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MAJOR ARTICLE

Canada-Wide Epidemic of *emm74* Group A *Streptococcus* Invasive Disease

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Background. The number of invasive group A *Streptococcus* (iGAS) infections due to hitherto extremely rare type *emm74* strains has increased in several Canadian provinces since late 2015. We hypothesized that the cases recorded in the different provinces are linked and caused by strains of an *emm74* clone that recently emerged and expanded explosively.

Methods. We analyzed both active and passive surveillance data for iGAS infections and used whole-genome sequencing to investigate the phylogenetic relationships of the *emm74* strains responsible for these invasive infections country-wide.

Results. Genome analysis showed that highly clonal *emm74* strains, genetically different from *emm74* organisms previously circulating in Canada, were responsible for a country-wide epidemic of >160 invasive disease cases. The emerging clone belonged to multilocus sequence typing ST120. The analysis also revealed dissemination patterns of *emm74* subclonal lineages across Canadian provinces. Clinical data analysis indicated that the *emm74* epidemic disproportionally affected middle-aged or older male individuals. Homelessness, alcohol abuse, and intravenous drug usage were significantly associated with invasive *emm74* infections.

Conclusions. In a period of 20 months, an *emm74* GAS clone emerged and rapidly spread across several Canadian provinces located more than 4500 km apart, causing invasive infections primarily among disadvantaged persons.

Keywords. Canada; emerging strain genotype; epidemic; group A *Streptococcus*; homeless; invasive disease; outbreak; populations at risk.

Group A *Streptococcus* (GAS) causes a wide variety of diseases, ranging from relatively mild pharyngitis and superficial skin infections to life-threatening invasive diseases such as necrotizing fasciitis and toxic shock syndrome [1]. Recovering patients may sometimes suffer from serious postinfection sequelae, such as rheumatic fever and glomerulonephritis [2]. GAS strains are differentiated into more than 240 types based on the DNA sequence of the hypervariable 5' end of gene *emm* encoding M protein, a major virulence factor with antiphagocytic properties [3–5]. Despite this diversity, less than 30 *emm* types appear to be responsible for the majority of GAS disease worldwide [6]. Cyclical patterns of change in *emm* type distribution in a community— appearance, transient or more persistent dominance of particular *emm* types, and eventual replacement by other *emm* types—are common features of GAS epidemiology, as are unexpected emergence and spread of rare *emm* types, which can sometimes lead to increases in invasive GAS (iGAS) disease incidence [7–12]. A recent example was the sudden emergence and rapid dissemination across Canada and vast areas of the United States of a type *emm59* clone that caused hundreds of iGAS infections in both countries in the period 2008–2015 [13–20].

In early 2016, an outbreak of iGAS infections was declared in a 543-bed shelter for homeless men in Toronto, Canada [21]. Most of the cases recorded during the outbreak were caused by strains of type *emm74* GAS, hitherto exceedingly rare in Canada. Here, we report that *emm74* iGAS disease cases have since dramatically increased across the country, with more than 160 emm74 iGAS cases recorded in several Canadian provinces by June 2017. To better understand *emm74* iGAS emergence and spread across Canada, we analyzed available clinical data from patients identified by population-based surveillance for iGAS diseases, in combination with whole-genome sequencing analysis of the *emm74* isolates responsible for these infections.

METHODS

Bacterial Isolate Collection and Case Definition

In Canada, laboratory surveillance of iGAS disease is primarily a passive system where isolates are forwarded by provincial

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public health laboratories to the National Microbiology Laboratory (NML), Public Health Agency of Canada. System limitations include variable regional standards, availability of bacterial isolates for testing, and over-representation of more invasive strains for which medical treatment was sought. However, data gathered by passive laboratory surveillance account for >90% of all iGAS cases reported in the National Notifiable Disease Surveillance System. In metropolitan Toronto and Peel region (henceforth the greater Toronto area), the Toronto Invasive Bacterial Diseases Network (TIBDN) operates an active surveillance program for iGAS disease (sensitivity estimated at 95%) that includes all hospitals and microbiology laboratories in the area. Our bacterial collection comprised 1 invasive isolate per each of the 168 patients with *emm74* iGAS disease recorded nationally during the period May 2012 to June 2017. Isolates were from the provinces of Alberta (n = 25), British Columbia (n = 18), Quebec (n = 11), Saskatchewan (n = 2), and Ontario (n = 112, of which 54 were collected by passive laboratory surveillance, and 58 by TIBDN active surveillance; there was no overlap) (Supplementary Table 1). iGAS disease cases met the following criteria: (1) acute illness in association with isolation of GAS from a normally sterile site or (2) isolation of GAS from a nonsterile site (eg, skin, sputum) in the presence of confirmed or probable streptococcal toxic shock syndrome and/or soft tissue necrosis (including necrotizing fasciitis), meningitis, or death [22]. A temporally matched collection of 27 *emm74* isolates recovered from infections that did not meet the criteria for iGAS disease (ie, superficial wounds or skin lesions) was also included (Supplementary Table 1). In addition, we included 6 historic *emm74* iGAS isolates recovered in the 1990s and 2000s (Supplementary Table 1). Isolates were cultured on Columbia blood agar plates containing 5% sheep blood or in Todd-Hewitt broth supplemented with 0.2% yeast extract at 37°C with 5% CO_2. DNA was prepared from overnight cultures using the QIAamp DNA minikit (Qiagen, Toronto, ON, Canada). *emm* typing was performed by polymerase chain reaction and DNA sequencing, as previously described [23]. Data were compared with sequences available at the US Centers for Disease Control and Prevention *emm* database (ftp://ftp.cdc.gov/pub/infectious_diseases/biotech/tsemm/).

