Invasive group A streptococcal disease surveillance in Canada, 2020

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Abstract

Background: Invasive group A streptococcal (iGAS) disease (caused by *Streptococcus pyogenes*) has been a nationally notifiable disease in Canada since 2000. This report summarizes the demographics, *emm* types and antimicrobial resistance of iGAS infections in Canada in 2020.

Methods: The Public Health Agency of Canada's National Microbiology Laboratory (Winnipeg, Manitoba) collaborates with provincial and territorial public health laboratories to conduct national surveillance of invasive *S. pyogenes*. *Emm* typing was performed on all isolates using the Centers for Disease Control and Prevention *emm* sequencing protocol. Antimicrobial susceptibilities were determined using Kirby-Bauer disk diffusion according to Clinical and Laboratory Standards Institute guidelines. Population-based iGAS disease incidence rates up to 2019 were obtained through the Canadian Notifiable Disease Surveillance System.

Results: Overall, the incidence of iGAS disease in Canada has increased from 4.0 to 8.1 cases per 100,000 population from 2009 to 2019. The 2019 incidence represents a slight decrease from the 2018 rate of 8.6 cases per 100,000 population. A total of 2,867 invasive *S. pyogenes* isolates that were collected during 2020 are included in this report, representing a decrease from 2019 (n=3,194). The most common *emm* types in 2020 were *emm*49 (16.8%, n=483) and *emm*76 (15.0%, n=429), both increasing significantly in prevalence since 2016 ($p<0.001$). The former most prevalent type, *emm*1, decreased to 7.6% (n=217) in 2020 from 15.4% (n=325) in 2016. Antimicrobial resistance rates in 2020 included 11.5% resistance to erythromycin, 3.2% resistance to clindamycin and 1.6% nonsusceptibility to chloramphenicol.

Conclusion: Though the number of collected invasive *S. pyogenes* isolates decreased slightly in 2020 in comparison to previous years, iGAS disease remains an important public health concern. The *emm* distribution in Canada has been subtly shifting over the past five years, away from common and well-known *emm*1 and towards *emm*49 and *emm*76. It is important to continue surveillance of *S. pyogenes* in Canada to monitor expanding replacement *emm* types, as well as outbreak clones and antimicrobial resistance.

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Introduction

Invasive group A Streptococcus (*Streptococcus pyogenes*) is responsible for a wide range of human diseases, the most serious of which include bacteraemia, streptococcal toxic shock syndrome, necrotizing fasciitis and endocarditis (1). In Canada, the incidence of invasive group A streptococcal (iGAS) infections is increasing; doubling from 4.0 cases per 100,000 population in 2009 to 8.1 cases per 100,000 in 2019 (2). Though iGAS disease is a global cause of morbidity and mortality (3), many studies have indicated that certain populations are at particular risk of disease, including those who are disadvantaged or living in overcrowded conditions (4,5).

The M protein, encoded by the *emm* gene, is an important virulence factor and an epidemiological marker used to characterize *S. pyogenes* isolates (1). A significant amount of iGAS disease is caused by a small number of *emm* types; however, shifts in prevalence can cause substantial temporal and geographic variability. Studies have noted frequent fluctuations in *emm* type prevalence in so-called "epidemic behaviour", where new, emerging strains ultimately replace those previously circulating (1,6). Furthermore, the accumulation of mutations through acquisition of exogenous DNA may result in more virulent clones expanding in prevalence or causing new outbreaks of disease in vulnerable populations (6).

As rapid clonal spread and outbreaks of iGAS disease continue to occur in Canada (4–6), it has become increasingly important to monitor the constantly shifting virulence patterns associated with this organism. This report provides a summary of invasive *S. pyogenes* isolates collected in Canada in 2020.

