from one year to the next.

Conclusion
Overall, the results observed in 2022 were similar in many respects to those from 2021, with a few exceptions. The exposure incident rate was lower in 2022 than in 2021; however, it remains unclear if this was a true decrease, as the full effect of the COVID-19 pandemic on laboratory operations can only be assessed after a couple of years. Sharp-related incidents and issues related to standard operating procedures remain the most common occurrence types, while human interaction remain the most cited root cause of exposure incidents.

Authors’ statement
CA — Incident monitoring, methodology, data analysis, writing–original draft, writing–review and editing
AG — Data analysis, writing–original draft, writing–review and editing
AD — Conceptualization, writing–original draft, writing–review, editing and supervision
CE — Writing–original draft
NB — Methodology, writing–review and editing
AK — Writing–original draft, writing–review and editing
SBA — Writing–review and editing

Competing interests
There are no competing interests to declare.

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References


Appendix

Table A1: Definitions of main activity

<table>
<thead>
<tr>
<th>Main activity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal care</td>
<td>Activities such as attending to the daily care of animals and providing animals with treatment</td>
</tr>
<tr>
<td>Autopsy or necropsy</td>
<td>Post-mortem surgical examinations for purposes such as determining cause of death or to evaluate disease or injury for research or educational purposes</td>
</tr>
<tr>
<td>Cell culture</td>
<td>The process of growing cells under controlled conditions. It can also involve the removal of cells from an animal or plant</td>
</tr>
<tr>
<td>Education or training</td>
<td>Education or training of students and/or personnel on laboratory techniques and procedures</td>
</tr>
<tr>
<td>In vivo animal research</td>
<td>Experimentation with live, non-human animals</td>
</tr>
<tr>
<td>Maintenance</td>
<td>The upkeep, repair, and/or routine and general cleaning of equipment and facilities</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Activities involving the manipulation, isolation, or analysis of microorganisms in their viable or infectious state</td>
</tr>
<tr>
<td>Molecular investigations</td>
<td>Activities involving the manipulation of genetic material from microorganisms or other infectious material for further analysis</td>
</tr>
<tr>
<td>Serology</td>
<td>Diagnostic examination and/or scientific study of immunological reactions and properties of blood serum</td>
</tr>
<tr>
<td>Hematology</td>
<td>Scientific study of the physiology of blood</td>
</tr>
</tbody>
</table>

Table A2: Definitions of occurrence type

<table>
<thead>
<tr>
<th>Occurrence type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spill</td>
<td>Any unintended release of an agent from its container</td>
</tr>
<tr>
<td>Loss of containment</td>
<td>Includes malfunction or misuse of containment devices or equipment and other type of failures that results in the agent being spilled outside of, or released from, containment</td>
</tr>
<tr>
<td>Sharps-related</td>
<td>Needle stick, cut with scalpel, blade or other sharps injury (i.e. broken glass)</td>
</tr>
<tr>
<td>Animal-related</td>
<td>Includes animal bites or scratches, as well as other exposure incidents resulting from animal behavior (i.e. animal movement resulting in a needle stick)</td>
</tr>
<tr>
<td>Insect-related</td>
<td>Includes insect bites</td>
</tr>
<tr>
<td>PPE-related</td>
<td>Includes either inadequate PPE for the activity or failure of the PPE in some way</td>
</tr>
<tr>
<td>Equipment-related</td>
<td>Includes failure of equipment, incorrect equipment for the activity, or misuse of equipment</td>
</tr>
<tr>
<td>Procedure-related</td>
<td>Includes instances when written procedures were not followed, were inadequate or absent, or were incorrect for the activity</td>
</tr>
</tbody>
</table>

Abbreviation: PPE, personal protective equipment