Clinical Data Collection

Clinical data for the 168 *emm74* iGAS cases were limited to patient age and sex, date of infection, and anatomical source of isolation of the strain, with the exception of clinical data collected by TIBDN (58 type *emm74* iGAS cases and a temporally matched cohort of 54 *emm1* iGAS cases), which also included disease presentation and outcomes, as well as underlying diseases or conditions that might have predisposed patients to invasive disease (eg, alcohol abuse, chronic underlying organ system disease, immunosuppression, homelessness, history of illicit drug use). Extended data collection and analysis were approved by the Research Ethics Boards of all participating TIBDN institutions.

Whole-Genome Sequencing, Closure of Reference Genome, Bioinformatics, and Phylogenetic Analysis

The genome of 1 randomly chosen *emm74* isolate (strain NGAS979) was sequenced to closure using a combination of single-molecule real-time sequencing (Pacific Biosciences, Menlo Park, CA) and Illumina sequencing (Illumina, San Diego, CA). The genomes of 129 additional *emm74* iGAS isolates, recovered between 2012 and 2017 (ie, 100% of the Quebec, Saskatchewan, and British Columbia isolates and 96% and 66% of the Alberta and Ontario iGAS isolates, respectively), were sequenced using Illumina technology. The genomes of the 6 abovementioned historic iGAS *emm74* isolates and 11 of the 27 (41%) noninvasive *emm74* isolates from Ontario and New Brunswick were also sequenced, for a total of 147 *emm74* genomes (Supplementary Table 1). The A5 pipeline was used for de novo assembly of Illumina-generated sequences [24]. Single nucleotide polymorphisms (SNPs) and short insertions/deletions (indels) were identified relative to the genome of strain NGAS979 using VAAL [25] and/or Nucmer [26]. Whole-genome and/or core genome SNPs were used to construct neighbor-joining phylogenetic trees (1000 bootstrap replications) using SplitsTree4 [27]. Contigs were annotated with Prokka [28]. Recombination was evaluated using BRATNextGen [29]. Genome visualizations were created using BRIG [30]. Detailed bioinformatics methods are presented in the Supplementary Methods.

Statistical Analysis

Differences between groups were compared using the χ^2 or Fisher exact test. The odds ratios (ORs) and 95% confidence intervals were calculated using SAS software, version 9.3 (SAS Institute). *P* values <.05 were considered statistically significant.

RESULTS

Dramatic Increase of Invasive *emm74* Gas Disease in Canada Since 2015

Analysis of national surveillance data identified only 2 *emm74* isolates among the 4683 iGAS infections recorded in Canada between 2012 and 2014 (Figure 1A). Together with a recent investigation that found no *emm74* isolates among a collection of 1454 iGAS isolates recovered in 2015 by the Active Bacterial Core Surveillance of the US Centers for Disease Control and Prevention [20], the data indicate that *emm74* GAS has been very rare in North America. Surprisingly, in early 2016, an outbreak of GAS infections was declared in a 543-bed shelter for homeless men in Toronto that involved numerous type *emm74* infections [21], including 6 invasive cases. Since the outbreak, both active (TIBDN) and passive (Public Health Ontario Laboratory, PHOL) surveillance systems in the province of Ontario began to identify increased numbers of *emm74* iGAS isolates in the greater Toronto area and in other urban municipalities such as London and Peterborough, as well as in rural areas of Northwestern Ontario. The upsurge in *emm74* iGAS isolations prompted us to retrospectively analyze national surveillance data. We identified 9 other *emm74* iGAS cases that