Methods

Surveillance program

Surveillance of iGAS infections in Canada consists of a passive, laboratory-based system where invasive *S. pyogenes* isolates from all provincial and territorial public health laboratories (except Alberta) are sent to the National Microbiology Laboratory (NML) in Winnipeg for further testing. A total of 2,867 invasive *S. pyogenes* isolates were reported in 2020, including 1) 2,409 isolates submitted directly to NML by provincial and territorial public health laboratories and 2) data for a further 458 isolates collected and tested by the Provincial Laboratory for Public Health in Edmonton, Alberta (ProvLab Alberta) (**Table 1**). Isolates are collected from sterile clinical isolation sites, which include blood, cerebrospinal fluid, deep tissue, biopsy and surgical samples, bone and any clinical sources associated with necrotizing fasciitis or toxic shock syndrome.

Population-based incidence of iGAS disease up to 2019 was obtained through Canadian Notifiable Disease Surveillance System (CNDSS). Population data for incidence rates were obtained from Statistics Canada's July 1st annual population estimates.

Isolate testing

Streptococcus pyogenes isolates were confirmed by a positive PYR (pyrrolidonyl-β-naphthylamide) reaction and susceptibility to bacitracin (7). *Emm* typing was performed on all iGAS isolates submitted to NML and ProvLab Alberta using the Centers for Disease Control and Prevention (CDC) *emm* sequencing protocol. The sequences obtained were compared with the CDC *emm* database and results reported to the subtype level.

Table 1: Number of invasive *Streptococcus pyogenes* isolates collected by each Canadian province/region, 2020

Province	Age group (years)						Not given	Total
	Younger than 2	2–4	5–14	15–49	50–64	65 and older		
British Columbia	2	1	4	159	104	67	1	338
Alberta	16	3	9	248	121	61	0	458
Saskatchewan	13	2	3	168	58	28	0	272
Manitoba	12	10	4	114	70	58	0	268
Ontario	10	6	18	458	274	294	3	1,063
Quebec	12	7	8	143	74	101	0	345
New Brunswick	2	0	3	25	14	8	1	53
Atlantic[a]	2	1	5	48	25	17	1	99
Northern[b]	0	1	0	11	11	1	0	24
Total	67	31	51	1,349	737	627	5	2,867

[a] Includes isolates from New Brunswick, Prince Edward Island, Nova Scotia and Newfoundland and Labrador
[b] Includes isolates from Yukon, Northwest Territories and Nunavut

Antimicrobial susceptibilities for *S. pyogenes* (n=2,375) were determined using Kirby-Bauer disk diffusion for chloramphenicol (30 µg), erythromycin (15 µg), clindamycin (2 µg), penicillin (10 µg), ceftriaxone (30 µg) and vancomycin (30 µg) according to Clinical and Laboratory Standards Institute (CLSI) guidelines (8).

Supplementary testing was performed on a subset of *emm*1 isolates to determine the prevalence of the novel $M1_{UK}$ lineage. Genotypes for $M1_{UK}$ isolates were determined by mapping whole genome sequencing reads against reference strain MGAS5005 and identifying 27 characteristic genomic single-nucleotide variants (SNVs), as previously described (9,10).

Data analysis

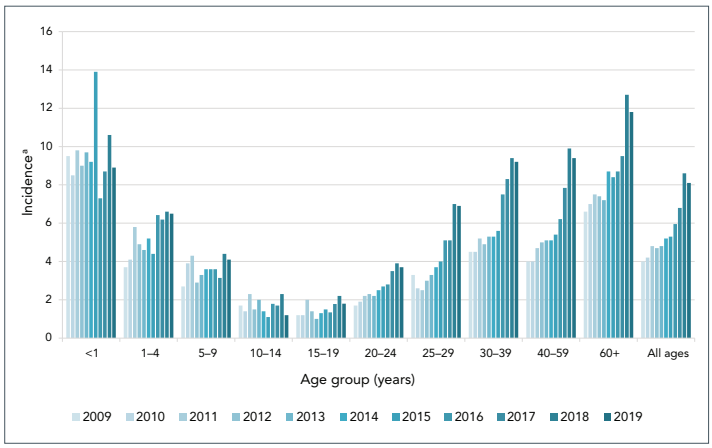
Data submitted with bacterial isolates included patient age, sex, clinical source, province and date of collection. Multiple isolates with the same *emm* type and collected from the same patient within 14 days were counted once with the most invasive isolation site assigned. Meningitis-related isolates were regarded as most invasive, followed by blood and then other sterile sites. The laboratory data were aggregated by age into younger than two, 2–4, 5–14, 15–49, 50–64 and 65 years and older age groups, and regionally into Western (British Columbia, Alberta, Saskatchewan, Manitoba), Central (Ontario and Québec), Eastern (New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador) and Northern (Yukon Territories, Northwest Territories and Nunavut) regions of Canada. Statistical significance of trends was assessed using the Cochran Armitage test of trend, with a *p*-value of <0.05 considered significant.