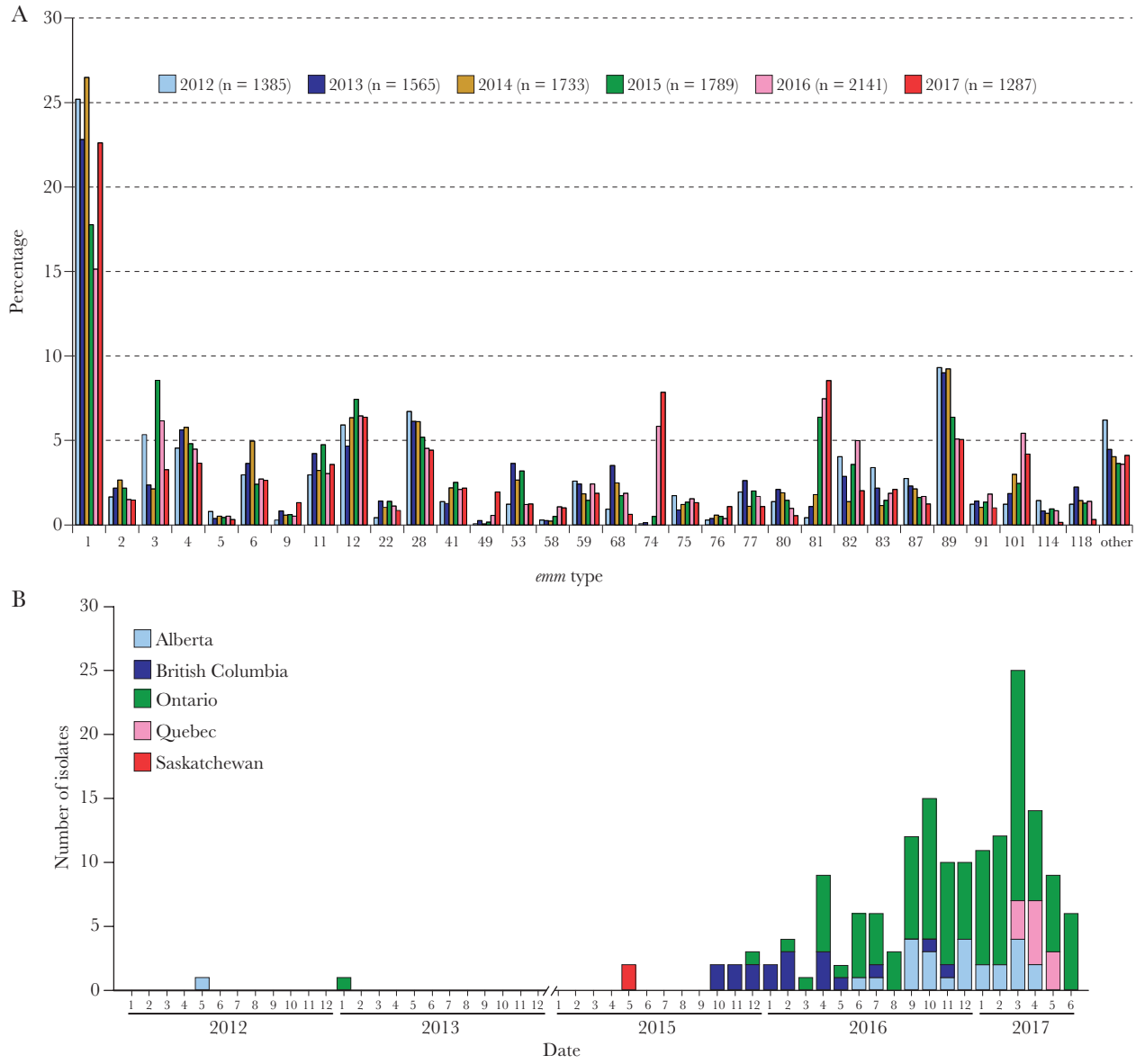

Figure 1. Canada-wide expansion of *emm74* group A *Streptococcus* invasive disease. A, Isolation of invasive group A *Streptococcus* (iGAS) isolates in all Canadian provinces and territories from January 2012 to June 2017. Bars show *emm* type distribution as a percentage of the total number of isolates in each year (first 6 months for year 2017). The percentage of *emm74* iGAS isolates, which were rarely seen in Canada, strikingly increased starting in 2015, spiked in 2016, and continued to be isolated in high numbers by June 2017, causing thus far more than 160 invasive cases in several Canadian provinces. B, Geographical origin and temporal distribution of 168 *emm74* isolates recovered in Canada from individual patients with *emm74* iGAS disease. For the period 2012 to 2014, only 2 *emm74* iGAS cases were recorded in Canada, 1 in the province of Alberta (May 2012) and 1 in the province of Ontario (January 2013). No further *emm74* invasive disease cases were observed until 2 years later, when 2 *emm74* iGAS strains were isolated in Saskatchewan during the second quarter of 2015. Then, beginning in late 2015 and continuing to June 2017, increasing numbers of *emm74* iGAS were isolated in the provinces of British Columbia, Ontario, Alberta, and Quebec.

occurred in 2015 (ie, prior to the Toronto outbreak) in British Columbia (n = 6), Ontario (n = 1), and Saskatchewan (n = 2) (Figure 1B). During 2016, *emm74* iGAS infections continued to be recorded in relatively high numbers in Ontario and British Columbia, and were noted in Alberta. By the end of 2016, *emm74* organisms were the fifth most common cause of iGAS disease in the country (Figure 1A). In the first 6 months of 2017 covered by this investigation, numerous additional *emm74* iGAS cases were recorded in Ontario and Alberta, and *emm74* iGAS disease was first reported in Quebec (Figure 1B), with a local *emm74* iGAS outbreak among homeless people declared in Montreal and adjacent municipalities. Thus, since 2015, *emm74* iGAS disease has increasingly been reported across the country in geographical areas located more than 4500 km apart.

Basic Demographic Characteristics of Patients With *emm74* iGAS Disease in Canada Since 2012

The median age of the 168 patients with *emm74* iGAS disease (range) was 52 (11–93) years, and only 3 cases (2%) occurred

in children under 18 years of age (Supplementary Table 1). A majority of cases (n = 115, 70.1%) occurred in men. The primary anatomical source from which *emm74* iGAS isolates were recovered was blood (n = 114, 67.9%), followed by abscesses or soft tissue specimens (n = 32, 19%) and synovial fluid (n =11, 6.5%) (Figure 2B).