Results

The overall incidence of iGAS disease in Canada decreased slightly in 2019 after successive annual increases from 2009 to 2018. The overall incidence rate in 2019 was 8.1 cases per 100,000 population—twice the rate observed in 2009 (**Figure 1, Supplemental material Table S1**). In 2020, 2,867 isolates of invasive *S. pyogenes* were collected, representing a decrease from 2019 (n=3,194).

Of the 2,867 invasive *S. pyogenes* isolates tested in 2020, 2,862 (99.8%) had patient ages. Infants younger than two years of age accounted for 1.7% (n=67), toddlers aged 2–4 years for 1.1% (n=31), children aged 5–14 years for 1.8% (n=51), teens/adults aged 15–49 years for 47.1% (n=1,349), adults aged 50–64 years for 25.7% (n=737) and seniors aged 65 years and older for 21.9% (n=627). Five isolates had no ages provided. Isolates from male patients represented 58.1% (n=1,635) of the isolates for which sex information was available. Blood was the main clinical isolation site, accounting for 67.9% (n=1,947) of isolates collected. Additional information on *emm* types by specimen source can be found in **Figures S1 to S5**.

Figure 1: Annual incidence rates of invasive *Streptococcus pyogenes* cases in Canada by age group, 2010–2019

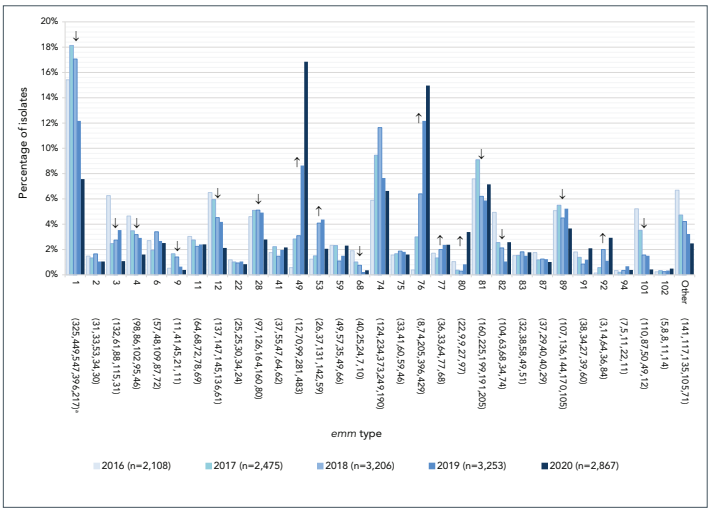


[a] Cases per 100,000 population

The most predominant *emm* types overall in 2020 were *emm*49 (16.8%, n=483) and *emm*76 (15.0%, n=429), which have increased significantly in prevalence since 2016 (from 0.6%, n=12 and 0.4%, n=8, respectively; $p<0.001$) (**Figure 2**). Other *emm* types that demonstrated significantly increasing trends from 2016 to 2020 include *emm*53 (1.2% to 2.1%, $p<0.001$), *emm*77 (1.7% to 2.4%, $p=0.005$), *emm*80 (1.0% to 3.4%, $p<0.001$) and *emm*92 (0.1% to 2.9%, $p<0.001$). Other *emm* types demonstrated significantly decreasing trends (see Figure 2), such as *emm*1 from 15.4% (n=325) of all invasive *S. pyogenes* isolates collected in 2016, to only 7.6% (n=217) in 2020 ($p<0.001$). Of note, 33% (n=138) of *emm*1 isolates sequenced in 2019 were the novel $M1_{UK}$ lineage; in comparison, only three $M1_{UK}$ isolates were identified in 2015.

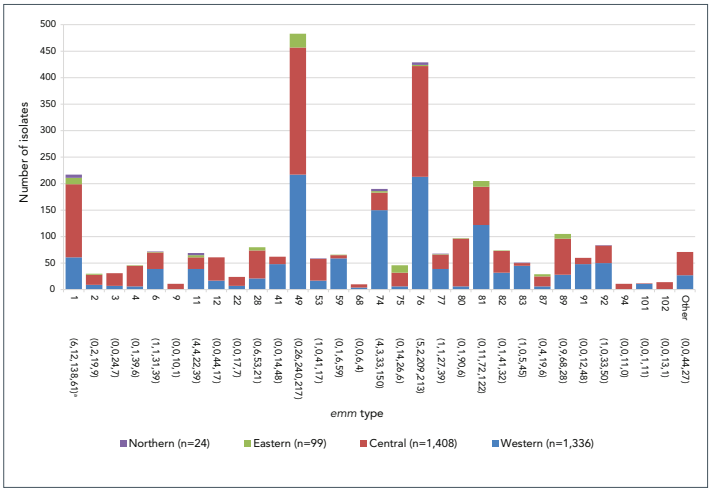
In 2020, the most common *emm* type from children younger than two years of age was *emm*49 (20.9%, n=14), while *emm*1 predominated for children 2–4 years (41.9%, n=13) and 5–14 years (37.3%, n=19) (**Figure S6**). In patients aged 15–49 and 50–64 years, *emm*49 was most common (17.9%, n=242; 17.9%, n=132, respectively), followed by *emm*76 (16.3%, n=220; 14.2%, n=105). For adults 65 years and older, *emm*76 (14.4%, n=90) and *emm*49 (14.2%, n=89) were also most common, but *emm*1 was also frequently identified (12.0%, n=75) (**Figure S7**). *Emm* types associated with Western Canada (**Figure 3**) included *emm*49 (16.2%, n=217), *emm*76 (15.9%, n=213), *emm*74 (11.2%, n=150) and *emm*81 (9.1%, n=122). In Central Canada, *emm*49 (17.1%, n=240) and *emm*76 (14.8%, n=209) were predominant, while *emm*49 (26.3%, n=26) and *emm*75 (14.1%, n=14) were most common in Eastern Canada. Isolates from Northern Canada were highly represented by *emm*1 at 25.0% (n=6), though only 24 isolates were submitted from this region (**Figures S8 to S11**).

Figure 2: Prevalence of invasive *Streptococcus pyogenes emm* types in Canada, 2016–2020[a,b,c]



[a] Number of isolates for 2016, 2017, 2018, 2019 and 2020, respectively
[b] Increase in 2016 and 2017 totals from previous annual reports is due to inclusion of submitted data from Alberta
[c] For *emm* types with an overall (2016–2020) n≥30: up or down arrows indicate statistically significant trends toward increasing or decreasing prevalence for the 2016–2020 timespan, using the chi-squared test for trend. *Emm* types with no arrow either did not demonstrate a statistically significant trend, or did not have an overall n≥30

Figure 3: Regional distribution of invasive *Streptococcus pyogenes* isolates collected in 2020, by *emm* type[a]