Emergence and Rapid Expansion of a Genetically Distinct *emm74* Clone

We used genomics to test the hypothesis that the *emm74* epidemic is due to the rapid expansion of a recently emerged *emm74* genotype. We first sequenced to closure the genome of a randomly selected *emm74* invasive organism (strain NGAS979, henceforth the reference strain, isolated in Ontario in 2016). The genome (GenBank accession number CP028140) was a circular chromosome of 1 790 938 bp (38.6% G+C content). A total of 1748 coding sequences, 8 prophage or prophage-like remnants, and 1 integrative conjugative element (ICE), some of which were integrated in well-described sites [31], were identified in the genome of the reference strain (Figure 3A; Supplementary Table 2). The organism was assigned to multilocus sequence typing ST120.

We next sequenced the genomes of 146 additional *emm74* strains (129 from iGAS infections and 11 from noninvasive infections) recorded from 2012 to June 2017 in Canada, as well as the genomes of 6 historic *emm74* iGAS isolates from the 1990s and 2000s recovered in Ontario and Alberta (Supplementary Table 1 lists Sequence-Read Archive [SRA] accession numbers). Whole-genome SNP-based phylogenetic analysis of newly sequenced *emm74* genomes and all 55 complete GAS genomes available in GenBank (as of October 2017, representing 25 other *emm* types) indicated that *emm74* organisms are a discrete GAS subpopulation and that they are more closely related to an *emm71* isolate associated with skin colonization [32] than to any other *emm* type (Figure 3B). As a population, *emm74* strains were relatively genetically diverse. However, consistent with our hypothesis, all analyzed *emm74* iGAS strains isolated in Canada since October 2015 (n = 136) were highly clonal and clustered tightly in a phylogenetic tree (Figure 3B, in red, and C). In addition to this cluster (henceforth "the epidemic clone"), minor *emm74* subpopulations were identified. These included "close outlier" strains from Ontario (n = 4, isolated in 1996, 2002, and 2013), 1 isolate from Alberta recovered in 2012, and 6 "distant outlier" strains from Ontario (n = 2, isolated in 1992 and 1995), Saskatchewan (n = 2, isolated in 2015), Alberta (n = 1, isolated in 2003), and the 2013 noninvasive *emm74* strain from New Brunswick (Figure 3C).

The lack of sequence identity with other GAS *emm* types (Figure 3B) suggests that the different *emm74* populations, and the epidemic clone in particular, have not arisen through *emm* type switching. Bayesian analysis of polymorphism distribution did not identify obvious signals of acquisition of foreign genetic material by the epidemic clone by means of recombination (Supplementary Figure 1). All *emm74* strains possessed the genes *speA*, *speG*, *speH*, *speI*, and *smeZ*, encoding exotoxins (Table 1). In addition, the epidemic clone and "close and distant outlier" strains from Ontario possessed the exotoxin-encoding gene *speC* and the DNase-encoding gene *spd1*. However, *speC* and *sdp1* were carried by different prophages in the different groups (Supplementary Figure 2). In comparison with "close outlier" strains, the epidemic clone had 1 SNP in the surface protein–encoding *epf* gene predicted to result in a D929E amino acid substitution in the predicted translated sequence of this protein