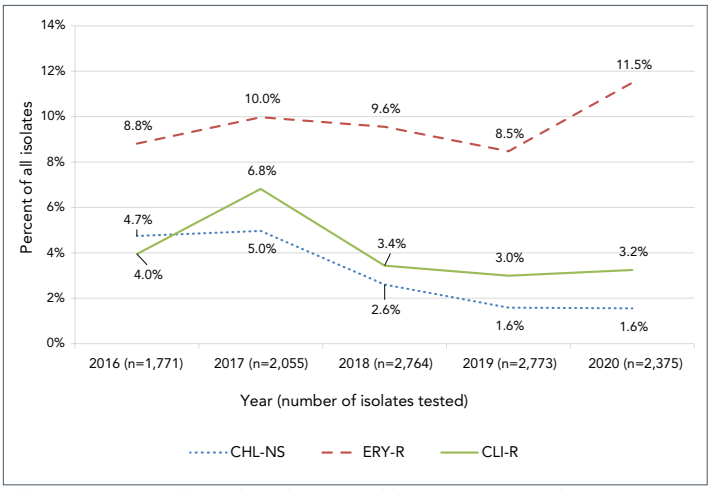


[a] Number of isolates in the Northern, Eastern, Central and Western regions of Canada, respectively

Upon request, NML provides assistance to provincial and territorial public health laboratories for *S. pyogenes* outbreak investigations. During 2020, NML assisted in six outbreak investigations from various jurisdictions, including *emm*6.4 (n=224 cases), *emm*74 (n=3), *emm*81 (n=9), *emm*92 (n=5) and two multi-*emm* type outbreaks (*emm*1, *emm*74, *emm*76 and *emm*92, n=14; *emm*1, *emm*76 and *emm*77, n=10).

Antimicrobial resistance among invasive *S. pyogenes* isolates remained low in 2020 (**Figure 4, Table S2**). After dropping to 8.5% (n=235) in 2019, erythromycin resistance increased to 11.5% (n=273) in 2020; however, the overall increase from 2016 to 2020 was not statistically significant. Chloramphenicol nonsusceptibility decreased significantly from 4.7% in 2016 to 1.6% in 2020 ($p<0.001$), and clindamycin resistance has remained relatively stable over the previous three years (3.0%–3.4%). There was no resistance observed to penicillin or vancomycin. *Emm* types associated with erythromycin and clindamycin resistance included *emm*11 (88.6%, n=39; 79.5%, n=35); *emm*77 (80.8%. n=42; 78.8%, n=41) *emm*83 (45.7%, n=21; 47.8%, n=22) and *emm*92 (97.4%, n=74; 93.4%, n=71; respectively) (**Figure S12, Table S3**).

Figure 4: Antimicrobial resistance of invasive *Streptococcus pyogenes* in Canada, 2016–2020



Abbreviation: CHL-NS, chloramphenicol-nonsusceptible (resistant or intermediate); CLI-R, constitutively clindamycin-resistant; ERY-R, erythromycin-resistant

Discussion

In 2019, 3,054 cases of iGAS disease were reported to CNDSS, with a national incidence rate of 8.1 cases per 100,000 population; more than double the lowest recorded national incidence (2.7 cases per 100,000 population in 2004) since iGAS disease became notifiable in Canada in 2000. Other countries have noted similar increases in iGAS disease over time (11–14), and have hypothesized that the overall increase could be due to increasing molecular diversity of the M protein, or expansion of particularly virulent strains of *S. pyogenes* (13,14). Horizontal gene transfer of large regions of genetic material has resulted in a number of unusually virulent clones that have become dominant worldwide, such as the pandemic *emm*1 clone that resulted from acquisition of a 36kb region, resulting in increased expression of the cytotoxins *nga* (NADase) and *slo* (streptolysin O) (15). It has also been shown that in addition to

increased toxin expression, no or low capsule production may also support the expansion of successful lineages (16); examples include *emm*89, *emm*28 and *emm*87 (16,17).

The number of invasive *S. pyogenes* isolates collected by NML decreased from 3,194 in 2019 to 2,867 in 2020. Though 2020 incidence data for iGAS disease was unavailable at the time of writing, it is likely there was a slight decrease between 2019 and 2020. This decrease may have been an indirect effect of the containment measures put in place in 2020 to prevent the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic virus. Several studies have noted that there was decreased invasive disease due to respiratory-transmitted pathogens in 2020; among other routes, *S. pyogenes* may also be transmitted via respiratory droplets, so the same non-pharmaceutical public health measures put in place to prevent the spread of coronavirus disease 2019 (COVID-19) may have prevented some spread of *S. pyogenes*, resulting in fewer cases of iGAS disease. The Invasive Respiratory Infection Surveillance Initiative noted worldwide decreases in invasive diseases caused by respiratory pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* due to containment measures and social changes caused by the pandemic (18). A Houston, Texas area hospital also identified a decrease in invasive pneumococcal disease and iGAS disease in 2020 due to COVID-19 containment measures (19).

The most prevalent *emm* type collected in Canada over the past decade was *emm*1, accounting for over 25% of reported iGAS cases in the early 2010s and reflecting levels reported in Europe and North America (20). Although *emm*1 has decreased in prevalence in Canada since 2014, an increasing number of sequenced isolates (138 isolates in 2019 in comparison to three in 2015) are the novel, hypertoxigenic $M1_{UK}$ lineage originally described by Lynskey *et al*. (10). Recent publications indicated that the prevalence of this lineage is variable: 64% of sequences *emm*1 isolates in the Netherlands grouped with $M1_{UK}$, while the United States has not seen significant expansion (21,22). It will be crucial to monitor the expansion of this lineage in Canada and determine whether it results in increasing prevalence or outbreaks of *emm*1.

Despite decreasing in prevalence for a number of years, *emm*1 has only been surpassed by *emm*76 in 2019 (2), and by *emm*49 in 2020, each of which accounted for fewer than 1% of reported iGAS cases in 2016. Many outbreaks of iGAS disease across Canada in recent years have been due to *emm*76 and *emm*49 (*unpublished data*). *Emm* type replacements such as these may often be driven by low population immunity to rare *emm* types, and intensified transmission of disease within at-risk populations such as people experiencing homelessness (PEH), people who inject drugs (PWID) and other closed/semi-closed populations; in fact, it has been noted that the distribution of *emm* types varies between non-risk and at-risk groups, and even between different risk groups (14,23). Valenciano *et al*. observed that the *emm* distribution in the United States varied between PEH, PWID and those with both risk factors (23). Rapid expansion of previously uncommon *emm* types has been noted recently in a number of countries: *emm*74 in various disadvantaged groups across Canada; *emm*6 in a semi-closed population of military trainees in Canada; *emm*26.3 in PEH in the United States; and *emm*66 in PEH/PWID in England (4,5,24,25).

Streptococcus pyogenes remains susceptible to penicillin—the most commonly chosen antimicrobial treatment for iGAS infections, however, there is growing resistance to second-line agents such as macrolides and clindamycin (1). In 2020, common *emm* types in Canada that had high levels (more than 40%) of erythromycin and clindamycin resistance included *emm*11, *emm*77, *emm*83 and *emm*92, and two of these types (*emm*77, *emm*92) also demonstrated increasing prevalence from 2016 to 2020. These *emm* types were also found to be significant sources of macrolide/lincosamide resistance in countries such as Spain and the United States (26,27), with the latter study also noting increases over time of *emm*11, *emm*77 and *emm*92 (27). Importantly, all four *emm* types are included in an investigational 30-valent M-protein-based vaccine currently undergoing clinical trials (28). Further clinical development and eventual use of this vaccine worldwide could help to reduce the burden of disease associated with antimicrobial resistant *emm* types.

Strengths and limitations

Caution should be exercised when interpreting the data presented in this report as the overall interpretation of the results is limited to only isolates available for testing. Only a subset of laboratory isolates from each province may have been submitted for testing and therefore this report does not reflect the true incidence or rates of disease in Canada. The representativeness of the proportions of isolates submitted for testing to NML as compared to the CNDSS are presented in **Table S4**. Not all provinces and territories report line list data to CNDSS and therefore only aggregated data are available at the national level; therefore, CNDSS data and NML laboratory data are presented differently in terms of age grouping.