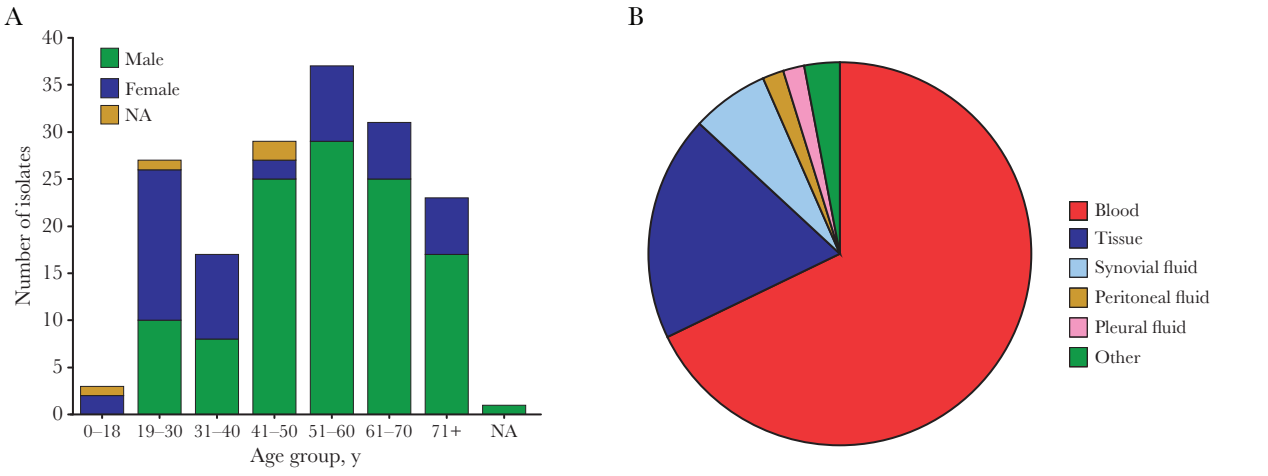

Figure 2. Demographics of patients with type *emm74* invasive disease in Canada and source of isolation of invasive *emm74* group A *Streptococcus* invasive strains responsible for these infections. A, Age and sex of patients with *emm74* iGAS disease in Canada for the period January 2012 to June 2017. Sex data were unavailable for 4 patients, and age was unavailable for 1 (indicated by NA). Overall, the distribution indicates that *emm74* iGAS disease disproportionately affects adult middle-aged or older males. B, Anatomical source of isolation of the 168 *emm74* iGAS isolates. Data are shown as percentage of the total number of isolates. The majority (n = 114, 67.9%) of isolates were recovered from blood, followed by abscesses and soft tissue (n = 32, 19%), synovial fluid (n = 11, 6.5%), peritoneal fluid (n = 3, 1.8%), and pleural fluid (n = 3, 1.8%). Five isolates (3%) were recovered from undetermined aspirates or from surgical specimens, collectively defined as "other" in the figure legend.

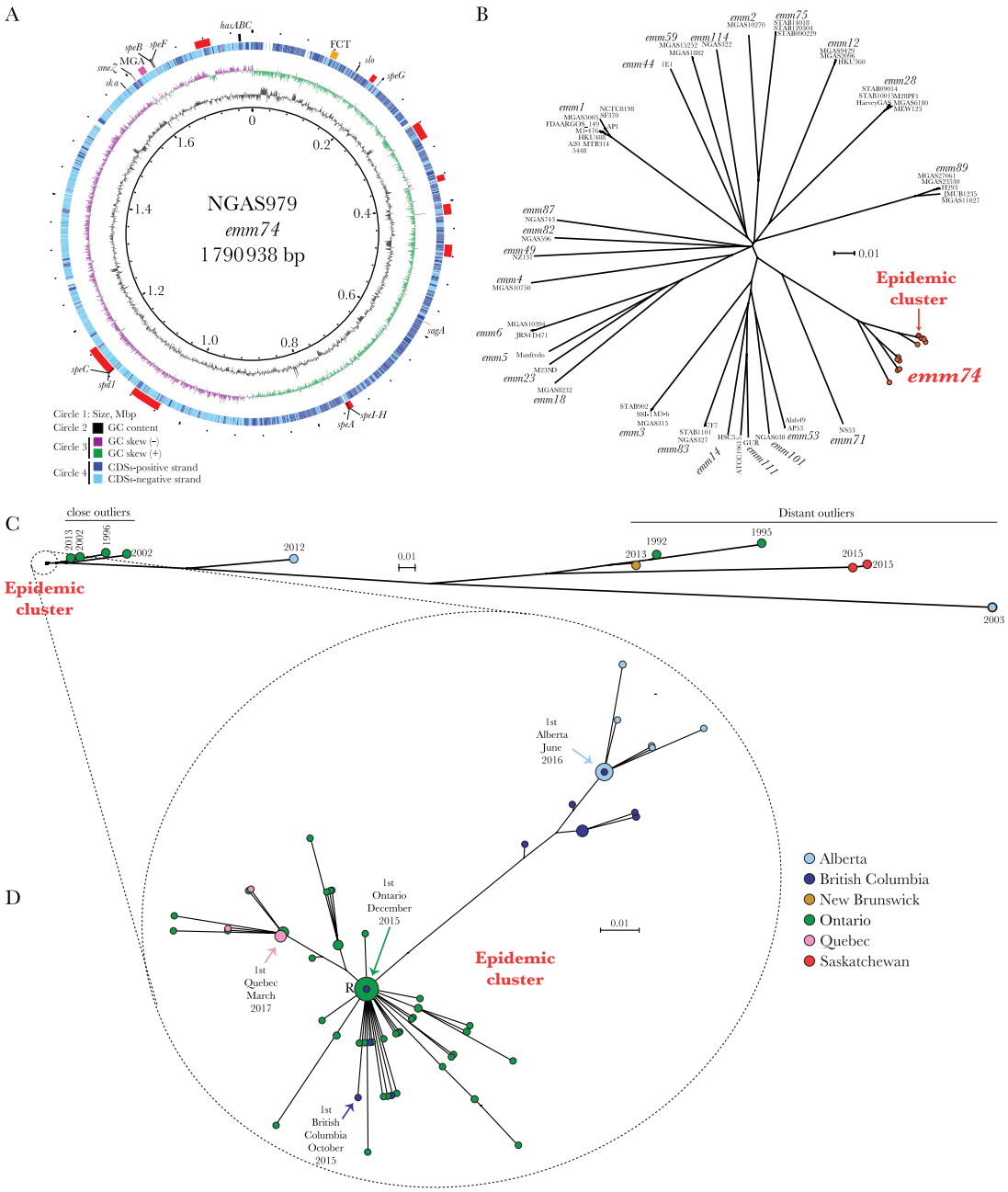

Figure 3. Genomic features and phylogenetic relationships of *emm74* invasive group A *Streptococcus* isolates. A, Genome atlas of *emm74* group A *Streptococcus* (GAS) reference strain NGAS979. Data from innermost to outermost circles in the atlas are described in the figure legend, with the exception of the outermost circle, which depicts genome landmarks such as mobile genetic element (prophages, prophage remnants, and integrative-conjugative elements, indicated by red boxes) and virulence genes, including those encoding superantigens. The *hasABC* locus is indicated by a black box, the FCT locus by a yellow box, and the *mga* regulon by a dark pink box. GC skew -or (G-C)/(G+C)- is averaged over a moving window of 10 000 bp. B, Inferred phylogenetic relationships between *emm*74 GAS strains and 55 strains of 25 other *emm* types, for which complete genome sequences are available in GenBank. A neighbor-joining phylogenetic tree was constructed using 76 311 nonredundant biallelic single nucleotide polymorphism (SNP) loci identified in the genomes of the strains relative to the core genome of the reference *emm74* strain NGAS979. Strain names and *emm* types for non-*emm74* strains are indicated at the tip of the branches. The reference *emm74* strain and all 136 *emm74* invasive and noninvasive isolates recovered since October 2015 in Canada clustered tightly in a discrete epidemic cluster (indicated in red). All other *emm74* isolates from Canada are depicted in orange. C, Inferred phylogenetic relationship among 147 *emm74* GAS strains from Canada. A neighbor-joining phylogenetic tree was constructed using 10 224 nonredundant biallelic SNP loci identified in the genomes of the *emm74* isolates relative to the core genome of the reference *emm74* strain NGAS979. The 136 *emm74* GAS isolates recovered in Canada since October 2015 for which we generated genome data (the epidemic cluster) are monoclonal and genetically distinct from previously isolated *emm74* strain SNPs. We arbitrarily divided these nonepidemic *emm74* isolates into 3 groups: a first group of "close outliers," comprising 4 isolates from Ontario in 1996, 2002, and 2013, a more distantly related single isolate from Alberta isolated in 2012, a group of 5 highly divergent "distant outlier" *emm74* isolates recovered in Alberta, Saskatchewan, and Ontario from invasive infections, and 1 noninvasive isolate from New Brunswick recovered in 2013. Provinces are indicated by different colors, as per the caption in (D). D, Diversification of the *emm74* GAS epidemic clone. The neighbor-joining phylogenetic tree was constructed using 71 nonredundant SNP loci identified among the 136 epidemic *emm74* isolates relative to the genome of the reference strain NGAS979. The circles are colored to indicate province of isolation, as per the figure caption, and their sizes are proportional to the number of isolates with identical genotypes. The location in the phylogenetic tree of the first *emm74* invasive isolate in each province is indicated by an arrow. Abbreviations: CDS, coding DNA sequence; GC, Guanine-cytosine.

Table 1. Superantigen- and Other Virulence Factor–Encoding Genes Found in the Different *emm74* Genotypes Circulating in Canada

		Superantigen-Encoding Gene											Virulence Factor-Encoding Gene			
Genotype	Strain	*speA*	*speC*	*speG*	*speH*	*speI*	*speJ*	*speK*	*speL*	*speM*	*smeZ*	*ssa*	*slaA*	*spd1*	*spd3*	*speB*
Epidemic clone (n = 136)	NGAS979 and 135 others	+	+	+	+	+	-	-	-	-	+	-	-	+	-[a]	+
Ontario close outliers (n = 4)	8198, 22173, 22351, NGAS664	+	+	+	+	+	-	-	-	-	+	-	-	+	-	+
Ontario distant outliers (n = 2)	1018, 5870	+	+	+	+	+	-	-	-	-	+	-	-	+	-	+
Alberta 2012 (n = 1)	SC173172	+	-	+	+	+	-	+	-	-	+	-	+	-	-	+
Saskatchewan distant outliers (n = 2)	SC152081, SC152083	+	-	+	+	+	-	+	-	-	+	-	+	-	-	+
New Brunswick distant outlier (n = 1)	SC132849	+	-	+	+	+	-	-	-	-	+	-	-	-	+	+
Alberta 2003 (n = 1)	SC173171	+	-	+	+	+	-	-	-	-	+	-	-	-	+	+

[a]One epidemic isolate was positive for *spd3*.

factor involved in keratinocyte adhesion and internalization [33]. Additionally, "close outliers" and epidemic strains differed by the presence of nonsynonymous SNPs in the 2 component regulator–encoding gene *vicR*, in *sagD*, a gene involved in streptolysin production, and in the global regulator–encoding gene *ropB*. Additional work will be needed to evaluate whether these or other additional SNPs (Supplementary Table 3) play a role in the virulence, fitness, or other biological traits of the epidemic clone.