Conclusion

Although the number of isolates collected decreased in 2020 in comparison to previous years, iGAS disease remains an important public health concern. In the past five years the *emm* distribution in Canada has shifted away from the common and well-known *emm*1 and towards previously uncommon *emm*49 and *emm*76. Continued surveillance of invasive *S. pyogenes* in Canada is imperative to monitor these expanding replacement *emm* types, as well as outbreak clones and antimicrobial resistance.

Authors' statement

ARG — Formal analysis, data curation, visualization, writing–original draft, review and editing of final version
AG — Formal analysis, validation, investigation, data curation, visualization, writing–review and editing
WHBD — Formal analysis, validation, investigation, data curation, visualization, writing–review and editing
GJT — Resources, methodology, writing–review and editing
JVK — Resources, methodology, writing–review and editing
AM — Resources, methodology, writing–review and editing
MCD — Resources, methodology, writing–review and editing
LH — Resources, methodology, writing–review and editing
JM — Resources, methodology, writing–review and editing
PVC — Resources, methodology, writing–review and editing
HS — Resources, methodology, writing–review and editing
DH — Resources, methodology, writing–review and editing
GZ — Resources, methodology, writing–review and editing
KM — Resources, methodology, writing–review and editing
LS — Resources, methodology, writing–review and editing
LS — Resources, methodology, writing–review and editing
AYL — Writing–review and editing
MRM — Methodology, writing–review and editing
IM — Conceptualization, validation, methodology, supervision, project administration, writing–review and editing

Competing interests

None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

Table S1: Annual incidence rates of invasive *Streptococcus pyogenes* cases in Canada by age group, 2009–2019
Figure S1: Clinical isolation sites of invasive *Streptococcus pyogenes* from children younger than 15 years of age in 2020 (n=149)
Figure S2: Clinical isolation sites of invasive *Streptococcus pyogenes* from patients 15 years of age and older in 2020 (n=2,718)
Figure S3: Percentage of invasive *Streptococcus pyogenes* isolates from blood in 2020, by *emm* type (n=1,947)
Figure S4: Percentage of invasive *Streptococcus pyogenes* isolates from other sterile sites in 2020, by *emm* type (n=910)
Figure S5: Percentage of invasive *Streptococcus pyogenes* isolates from cerebrospinal fluid in 2020, by *emm* type (n=10)
Figure S6: Prevalence of invasive *Streptococcus pyogenes emm* types isolated in 2020 for those younger than two, 2–4 and 5–14 years old
Figure S7: Prevalence of invasive *Streptococcus pyogenes emm* types isolated in 2020 for those 15–49, 50–64 and 65 years and older
Figure S8: Prevalence of the ten most common invasive *Streptococcus pyogenes emm* types collected from Western Canada in 2020
Figure S9: Prevalence of the ten most common invasive *Streptococcus pyogenes emm* types collected from Central Canada in 2020
Figure S10: Prevalence of the ten most common invasive *Streptococcus pyogenes emm* types collected from Eastern Canada in 2020
Figure S11: Prevalence of invasive *Streptococcus pyogenes emm* types collected from Northern Canada in 2020
Table S2: Antimicrobial resistant invasive *Streptococcus pyogenes* isolates by year, 2016–2020
Figure S12: Percentage of macrolide and lincosamide resistant invasive *Streptococcus pyogenes* isolates collected in 2020, by *emm* type
Table S3: Percentage of macrolide and lincosamide resistant invasive *Streptococcus pyogenes* isolates collected in 2020, by *emm* type
Table S4: Number of invasive *Streptococcus pyogenes* isolates typed by the National Microbiology Laboratory (NML) in comparison to the total number of cases reported to Canadian Notifiable Diseases Surveillance System (CNDSS) in 2019, by patient age group

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