Transmission Patterns of the Epidemic *emm74* Clone

As a population, the invasive and noninvasive *emm74* epidemic isolates recovered from October 2015 to June 2017 for which we generated genome data had only 92 nonredundant polymorphic loci relative to the core genome of the reference strain (Supplementary Table 4). Indels accounted for 21 of these loci. The vast majority of indels (n = 19, 90%) were isolate specific, and although they ranged in size from 1 to 126 bp, most (n = 15, 71%) were a single nucleotide event. The remaining 71 polymorphisms were biallelic SNPs, of which 12 occurred in noncoding regions. Predicted coding sequences accounted for 85.6% of the NGAS979 core genome, and a relatively similar percentage (83.1%) of the core SNPs occurred in coding sequences. Nonsynonymous SNPs accounted for 59% (n = 35/59 coding SNPs), while synonymous SNPs accounted for 41% (n = 24/59). Most of the SNPs were strain specific, and only a small percentage the SNP loci (n = 18, 25.4% of total SNP loci) were present in 2 or more of the epidemic strains and therefore were phylogenetically informative (Supplementary Table 4). Despite the minimal genetic differences, when analyzed together with temporal data, the inferred phylogenetic relationships permitted us to conclude that (1) older (late 2015 and early 2016) epidemic strains causing disease in British Columbia and Ontario constitute a single *emm74* subclone; (2) Alberta isolates are likely derived from a second *emm74* GAS subclone previously circulating in British Columbia; and (3) the Quebec isolates are a genetic *emm74* sublineage whose origin can be traced back to strains circulating in Ontario (Figure 3D).

Risk Factors for Epidemic *emm74* Disease

Centralized GAS typing at the provincial and national levels permits efficient tracking of iGAS epidemiology in Canada. However, capture of comprehensive patient clinical data for iGAS infections enabling enhanced investigation of epidemics is limited to select areas. Here, we used data from TIBDN active surveillance to assess *emm74* iGAS disease characteristics and patient risk factors. While the geographical area covered by TIBDN is limited to the metropolitan Toronto-Peel region, TIBDN isolates represented almost 35% (n = 58/168) of the total number of epidemic invasive cases recorded in the country since October 2015. Initial inspection of the data revealed that most *emm74* iGAS cases presented primarily as soft tissue infections, followed by arthritis and bacteremia without focus (Table 2). We next compared the subset of patients with *emm74* iGAS disease with a matched cohort comprising all patients with *emm1* iGAS disease ($n = 54$) in the same population area during the same time period (December 2015 to June 2017). The analysis showed that compared with *emm1* iGAS disease, *emm74* iGAS disease was significantly more associated with non-necrotizing fasciitis soft tissue infections ($P = .012$) and significantly less associated with respiratory tract infections ($P < .0001$) (Table 2). Proportionally fewer patients with *emm74* iGAS disease had streptococcal toxic shock syndrome, and significantly fewer required intensive care unit admission ($P = .05$) (Table 2). Homelessness, alcohol abuse, and intravenous drug use were significantly associated with *emm74* iGAS disease (Table 2).

DISCUSSION

Emergence and rapid spread of a novel *emm74* clone has caused more than 160 iGAS disease episodes in Canada since October 2015. Available data showed that cases were primarily associated with soft tissue infections and arthritis and that the disease disproportionally affected older middle-aged males and the homeless population. Alcohol abuse and intravenous drug

Table 2. Clinical Features of Invasive Group A Streptococcal Disease due to *emm74* and *emm1* in Residents of Metropolitan Toronto and Peel Region, Canada, 12/2015–5/2017

	No. (%) of Isolates			
	emm74 (N = 58)	*emm1* (N = 54)	*P* Value	Odds Ratio (95% CL)
Age group, y				
0–18	0	11 (20)	.0002	
19–40	13 (22)	11 (20)	.8	
41–60	22 (38)	9 (17)	.02	
≥61	23 (40)	23 (43)	.9	
Male sex	38 (66)	30 (56)	.3	
Risk factor for infection				
Alcohol abuse	12 (21)	2 (3.7)	.009	6.8 (1.4–32)
Homeless	17 (29)	0 (0)	<.0001	N/A
IV drug user	13 (22)	1 (1.9)	.001	15 (1.9–122)
Underlying chronic disease				
Any	53 (91)	40 (74)	.02	3.7 (1.2–11)
Cardiac disease	9 (16)	10 (19)	.8	
Diabetes mellitus	11 (19)	6 (11)	.3	
Malignancy (last 2 y)	5 (8.6)	5 (9.3)	1.0	
HIV infection	3 (5.2)	0 (0)	.2	
Clinical presentation[a]				
Soft tissue infection (all)	31 (53)	19 (35)	.06	
Non-necrotizing fasciitis	29 (50)	14 (26)	.01	2.9 (1.3–6.3)
Necrotizing fasciitis	2 (3.4)	5 (9.3)	.3	
Respiratory tract infection	4 (6.9)	22 (41)	.0001	0.11 (0.03–0.34)
Bacteremia without focus	9 (16)	9 (17)	1.0	
Arthritis	10 (17)	7 (13)	.6	
Other[b]	6 (10)	5 (9.3)	1.0	
Streptococcal toxic shock syndrome	8 (14)	12 (22)	.3	
Outcomes				
ICU admission	17 (29)	26 (48)	.05	0.45 (0.20–0.97)
Death	5 (8.6)	6 (11)	.8	

Abbreviations: CL, confidence limit; ICU, intensive care unit; IV, intravenous.

[a]Totals are greater than the number of cases because patients may present with more than 1 site of infection.

[b]Other includes 4 cases of osteomyelitis (2 each *emm74* and *emm1*); 2 of peritonitis (1 each *emm74* and *emm1*), and 1 case each of endocarditis (*emm74*), mastoiditis/meningitis (*emm1*), peripartum infection (*emm1*), other gynecologic infection (*emm74*), and urinary tract infection (*emm74*).

use were common among patients with *emm74* iGAS disease. Overall, similar disease manifestations and patient risk factors were identified in a previous *emm59* GAS epidemic that occurred Canada-wide in 2006–2010 [17], suggesting that a disadvantaged population continues to be at higher risk for GAS soft tissue infections.

Recent reports have described GAS outbreaks affecting homeless populations that were caused by strains of *emm* types 82, 83, 87, 101, and 114 in Canada [7], 44 in France [34], and 32 and 66 in Great Britain [35, 36]. One common theme between the current *emm74* and prior *emm59* epidemics, as well as in these other reports, is that the offending GAS strains belong to *emm* types of pattern D (skin tropism) or E (generalist, ie, both throat and skin tropism) [37, 38]. However, while strain genetics is expected to play a role in the observed overabundance of skin and soft tissue infections among homeless patients, it is unlikely to be the only factor. For example, a recent outbreak among the homeless population in Alaska that was also characterized by a high incidence of soft tissue infections was caused by *emm26* GAS strains (ie, a pattern A-C *emm* type with throat tropism) [12]. Thus, the poor environmental and hygienic conditions commonly associated with homelessness and homeless shelters (crowding, poor sanitation, frequent skin breakdown), the weak immune response to GAS in the skin [39], and/or the underlying alcohol and intravenous drug use are undoubtedly major contributors to the overabundance of soft tissue infections among homeless patients.

Our genomic data unambiguously show that the current epidemic has been caused by *emm74* GAS organisms that are genetically homogeneous, with epidemic strains differing from one another on average by fewer than 5 genetic polymorphisms genome-wide. In addition to the main clinical outcomes, another key similarity between the current *emm74* and previous *emm59* [13, 18, 19] Canadian epidemics is the fact that both were caused by highly clonal strains that spread very rapidly across vast geographic

areas. During the first 5 years of the *emm59* iGAS disease epidemic, *emm59*-specific pharyngitis was rarely observed, leading to the notion that *emm59* organisms had a restricted population size [18]. Similarly, *emm74* organisms appear to be also very rarely associated with pharyngitis [40]. Thus, a restricted *emm74* population size may be 1 reason for the minimal strain genetic variation reported here. However, compared with the *emm59* epidemic reports [13, 18, 19], less time has elapsed between the inception of the *emm74* epidemic and our analysis (22 months). Thus, the relatively short time involved in the current epidemic is also likely a factor explaining the very modest genetic diversity observed among *emm74* strains. Although minimal, genetic differences among strains revealed by whole-genome-based phylogenetic analysis permitted us to identify clear patterns of interprovincial *emm74* GAS subclone dissemination.

Genomic investigations can provide definite proof that introduction of novel GAS clones within a naïve population can lead to a rapid increase in iGAS incidence [9, 41, 42]. Genomics identified that a single epidemic clone was responsible for the prior Canada-wide *emm59* epidemic, and as no cases of *emm59* iGAS disease had occurred in the country in the approximately 20 years preceding the epidemic [18, 19], this clone was most likely introduced from abroad. Similarly, it can be hypothesized that the epidemic *emm74* clone has recently been introduced to Canada from elsewhere. Although rare in North America and Europe, *emm74* iGAS disease, including clusters of *emm74* infections, has been described in Africa, India, New Zealand, New Caledonia, and Hawaii [8, 20, 40, 43–46]. We were unable to obtain isolates or genomic data for *emm74* organisms isolated in these other geographic locations to test this hypothesis. However, in contrast to the *emm59* epidemic, other *emm74* genotypes were circulating in Canada prior to the sudden emergence of the *emm74* epidemic clone. It might be possible that the epidemic *emm74* clone originates from one of these prior, relatively closely related genotypes, which by acquisition of additional genetic material now possess enhanced ability to spread and/or to cause disease. Despite extended comparisons of the genome sequences of the epidemic clone and other *emm74* genotypes, we were unable to identify obvious gains of genetic regions or single genes encoding known or putative virulence factors by the epidemic clone. However, the epidemic clone and older *emm74* genotypes from Ontario possessed the virulence factor–encoding genes *speC* and *spd1*, carried on different prophages (Supplementary Figure 2). It might be possible that *speC* and *spd1* are differentially regulated in the epidemic clone and that this results in epidemic *emm74* strains that have enhanced ability to spread. Recently, an *emm3* GAS lineage that acquired a prophage carrying the *speC* and *spd1* genes was found to be responsible for an upsurge in iGAS infections in the United Kingdom [47]. Further experiments are needed to test this hypothesis.

In summary, we describe here a large epidemic of invasive GAS disease affecting primarily a specific group of disadvantaged patients. The epidemic is caused by strains of a single *emm74* GAS clone that expanded across 4 Canadian provinces in a very short period of time. Our unpublished surveillance data indicate that the epidemic is still ongoing, and we have very recently become aware of additional *emm74* iGAS cases in other Canadian jurisdictions. Based on the similarities with a previous *emm59* epidemic [13, 18, 19], further spread of the *emm74* epidemic clone into additional areas of Canada and/or into the United States is likely. Continued monitoring for invasive *emm74* GAS infections is warranted.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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